CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217242Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	217242
Priority or Standard	Standard
Submit Date(s)	February 16, 2023
Received Date(s)	February 16, 2023
PDUFA Goal Date	December 16, 2023
Division/Office	Division of Dermatology and Dentistry
Review Completion Date	12/13/2023
Established/Proper Name	Roflumilast
(Proposed) Trade Name	Zoryve
Pharmacologic Class	Phosphodiesterase-4 Inhibitor
Code name	ARQ-154
Applicant	Arcutis Biotherapeutics, Inc.
Dosage form	Topical Foam, 0.3%
Applicant proposed Dosing Regimen	Once a day
Applicant Proposed Indication(s)/Population(s)	Treatment of Seborrheic Dermatitis in patients ≥9 years of age
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Seborrheic dermatitis (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of Seborrheic Dermatitis in patients ≥9 years of age
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Seborrheic dermatitis (disorder)
Recommended Dosing Regimen	Once a day

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Abbreviations: DHOT, Division of Hematology, Oncology, and Toxicology; OCP, Office of Clinical Pharmacology; OHOP, Office of Hematology and Oncology Products

Additional Reviewers of Application

OPQ	
Microbiology	
OPDP	
OSI	
OSE/DEPI	
OSE/DMEPA	
OSE/DRISK	
Other	

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

Signatures

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Glossary

AC	advisory committee
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
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
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LTS	long-term safety
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MuST	maximal use study
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
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
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
VC	vehicle-controlled

1. Executive Summary

1.1. Product Introduction

Zoryve (roflumilast foam, 0.3%) is a phosphodiesterase-4 (PDE-4) inhibitor developed by the Applicant under IND 142047 for the indication of topical treatment of seborrheic dermatitis (SD).

Roflumilast oral tablets (250 mcg, 500 mcg) were approved by the FDA in 2011 (Daliresp, NDA 022522) for the indication of "treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations."

The Applicant has acquired right of reference to relevant clinical, nonclinical, and chemistry, manufacturing, and controls (CMC) information in NDA 022522, and submitted NDA 217242 under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act (FD&C Act) for marketing Zoryve for the indication of topical treatment of SD in patients ≥9 years of age.

Additionally, the Applicant has cross-referenced the nonclinical and clinical data submitted under their NDA 215985 (approved on 7/29/2022) for roflumilast cream, 0.3% for the indication of topical treatment of subjects with plaque psoriasis in support of the approval of NDA 217242.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from two adequate and well-controlled trials, ARQ-154-203 and ARQ-154-304 (Trials -203 and -304) which provided evidence of the effectiveness of roflumilast foam, 0.3% for the topical treatment of seborrheic dermatitis in the target population. Both trials assessed Investigator's Global Assessment (IGA) success compared to vehicle at Week 8, defined as the proportion of subjects who achieved an IGA Score of clear (0) or almost clear (1) and ≥2 grade improvement from baseline.

Roflumilast foam, 0.3% was statistically superior to vehicle on the primary efficacy endpoint in both trials. The Applicant has demonstrated that roflumilast foam, 0.3% 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.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Seborrheic dermatitis (SD) is a chronic, relapsing, usually mild dermatitis that is usually characterized by well-demarcated, erythematous plaques with greasy-looking, yellowish scales distributed on areas rich in sebaceous glands, such as the scalp, the external ear, the center of the face, the upper part of the trunk, and the intertriginous areas (refer to Section 2 of this Unireview for a discussion of SD and available treatment options). The Applicant proposes Zoryve (roflumilast) foam, 0.3% applied daily for the topical treatment of subjects (≥9 years of age) with SD and is seeking approval of this product via a 505(b)(1) regulatory pathway.

The Applicant submitted efficacy and safety data from one Phase 2 (ARQ-154-203) and one Phase 3 (ARQ-154-304) randomized, double-blind, vehicle-controlled trial. Additionally, the Applicant submitted safety data from one open-label, long-term safety study (ARQ-154-214) and safety/PK data from a Phase 1, maximal use study (MuST), ARQ-154-116.

Efficacy

Roflumilast foam, 0.3% was statistically superior to the vehicle foam for the primary efficacy endpoint in Trial ARQ-154-203; however, Trial ARQ-154-203 was not adequately designed to support labeling claims for the secondary efficacy endpoints.

Roflumilast foam, 0.3% was statistically superior to the vehicle foam for the primary and the following secondary efficacy endpoints in Trial ARQ-154-304 (prespecified in the protocol and controlled for multiplicity), for the ITT population at Week 8:

1. For the primary efficacy endpoint of Investigator's Global Assessment (IGA) response (IGA score =0 or 1 with ≥2-grade improvement from baseline) at Week 8, the roflumilast group, compared to the vehicle group, achieved a response of 79.5% vs. 58.0% (p-value < 0.0001) [a treatment effect of 20.6%] in Trial ARQ-154-304, and 73.1% vs. 40.8% (p-value < 0.0001) [a treatment effect of 33.8%] in Trial ARQ-154-203.
2. For the secondary efficacy endpoint of worst itch numeric rating scale (WI-NRS) success (≥4-points improvement from baseline) at Week 8, the roflumilast group, compared to the vehicle group, achieved a response of 62.8% vs. 40.6% (p<0.0001), [a treatment effect of 25.7%] in Trial ARQ-154-304, and 64.6% vs. 34.0% (p-value< 0.0007) [a treatment effect of 29.9] in Trial ARQ-154-203.
3. For the secondary efficacy endpoint of (IGA = 0) at Week 8, the roflumilast group, compared to the vehicle group, achieved a response of 50.6% vs. 27.7% (p<0.0001), [a treatment effect of 22.5%] in Trial ARQ-154-304, and 35.5% vs. 15.2% (p-value = NA) [a treatment effect of 20.3%] in Trial ARQ-154-203.

Safety

Analysis of the vehicle-controlled (VC) safety pool (Trials-203/-304) did not identify any significant safety signals and was adequate to characterize the safety profile of roflumilast foam, 0.3% for the treatment of moderate to severe SD. Adverse events reported in the VC pool through Week 8 in ≥1% of subjects treated with roflumilast (and more frequently than subjects receiving vehicle), compared to the vehicle group, included COVID-19 (2.6% v. 2.2%), nasopharyngitis (1.5% v. 0.4%), nausea (1.3% v. 0), contact dermatitis (1.3% v. 0.9%), and headache (1.1% v. 0). COVID-19 and contact dermatitis were deemed by the review team as not related to the study drug (b) (4)

Roflumilast foam, 0.3% offers an alternative treatment option to a number of products available in the US and has an acceptable risk-benefit profile for the treatment of moderate to severe SD. Available treatments do not cure SD and require continued or repeated intermittent treatment to prevent recurrence. The main goal of therapy is to clear the visible signs of the disease and reduce associated symptoms, such as erythema and pruritus. None of the available treatments provides a permanent cure or universal response, and all are associated with one or more risks. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is still a need for additional therapeutic options for this group of patients with SD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Seborrheic dermatitis is a chronic, relapsing, usually mild dermatitis of an unknown etiology characterized by well-demarcated, erythematous plaques with greasy-looking, yellowish scales distributed on areas rich in sebaceous glands, such as the scalp, the external ear, the center of the face, the upper part of the trunk, and the intertriginous areas. The prevalence of clinically significant SD is approximately 3%, peaking in the third and fourth decades. Males are affected more frequently than females. Severity of SD may vary from minimal, asymptomatic scaliness of the scalp (dandruff) to more widespread involvement. Affected individuals are usually healthy.	Because of its chronicity and impact on quality of life, the main goal of therapy is to clear the visible signs of the disease and reduce associated symptoms, such as erythema and pruritus. Repeated treatment or long-term maintenance treatment is often necessary.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Available treatment options for the treatment of SD include topical products (most are available as generics) commonly used for the treatment of SD, including antifungal agents, corticosteroids, topical calcineurin inhibitors (TCI) (not FDA-approved for SD), and miscellaneous agents (selenium sulfide and zinc pyrithione). • Oral antifungal agents (itraconazole, ketoconazole, fluconazole, and terbinafine) are a treatment option for severe, refractory, recalcitrant disease not adequately controlled with topical therapies or involving multiple body areas. Ultraviolet-B phototherapy may be considered as an option for extensive or recalcitrant disease.	There are several products with an acceptable benefit-risk profile for the treatment of SD. Although the efficacy varies, no product produces a response in all patients or provides a permanent cure. Phototherapy may be impractical due to office-based administration requirements. Systemic antifungal products may have one or more serious adverse reactions. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is a need for additional therapeutic options.
Benefit	• For the Phase 3 trial (ARQ-154-304) and Phase 2 trial (ARQ-154-203), the primary efficacy endpoint (IGA success, defined as IGA =0 or 1 and ≥2-point improvement from baseline at Week 8) results showed that in the ITT population, roflumilast foam, 0.3% was statistically superior to vehicle foam: - Trial ARQ-154-304: 79.5% v. 58.0% (treatment difference of 20.6%, 95% CI (11.2%, 30.0%)) - Trial ARQ-154-203: 73.1% v. 40.8% (treatment difference of 33.8%, 95% CI (20.3%, 47.4%)). • For the Phase 3 trial (ARQ-154-304), among subjects with a baseline WI-NRS score of >= 4, subjects in the roflumilast group compared to subjects in the vehicle group achieved the secondary efficacy endpoint of	The data submitted by the Applicant met the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use. Trials ARQ-154-203 and ARQ-154-304 were adequate and well-controlled; and the results are persuasive.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	WI-NRS success (>= 4 points reduction from baseline) at Week 8 in (62.8% vs. 40.6%), for a treatment difference of 25.7%, 95% CI of (13.4, 38.1).	
Risk and Risk Management	• The primary safety database (comprised of the VC trials, ARQ-154-304 and ARQ-154-203) consisted of 683 subjects treated once daily for 8 weeks. In addition, one long-term, open-label safety study (ARQ-154-214) [of duration 26 weeks, subsequently extended to 52 weeks] resulted in exposures to roflumilast foam of ≥24 weeks in 329 subjects, and ≥52 weeks in 41 subjects. The safety database is adequate to characterize the safety profile of roflumilast foam, 0.3% for SD. The following adverse events were reported for the VC trials: - SAEs occurred in 1/458 (0.2%) subject in the roflumilast group (not related to roflumilast) and no subject in the vehicle group. - Adverse drug reactions (possibly, probably, or likely related to study drug) occurred in 11/458 (2.4%) of subjects in the roflumilast group, compared to 8/225 (3.6%) subjects in the vehicle group. - The most common adverse events (reported in ≥1% of subjects in the roflumilast group, and greater than in placebo group) were COVID-19 (2.6% v. 2.2%), nasopharyngitis (1.5% v. 0.4%), nausea (1.3% v. 0), contact dermatitis (1.3% v. 0.9%), and headache (1.1% v. 0). • The effects of roflumilast foam on pregnant or lactating women are unknown.	The safety profile of roflumilast foam, 0.3% has been adequately characterized by the premarket safety data for seborrheic dermatitis. Prescription labeling, patient labeling and routine pharmacovigilance are adequate to manage the potential risks of the product.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

□	**The patient experience data that were submitted as part of the application include:**			**Section of review where discussed, if applicable**
	□	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	WI-NRS, C-SSRS, PHQ-8/-A, CDI-2, DLQI, Scalpdex, LTA by subject
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	IGA, overall assessment of scaling score, overall assessment of erythema score, BSA, LTA by investigator, pigment assessment
		□	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.**			

Abbreviations: BSA, body surface area; CDI-2, Children's Depression Inventory 2; C-SSRS, Columbia-Suicide Severity Rating Scale; DLQI, Dermatology Life Quality Index; IGA, Investigator Global Assessment; LTA, Local Tolerability Assessment; PHQ-8, Patient Health Questionnaire Depression Scale; PHQ-A, Modified Patient Health Questionnaire-9 for Adolescents; WI-NRS, Worst Itch – Numeric Rating Scale

2. Therapeutic Context

2.1. Analysis of Condition

Seborrheic dermatitis (SD) is a chronic, relapsing, usually mild dermatitis that occurs in infants and adults (biphasic incidence) (Sasseville et al. 2023b). Seborrheic dermatitis that occurs in infants between the ages of 3 weeks and 12 months (cradle cap) typically manifests as a self-limiting, asymptomatic, and noninflammatory accumulation of yellowish, greasy scales on the scalp. Cradle cap is considered to be distinct from seborrheic dermatitis in adolescents and adults and will not be discussed further in this review.

SD is usually characterized by well-demarcated, erythematous plaques with greasy-looking, yellowish scales distributed on areas rich in sebaceous glands, such as the scalp, the external ear, the center of the face, the upper part of the trunk, and the intertriginous areas. SD severity may vary from minimal, asymptomatic scaliness of the scalp (dandruff) to more widespread involvement. Affected individuals are usually healthy, although SD has been associated with human immunodeficiency virus (HIV) infection, Parkinson disease and other neurologic disorders, and use of neuroleptic medications (Sasseville et al. 2023a). The prevalence of clinically significant SD is approximately 3%, peaking in the third and fourth decades. Males are affected more frequently than females.

The etiology of SD is not known. SD is not a disease of the sebaceous glands; however, sebaceous glands appear to be involved in the development of SD as indicated by the predilection of SD for body sites with larger and more numerous sebaceous glands. Sebaceous glands may contribute to the pathogenesis of SD by creating a favorable environment for the growth of lipid-dependent fungi *Malassezia* (formerly *Pityrosporum ovale*). SD diagnosis is usually made clinically based on the appearance and location of the lesions. The differential diagnosis of SD includes psoriasis, rosacea, tinea versicolor, pityriasis rosea, tinea corporis, secondary syphilis, systemic lupus erythematosus (SLE), pemphigus foliaceous, and allergic contact dermatitis.

Available treatments do not cure SD and require continued or repeated intermittent treatment to prevent recurrence. The main goal of therapy is to clear the visible signs of the disease and reduce associated symptoms, such as erythema and pruritus.

2.2. Analysis of Current Treatment Options

Topical agents are the most commonly used products for the treatment of SD and include Antifungal agents, Corticosteroids, topical Calcineurin Inhibitors (TCI), and miscellaneous agents Selenium sulfide and zinc pyrithione (most topical agents are available as generics). Randomized trials provide support for the use of several topical agents. Other topical treatment options (not available in the United States) include Lithium salts and the antifungal agent, Bifonazole.

Oral antifungal agents, including itraconazole (200 mg QD x 7 days), ketoconazole, fluconazole, and terbinafine, are a treatment option for severe or refractory SD, SD involving multiple body areas, and recalcitrant SD not adequately controlled with topical therapies. Limited efficacy data for the use of oral antifungal products for the treatment of SD is available, and potential adverse reactions are associated with their use.

Ultraviolet B phototherapy may be considered as an option for extensive or recalcitrant SD, but it has not been studied in randomized trials; adverse reactions include burning and itching, and long-term treatment raises skin carcinogenicity concerns (Naldi and Rebora 2009).

Table 1. Topical Agents for the Treatment of Seborrheic Dermatitis (Available in the United States)

Treatment Classification	Formulation	Dosing/ Administration	Adverse Effects	Comments
Antifungal agents				
Ketoconazole	2% in shampoo, foam, gel, or cream (by Rx). (1% in OTC)	Scalp: twice/wk for clearance, then once/wk or every other wk for maintenance; other areas: from twice daily to twice/wk for clearance, then from twice/wk to once every other wk for maintenance	Irritant contact dermatitis in <1% of patients; itching and burning sensation in about 3% of patients; teratogenic in rats.	Generic available; more data to provide support for efficacy are available for scalp lesions than for lesions elsewhere; some formulations such as foam are expensive
Ciclopirox olamine (also called ciclopirox)	1.0% or 1.5% in shampoo or cream	Scalp: twice to 3 times/wk for clearance, then once/wk or every 2 wk for maintenance; other areas: twice daily for clearance, then once daily for maintenance	Irritant contact dermatitis in <1% of patients; itching and burning sensation in about 2% of patients; rare cases of allergic contact dermatitis can occur.	Generic available; studied in facial and scalp lesions and in short term maintenance regimens; more expensive than ketoconazole
Corticosteroids				
Hydrocortisone	1% in cream	Areas other than scalp: once or twice daily	Skin atrophy and excessive hair growth with prolonged, continuous topical use and systemic effects with extensive use. Observational studies suggest an increased risk of low birthweight infants with the use of >300 grams of potent or very potent topical corticosteroid during a pregnancy	Generic available; limited evidence available; potent topical corticosteroids should not be used on the face. Topical corticosteroids are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.
Betamethasone dipropionate	0.05% in lotion	Scalp and other areas: once or twice daily		
Clobetasol 17-butyrate	0.05% in cream	Areas other than scalp: once or twice daily		
Clobetasol dipropionate	0.05% in shampoo	Scalp: twice weekly in a short contact fashion (up to 10 min application, then washing)		
Desonide	0.05% in lotion	Scalp and other areas of skin: twice daily		

Treatment Classification	Formulation	Dosing/ Administration	Adverse Effects	Comments
Calcineurin inhibitors				
Pimecrolimus cream, 1% (or tacrolimus ointment, 0.1%) (not FDA-approved for SD)	1% in cream Or 0.1% in ointment	Areas other than scalp: twice daily	Higher rate of local reactions compared to placebo (26% vs. 12%); possible increased risk of skin cancer with prolonged use.	Limited evidence of effectiveness in moderate-to-severe facial lesions; possible advantage over topical corticosteroids is absence of atrophy with continuous use
Miscellaneous agents				
Selenium sulfide	2.5% in shampoo (OTC)	Scalp: twice weekly	Irritant local reactions in about 3% of treated patients, lightening and bleaching of hair color reported.	Generic available; limited evidence available; less expensive than most other options
Zinc pyrithione	1% in shampoo (OTC)	Scalp: twice weekly	Irritant local reactions in about 3% of treated patients	Limited evidence available

Source: Adapted from Table 3, Naldi, Luigi, and Alfredo Rebora. "Seborrheic Dermatitis." The New England journal of medicine 360.4 (2009): 387–396 (Naldi and Rebora 2009).
Note: Most OTC drugs are not reviewed and approved by FDA, however they may be marketed if they comply with applicable regulations and policies (e.g., monograph).
Abbreviations: OTC, over-the-counter; Rx, prescription; SD, seborrheic dermatitis

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Roflumilast foam has not been approved for marketing in any country.

Oral roflumilast tablets (Daliresp) was approved under NDA 022522 by the FDA in 2011 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.

Roflumilast cream, 0.3% (ZORYVE) was approved under NDA 215985 on 7/29/2022 for the indication of topical treatment of subjects with plaque psoriasis.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed roflumilast foam, 0.3% for topical treatment of SD under IND 142047 and submitted their marketing application for NDA 217242 under 505(b)(1) regulatory pathway. Milestone interactions with the Applicant are included below.

Pre-IND WRO Meeting on 8/13/2019

Discussed target population, IGA scale, safety assessments (including pigment changes, and gastrointestinal AEs/weight loss).

End-of-Phase 2 (EOP2) Teleconference Meeting on 12/16/2020

Phase 3 development plans were discussed, including:

- Inclusion of subjects ≥9 years of age in the Phase 3 trial -304, the Phase 2 LTS study -214, and the MuST study -116.
- General design of the Phase 3 trial.
- Primary efficacy endpoint (IGA success) and secondary efficacy endpoint of pruritus responder (4-point reduction in Worst Itch-Numerical Rating Scale [WI-NRS]; WI-NRS data to be collected daily during trial).
- Applicant's proposed IGA scale category descriptors (inclusion of "trace scaling" in "Almost clear" category).
- Safety assessments to include AEs, C-SSRS, PHQ-8/-A, application site pigment changes, and safety laboratory measurements. (Note: electrocardiograms (ECGs) were conducted only for the MuST -116 for roflumilast foam, 0.3% for the SD program, following FDA agreement during the EOP2 meeting (on 10/23/2019) for roflumilast cream, 0.3% for the psoriasis program that no ECG monitoring would be required for psoriasis Phase 3 trials).

- Size of the safety database.
- Provocative dermal safety studies conducted with roflumilast cream could be used to support the roflumilast foam program.

Agreed iPSP Agreement Letter on 6/3/2021

Included the plan to request a waiver for ages 0 to less than <9 years, no requests for deferral, and inclusion of subjects between 9 years to <17 years of age in the Phase 3 trial.

Type C (CMC) WRO Meeting on 4/27/2022

Type C WRO (ISE/ISS Data Analysis) on 6/3/2022

Discussed addition of weighted exposure adjusted incidence rates (wEAIR) and associated 95% confidence intervals (CIs), a change in the frequency benchmark for most common PTs for TEAEs, and addition of EAIRs for selected TEAEs in the Phase 2 LTS study -214.

Type B Pre-NDA Meeting on 9/14/2022

Discussed the following topics:

- Applicant's plan for pooling data in the integrated summary of safety (ISS) from Phase 2 and 3 trials (ARQ-154-203/-304) were reasonable.
- Protocol Amendment 2 and final statistical analysis plan (SAP) for trial ARQ-154-304 comments.
- Contents and format for the ISS to include subject narratives and case-report forms for all pregnancies, hypersensitivity reactions, deaths, SAEs, severe AEs, all subject discontinuations, and AEs resulting in permanent discontinuation; requested electronic links for all deaths, SAEs, severe AEs, and subject discontinuations regardless of reason.

TQT Waiver Request Agreement Letter on 1/12/2023

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

4.1. Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission was adequate. All trials were conducted at sites in the U.S. and Canada. Because of the history of recent approval of roflumilast cream, 0.3% for the indication of treatment of psoriasis, no deviation from the good clinical practice (GCP), or concerns with any sites identified by the statistical reviewer (Kathleen Fritsch, PhD.), the Division did not request that the Office of Scientific Investigations conduct clinical inspections of any sites.

4.2. Product Quality

An Integrated Quality Review Memorandum by the Office of Pharmaceutical Quality (in DARRTS on 11/5/2023) made the following Recommendations and Conclusions on Approvability: "The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed Zoryve (roflumilast) topical foam, 0.3%.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has made a final overall "Approval" recommendation for the facilities involved in this application.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The label/labeling issues have been satisfactorily addressed.

Therefore, from the OPQ perspective, this NDA is recommended for approval with expiration dating period of 24 months".

4.3. Clinical Microbiology

Not applicable to roflumilast foam, 0.3% drug product.

4.4. Devices and Companion Diagnostic Issues

Not applicable to roflumilast foam, 0.3% drug product.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Roflumilast is a small molecule inhibitor of phosphodiesterase 4 (PDE4), which is an intracellular enzyme that hydrolyzes cyclic 3,5-adenosine monophosphate (cAMP). Inhibition of PDE4 by roflumilast results in accumulation of cAMP in cells. The Applicant has obtained a Letter of Authorization (LOA) for Daliresp (NDA 022522), allowing for use of all relevant nonclinical data to support the current application, NDA 217242. Daliresp® (roflumilast) oral tablets are approved for the treatment of COPD, with the maximum recommended human daily dose of 0.5 mg. The drug product under NDA 217242, roflumilast foam, 0.3%, has been proposed for the topical treatment of seborrheic dermatitis in patients 9 years of age and older.

Roflumilast was tested for repeat-dose toxicity in the mouse, rat, hamster, dog, and monkey via the oral route with treatment duration of 6, 6, 3, 12, and 10 months, respectively, and in the minipig via the dermal route with the treatment duration of 9 months. In the oral toxicity studies, the target organs of toxicity included nasal cavity, cardiovascular system, gastrointestinal tract, and reproductive system. In the dermal toxicity study, roflumilast topical cream at dose strengths up to 1% applied in the amount of 2 mL/kg to 10% body surface area (BSA) had no overt toxicological effects in minipigs.

Roflumilast tested positive in an in vivo mouse micronucleus test, but negative in the following assays: the Ames test, an in vitro chromosome aberration assay, an in vitro hypoxanthine phosphoribosyl transferase (HPRT) gene mutation assay, an in vitro micronucleus test, a DNA adduct formation assay in rat nasal mucosa, liver, and testes, and an in vivo mouse bone marrow chromosome aberration assay. The major metabolite roflumilast N-oxide tested negative in the Ames test and an in vitro micronucleus test.

Roflumilast was tested for carcinogenicity in two 2-year oral carcinogenicity studies in hamsters, a 2-year oral carcinogenicity study in mice, and a 2-year dermal carcinogenicity study in mice. In the studies in hamsters, roflumilast treatment resulted in dose-dependent increases in the incidence of undifferentiated carcinomas of nasal epithelium at ≥ 8 mg/kg/day. The tumorigenicity was most likely due to a reactive metabolite of ADCP N-oxide, itself a roflumilast metabolite formed in the rodent nasal cavity. In mice, treatment with roflumilast either at the oral doses up to 12 mg/kg/day in females and 18 mg/kg/day in males or at the dermal doses up to 1% roflumilast cream (equivalent to 20 mg/kg/day) did not cause tumor formation.

In a rat fertility study, roflumilast decreased fertility rates at 1.8 mg/kg/day, which were accompanied by morphological changes in the male reproductive organs such as testicular tubular atrophy and spermatogenic granuloma in the epididymides. The no observed adverse effect level (NOAEL) was 0.6 mg/kg/day for male fertility. In a female rat fertility study, there were no effects on fertility observed at doses up to the highest dose of 1.5 mg/kg/day.

In a rat fertility and embryofetal development (EFD) study, animals were given roflumilast orally at doses up to 1.8 mg/kg/day for 10 weeks in males and 2 weeks in females prior to pairing and

throughout the organogenesis period. Roflumilast did not cause fetal malformations at doses up to 1.8 mg/kg/day but induced pre- and post-implantation loss at ≥ 0.6 mg/kg/day.

In a rat EFD study, pregnant rats were dosed orally at doses up to 1.8 mg/kg/day during the period of organogenesis. Fetal malformations or effects on the number of living fetuses were not observed; however, increases in the incidence of incomplete ossification of skull bones were observed at the doses of 0.6 and 1.8 mg/kg/day. The NOAEL was 0.2 mg/kg/day for embryofetal development.

In a rabbit EFD study, pregnant rabbits were dosed orally with roflumilast at doses up to 0.8 mg/kg/day during the period of organogenesis. Roflumilast did not cause fetal malformations at any dose and the NOAEL for embryofetal development was the highest dose of 0.8 mg/kg/day.

In a pre- and post-natal developmental (PPND) study in mice, dams were dosed orally with roflumilast at doses up to 12 mg/kg/day during the period of organogenesis and lactation. Roflumilast prolonged pregnancy duration and caused stillbirth at ≥2 mg/kg/day. In a second PPND study in mice, dams were dosed orally with roflumilast at doses up to 6 mg/kg/day. Roflumilast decreased the overall pup viability at 6 mg/kg/day, and in the surviving pups, roflumilast decreased pup rearing frequencies at the maternal dose of 6 mg/kg/day.

In a juvenile rat oral toxicity study, animals were given roflumilast orally at doses up to 0.8 mg/kg/day for three months. Target organs of toxicity included liver, epididymis, heart, lung, and spleen. The NOAEL was 0.2 mg/kg/day in males and 0.5 mg/kg/day in females. There was no increased sensitivity with respect to male reproductive organ toxicity when compared to a 3-month adult rat oral toxicity study. The target organs in the 3-month adult study, i.e., nasal cavities, testes, epididymis, and thymus, were not identified in juvenile animals with the exception of epididymis.

Roflumilast cream 1% was not an irritant in a bovine corneal opacity and permeability test. Roflumilast cream 1% did not show skin sensitization potential in a Buehler assay in guinea pigs. Roflumilast did not show phototoxic potential in a neutral red uptake phototoxicity assay in vitro.

This NDA is approvable from a nonclinical perspective. There are no recommended nonclinical postmarketing commitments or postmarketing requirements for this NDA.

5.2. Referenced NDAs, BLAs, DMFs

For pivotal nonclinical data that were reviewed under NDA 022522 and associated INDs, summary pharmacology/toxicology information is provided in this review. Code name ARQ-151 was for roflumilast.

5.3. Pharmacology

Roflumilast and its active metabolite roflumilast N-oxide are inhibitors of PDE4, which is a cAMP-degrading enzyme highly expressed in immune cells. The respective IC_{50} values of

roflumilast and roflumilast N-oxide were 0.3 and 0.8 µg/mL for PDE4 from human neutrophils, and 0.1-1.2 µg/mL and 0.3–2.9 µg/mL for recombinant PDE4s. Inhibition of PDE4 by roflumilast and roflumilast N-oxide leads to accumulation of intracellular cAMP, thereby amplifying signaling pathways downstream to cAMP which include anti-inflammatory pathways. The specific mechanism(s) by which roflumilast exerts its therapeutic action on seborrheic dermatitis is not well defined.

Safety Pharmacology

Neurological Effects

In mice, oral administration of roflumilast at a single dose of 3-100 mg/kg decreased grip strength by up to 89% and reduced the threshold for pentetrazol-induced seizures by 30-93%. Other signs included reduced activity and vigilance, stalking gait, tremor, segregation, limb splay lying, touch escape with vocalization, decreased palpebral fissure, head twitches, and forepaw shaking. The no effect dose level (NOEL) was 1 mg/kg. In a potentiation test in mice on pentetrazol-induced seizures, roflumilast at the single oral dose of 30 mg/kg increased the number of animals with tonic convulsions and death, and at 10 and 30 mg/kg shortened the time to tonic convulsions and death. In rats, oral administration of roflumilast at a single dose of 3-30 mg/kg prolonged hexobarbital-induced loss of righting reflex (up to 590%) and caused a dose-dependent increase in ethanol-induced sleeping time (up to 368%).

Respiratory Effects

Mongrel cats were anaesthetized and received intravenous infusion of roflumilast at the single doses of 0.1, 0.2, 0.7, 2, and 7 mg/kg. Breathing rate and respiratory minute volume increased dose-dependently, with the increases being 33% and 32%, respectively, at the dose of 7 mg/kg.

Cardiovascular Effects

In vitro, roflumilast did not affect the human ether-a-go-go related gene (hERG) channel current at concentrations up to 24 ng/mL (60 nM).

Roflumilast at the oral dose of 10 mg/kg caused a significant increase in heart rate (62%) and a decrease in blood pressure (12-26 mm Hg) in male normotensive rats. A cumulative IV injection of roflumilast at 0.3-20 µmol/kg in anesthetized male rats increased systolic arterial pressure (16%) and dP/dt max (9%) at the high dose and decreased diastolic pressure (24-29%).

In anaesthetized mongrel cats receiving intravenous infusion of roflumilast, roflumilast at the doses of 0.1, 0.2, 0.7, 2, and 7 mg/kg caused sustained increase in blood pressure (left ventricular pressure and systolic and diastolic arterial pressure, up to 46-63%), heart rate (up to 18%), and cardiac contractility (up to 3-fold). Blood pressure and contractility reacted biphasically with an overshoot in the drug-infusion period at the three higher doses; however, at the two lower doses the changes were much smaller and monophasic. An increase in the ST-segment in the ECG was observed in 3/5 animals at 2 mg/kg and 2/5 animals at 7 mg/kg, which

was correlated with the increase in contractility. No arrhythmias were noted throughout the experiments.

5.4. ADME/PK

Table 2. ADME/PK Studies and Associated Findings

Type of Study	Major Findings
Absorption	
ARQ-151: A 7-day dermal tolerability study in minipigs/ (b) (4) -2621-001	Systemic exposure to roflumilast and roflumilast N-oxide was observed in minipigs following multiple topical administrations of 1% roflumilast cream (20 mg/kg/day) over 10% BSA. On Day 7, T_{max} for both roflumilast and roflumilast N-oxide was 1.3 hrs, C_{max} values were 13.6 and 3.6 ng/mL, respectively, and AUC_{0-24h} values were 195 and 46.1 hr*ng/mL, respectively.
Distribution	
Summary information from nonclinical review for NDA 22522	Following oral administration, roflumilast was widely distributed in the body. Highest drug concentrations were found in the adrenals and liver in mice and hamsters, and in the liver and nose in rats. Other organs with relatively high roflumilast concentrations were (in a descending order) kidney, fat, lung, heart, testes, and brain. In the plasma, roflumilast was predominantly protein-bound, with the free fraction of 3.7%, 2.0%, 2.9%, 2.2%, 1.6%, and 2.1% in mice, rats, hamsters, rabbits, dogs, and monkeys, respectively.
Metabolism	
Summary information from nonclinical review for NDA 22522	Roflumilast was metabolized by CYP3A4, CYP1A2, and CYP2G1 to form at least 17 roflumilast metabolites in animals and humans. The metabolites were formed through N-oxidation, O-dealkylation, or oxidative mono-dechlorination followed by conjugation. The three major metabolites are roflumilast N-oxide, 4-amino-3,5-dichloropyridine (ADCP), and ADCP N-oxide, with roflumilast N-oxide being the most abundant in all studied species.
Excretion	
Summary information from nonclinical review for NDA 22522	Roflumilast was excreted via feces and urine. The proportion of excretion by each route varied depending on species. Following oral administration, fecal excretion was predominant in mice and dogs and the major route in rats and hamsters. Urine excretion was predominant in humans and the major route in monkeys and rabbits. Roflumilast was excreted in rat milk. In lactating rats, 8 hours after an oral dose of 1 mg/kg, roflumilast and/or its metabolite concentrations were 0.32 and 0.02 µg/g in the milk and pup liver, respectively.
TK data from general toxicology studies	

Type of Study	Major Findings
A 6-month oral (gavage) toxicity study in B6C3F1 mice (Study# RCC 798096)	Mouse at the NOAEL of 4 mg/kg/day (LD) in Week 26 T_{max}: 0.5 hr $AUC_{0\text{-}24h}$: 156 (R) and 515 (RN) μg·hr/L C_{max}: 44 (R) and 131 (RN) μg/L Accumulation: No Dose proportionality: Exposure was more than dose proportional.
A 6-month oral toxicity study in Wistar rats (Study# 14/96)	Rat at the NOAEL of 0.5 mg/kg/day (LD) on Day 184 T_{max}: 1.6 hrs $AUC_{0\text{-}8h}$: 9.7 (R) μg·hr/L C_{max}: 2.6 (R) μg/L Accumulation: No Dose proportionality: Exposure was more than dose proportional.
A 2nd 6-month oral toxicity study in Wistar rats (Study# 191/2000)	Rat at the NOAEL of 0.8 mg/kg/day on Days 160-168 T_{max}: 1 hr $AUC_{0\text{-}24h}$: 31 (R) and 755 (RN) μg·hr/L C_{max}: 5 (R) and 98 (RN) μg/L Accumulation: N/A Dose proportionality: N/A
A 12-month oral toxicity study in beagle dogs (Study# 132/2000)	Dog at the NOAEL of 0.6 mg/kg/day (MD) in Week 52 T_{max}: 1.4 hrs $AUC_{0\text{-}24h}$: 510 (R), 66 (RN) μg·hr/L C_{max}: 99 (R) and 11 (RN) μg/L Accumulation: No Dose proportionality: Exposure was dose proportional from 0.2 to 0.6 mg/kg/day and less than dose proportional from 0.6 to 2 mg/kg/day.
Combined 4-week/42-week oral gavage toxicity study in adult cynomolgus monkeys (Study# 232-2001)	Monkey at the NOAEL of 0.1 mg/kg/day (LD) in Week 42 T_{max}: 1 hr $AUC_{0\text{-}24h}$: 80 (R) and 340 (RN) μg·hr/L C_{max}: 16 (R) and 34 (RN) μg/L Accumulation: No Dose proportionality: Exposure was more than dose proportional.
A 13-week dermal toxicity study in CD-1 mice (Study# (b) (4)-2621-006)	Mouse at the NOAEL of 1% cream (20 mg/kg/day, HD) on Day 91 T_{max}: 1 hr $AUC_{0\text{-}24h}$: 194 (R) and 1277 (RN) μg·hr/mL C_{max}: 17 (R) and 78 (RN) μg/mL Accumulation: No Dose proportionality: Exposure was less than dose proportional.
A 39-week dermal toxicity study in Göttingen minipigs (Study# 2621-012)	Minipig at the NOAEL of 1% cream (20 mg/kg/day, HD) on Day 273 T_{max}: 4 hrs $AUC_{0\text{-}24h}$: 329 (R) and 12 (RN) μg·hr/mL C_{max}: 26 (R) and 0.7 (RN) μg/mL Accumulation: Yes, up to ~14-fold when AUC values are compared.

Type of Study	Major Findings
	Dose proportionality: Exposure was less than dose proportional.
TK data from reproductive and developmental toxicology studies	TK analysis was not conducted in reproductive toxicology studies or the 3-month juvenile toxicity study in rats.
TK data from carcinogenicity Studies	
A 2-year oral (gavage) carcinogenicity study in B6C3F1 mice (Study# PR 97/2001)	Mouse at the NOAEL of 12 mg/kg/day in females and 18 mg/kg/day in males in Month 24 $AUC_{0\text{-}24h}$: 12 mg/kg/day (female): 663 (R) and 2145 (RN) μg·hr/L 18 mg/kg/day (male): 961 (R) and 3736 (RN) μg·hr/L Accumulation: No Dose proportionality: Exposure was slightly higher than dose proportional
A 2-year oral (gavage) carcinogenicity study in Syrian hamsters (Study# PR 7/2002)	Hamster at the NOAEL of 4 mg/kg/day in females and 8 mg/kg/day in males in Month 24 $AUC_{0\text{-}24h}$: 4 mg/kg/day (female): below the low limit of detection (R) and 937 (RN) μg·hr/L 8 mg/kg/day (male): 53 (R) and 2721 (RN) μg·hr/L Accumulation: Not noted after Month 3 Dose proportionality: Exposure was less than dose proportional for roflumilast and roughly dose-proportional for roflumilast N-oxide.

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; NOAEL, no observable adverse effect level; R, roflumilast; RN, roflumilast N-oxide; TK, toxicokinetic; T_{max}, time to maximum drug concentration

5.5. Toxicology

5.5.1. General Toxicology

Repeat-dose oral toxicity studies for roflumilast have been reviewed under NDA 22522, which included the studies conducted in mice, rats, hamsters, dogs, and monkeys with treatment durations up to 6, 6, 3, 12, and 10 months, respectively. The target organs of toxicity included cardiovascular system, gastrointestinal tract, nasal cavity, and reproductive system. Significant nonneoplastic nasal lesions (epithelial disorganization, degeneration, necrosis, and nerve fiber atrophy of the olfactory area) were observed in rodents, i.e., mice, rats, and hamsters, but not in dogs or monkeys. Cardiovascular toxicities (focal hemorrhage, myocarditis, or vasculitis) were observed in mice, dogs, and monkeys. Toxicities in the gastrointestinal tract (serositis, inflammation, peritonitis, and stomach erosion) were observed in rats and monkeys. Toxicities in the male reproductive organs were observed in mice, rats, hamsters, and dogs, and the affected organs may include the following: prostate (atrophy), testes (tubular atrophy degeneration and atrophy, spermatogenic disturbances), epididymides (oligospermia and granuloma), and seminal vesicles (atrophy). Toxicities in female reproductive organs (uterine and cervical atrophy) were observed in mice. In rats and monkeys, disruption of female reproductive physiology (decreases in estrus events and estradiol levels) was observed. The

overall NOAEL values in mice, rats, hamsters, dogs, and monkeys were 4, 0.8, 4, 0.6 and 0.25 mg/kg/day, respectively.

A 39-week repeat dose dermal toxicity study was conducted with roflumilast cream in minipigs (Study# 2621-012, previously reviewed under the associated IND). The cream formulation used was very similar to the to-be-marketed foam formulation except that there were higher amounts of (b) (4) isopropyl palmitate (b) (4), and white petrolatum (b) (4) as excipients as well as the absence of (b) (4). The 39-week dermal minipig study conducted with roflumilast cream supports the safety of roflumilast foam. Roflumilast cream at the dose strengths of 0 (vehicle), 0.15%, 0.5%, and 1% (3, 10, and 20 mg/kg/day, applied at 2 mL/kg to 10% BSA) were applied topically to Göttingen minipigs (4/sex/dose) once daily for 9 months. The animals were assessed for mortality, clinical observations, dermal irritation scores, body weight, food consumption, ophthalmology, ECG, clinical pathology (hematology, clinical chemistry, and urinalysis), gross pathology, organ weights, and histopathology. There was no notable toxicity observed in the study. The NOAEL was the highest dose 1% roflumilast cream, or 20 mg/kg/day of roflumilast.

5.5.2. Genetic Toxicology

Roflumilast tested positive in an in vivo mouse micronucleus test, but negative in the following assays: the Ames test, an in vitro chromosome aberration assay in human lymphocytes, an in vitro HPRT gene mutation assay in V79 cells, an in vitro micronucleus test in V79 cells, a DNA adduct formation assay in rat nasal mucosa, liver and testes, and an in vivo mouse bone marrow chromosome aberration assay. Roflumilast N-oxide was negative in the Ames test and an in vitro micronucleus test in V79 cells.

5.5.3. Carcinogenicity

Carcinogenicity studies included two 2-year oral carcinogenicity studies in hamsters, a 2-year oral carcinogenicity study in mice, and a 2-year dermal carcinogenicity study in mice. The oral carcinogenicity studies have been reviewed under NDA 22522. The dermal carcinogenicity study was reviewed under a sister NDA, NDA 215985.

Hamster Two-Year Oral Carcinogenicity Studies

In the 2-year oral carcinogenicity studies in hamsters, roflumilast treatment resulted in dose-dependent increases in the incidence of undifferentiated carcinomas of nasal epithelium at ≥8 mg/kg/day. The tumorigenicity was most likely due to a reactive metabolite of ADCP N-oxide, itself a roflumilast metabolite formed in rodent nasal cavity by cytochrome P450 enzyme CYP2G1. Mice, however, did not show evidence of tumorigenicity at maximum tolerated doses, i.e., 12 mg/kg/day in females and 18 mg/kg/day in males.

Mouse Two-Year Dermal Carcinogenicity Study

In the 2-year dermal carcinogenicity study in mice, roflumilast topical cream at dose strengths of 0 (untreated control), 0 (vehicle control), 0.15%, 0.5%, and 1.0% were applied to CD-1 mice

(2 mL/kg to 10% BSA) once daily for two years. The roflumilast doses were equivalent to 3, 10, and 20 mg/kg/day, respectively. There were no roflumilast-related dermal observations at the administration sites, nor there were any roflumilast-related neoplastic findings in this study. TK data were not provided in this carcinogenicity study. However, the same topical doses were tested previously in a 13-week mouse dermal toxicity study, whose TK data can be used for safety margin calculation. This 2-year dermal mouse carcinogenicity study has been reviewed by the Executive Carcinogenicity Assessment Committee (ECAC). The Committee concluded that this study was adequate and there was no evidence of drug-related neoplasms in this study.

5.5.4. Reproductive and Developmental Toxicology

Oral reproductive and developmental toxicity studies have been reviewed under NDA 022522.

Rat Fertility Study

In a rat fertility study, roflumilast decreased fertility rates at 1.8 mg/kg/day, which were accompanied by morphological changes in the male reproductive organs such as testicular tubular atrophy and spermatogenic granuloma in the epididymides. The NOAEL was 0.6 mg/kg/day for male fertility. In a female rat fertility study, there were no effects on fertility observed at doses up to the highest dose of 1.5 mg/kg/day.

Rat EFD Study

In an embryofetal development study, pregnant rats were given roflumilast orally during the period of organogenesis at doses up to 1.8 mg/kg/day. Fetal malformations or effects on the number of living fetuses were not observed; however, increases in the incidence of incomplete ossification of skull bones were observed at the doses of 0.6 and 1.8 mg/kg/day. The NOAEL was 0.2 mg/kg/day for embryofetal development.

Rat Fertility and EFD Study

In a rat fertility and embryofetal development study, male rats were dosed orally with up to 1.8 mg/kg/day roflumilast for 10 weeks and females for 2 weeks prior to pairing and throughout the organogenesis period. Roflumilast did not cause fetal malformations at maternal oral doses up to 1.8 mg/kg/day but induced pre- and post-implantation loss at ≥0.6 mg/kg/day.

Rabbit EFD Study

In an embryofetal development study in rabbits, pregnant rabbits were dosed orally with roflumilast at doses up to 0.8 mg/kg/day during the period of organogenesis. Roflumilast did not cause fetal malformations at any dose and the NOAEL for embryofetal development was the highest dose 0.8 mg/kg/day.

Mouse PPND Study

In a pre- and post-natal developmental (PPND) study in mice, dams were dosed orally with roflumilast at doses up to 12 mg/kg/day during the period of organogenesis and lactation. Roflumilast prolonged pregnancy duration and caused stillbirth at ≥2 mg/kg/day (LD).

In a second PPND study in mice, dams were dosed orally with roflumilast at doses up to 6 mg/kg/day during the period of organogenesis and lactation. Roflumilast decreased the overall pup viability at 6 mg/kg/day. Roflumilast decreased pup (postweaning) rearing frequencies at the maternal dose of 6 mg/kg/day.

Juvenile Rat Oral Toxicity Study

In a juvenile rat oral toxicity study, animals (Wistar rats, 3 weeks old) were given roflumilast at doses of 0 (vehicle: 4% Methocel), 0.2, 0.5, and 0.8 mg/kg/day once daily for three months, with an 8-week recovery period. Target organs of toxicity included liver (centrilobular hypertrophy), epididymis (lympho-histiocytic infiltration), heart (myocardial degeneration), lung (lympho-histiocytic infiltration, interstitial pneumonia), and spleen (hemosiderosis). The NOAEL was 0.2 mg/kg/day in males and 0.5 mg/kg/day in females, comparable to that identified in a previous 3-month adult rat oral toxicity study (0.2 mg/kg/day). There was no increased sensitivity with respect to male reproductive organ toxicity when compared to the previous study. The target organs in the 3-month adult study, i.e., nasal cavities, testes, epididymis, and thymus, were not identified in juvenile animals with the exception of epididymis.

5.5.5. Other Toxicology Studies

Ocular Irritation

A bovine corneal opacity and permeability test was conducted with 1% roflumilast cream (Study# (b) (4) 17-25378-09, reviewed under associated IND). Roflumilast cream was not an irritant ed on an in vitro irritancy score (IVIS) of -1.97.

Dermal Sensitization

A Buehler assay to assess the dermal sensitization potential of roflumilast was conducted in Hartley Albino guinea pigs (Study# (b) (4) 17-25378-06, reviewed under associated IND). Animals were treated with 1% roflumilast cream topically once a week for three weeks in the induction Phase, and then challenged with 0.5% roflumilast cream two weeks after the third induction dose. There were no significant dermal effects observed and therefore, roflumilast cream was not a dermal sensitizer in this study.

Phototoxicity

The phototoxic potential of roflumilast was assessed in a neutral red uptake phototoxicity assay (Study# (b) (4) -20122622, reviewed under associated IND). BALB/c 3T3 mouse fibroblasts were exposed to the test article, subjected to ultraviolet radiation, and observed for cell viability,

which was compared with the viability of fibroblasts exposed to the test article in the absence of ultraviolet radiation. The tested roflumilast concentrations were 0.1, 0.316, 1.00, 3.16, 10.0, 31.6, 100, and 178 µg/mL. Cells were exposed to 5 J/cm2 UVA and 21 mJ/cm2 UVB from a xenon arc solar simulator. Roflumilast did not show phototoxic potential in this assay.

Impurity Qualification

All drug substance and drug product impurities are controlled below the respective qualification thresholds, or otherwise have been qualified in the sister NDA, NDA 215985.

Excipient Qualification

Roflumilast foam, 0.3%, does not contain novel excipients. All excipients are present at the same or lower levels when compared to levels in previously approved topical drug products.

Extractables Qualification

The Applicant conducted extractables studies on the container closure system (CCS) and indicated not to conduct leachables studies. Roflumilast foam is indicated as needed for flare-ups of seborrheic dermatitis and not intended for daily use over a lifetime. The cumulative duration of treatment in most seborrheic dermatitis patients is likely to be >1- 10 years, but in some it can be >10 years to lifetime. A conservative safety concern threshold (SCT) of (b) (4) may be applied for toxicological assessment of extractable compounds. However, the drug is for topical use and therefore an SCT of (b) (4) is acceptable, assuming a dermal absorption rate of 10% for the extractable compounds. The following equation can be used to calculate the maximum daily exposure (MDE) of each extractable based on the maximum daily dose (MDD) of (b) (4) g roflumilast foam:

Equation 1. Maximum Daily Exposure of Extractables

(b) (4)

Source: Applicant MDE equation from extractables studies.
Note: X is the quantitative or semi-quantitative result for an individual extractable compound in the unit of µg/component.

The Applicant used the MDD of (b) (4) roflumilast foam, which is only slightly different from the MDD of (b) (4). For convenience of this review, the MDEs calculated by the Applicant are considered for toxicological assessment.

The extractables studies for the can (b) (4) system of the CCS reported 174 compounds, among which 99 had confirmed identities while the other 75 were labelled as "unknown". The Applicant grouped the 99 identified compounds into 15 groups.

- Group 8 are (b) (4), with a combined MDE of (b) (4) There is no safety concern for the two (b) (4) at this MDE level.

- Group 10 are [redacted] with a combined MDE of [redacted] were not genotoxic, had no skin sensitization potential, and had the NOAEL of [redacted] in a 90-day rat oral toxicity study, based on the ECHA registration dossier for the representative [redacted]. Therefore, there is no safety concern for the [redacted] at their combined MDE level.
- Group 11 are [redacted] with a combined MDE of [redacted] The amount of extracted [redacted] is negligible compared to the amount of [redacted] in the drug product.
- Group 12 are [redacted], with a combined MDE of [redacted]. MDE of [redacted] is less than [redacted] and therefore requires no safety assessment. [redacted] was not genotoxic, did not cause skin sensitization, and had a NOAEL of [redacted] in a 90-day rat oral toxicity study, based on the ECHA registration dossier. Therefore, there is no safety concern for [redacted] at its MDE level.
- Group 13 are [redacted], with a combined MDE of [redacted]. [redacted]) was not genotoxic, did not cause skin sensitization, and had a NOAEL of [redacted] in a 28-day rat oral toxicity study, based on the ECHA registration dossier. Therefore, there is no safety concern for Group 13 compounds at their combined MDE level.
- All other compounds had MDE less than [redacted] and therefore require no safety assessment. [redacted] were not detected.

For the 75 extractable compounds labelled as "unknown", 10 had MDEs exceeding the SCT of [redacted] µg/day. Among the 10, two were extracted by [redacted] with the [redacted] being the highest, two were extracted by [redacted] with the MDE of [redacted] being the highest, and six were extracted by [redacted] with the MDE of [redacted] being the highest and [redacted] being the second highest. Considering that the extractables studies used very harsh conditions, the ultimate amount of such "unknown" compounds present in the final drug product is expected to be significantly lower if there is any. During the real-world process of applying roflumilast foam to the skin, a waste of foam is typically expected. Further, the cumulative duration of use of roflumilast foam in most seborrheic dermatitis patients is likely to be less than 10 years. Combined together, such low amounts of "unknown" extractable compounds pose low safety concerns from a nonclinical perspective.

Overall, the extractable compounds pose low or no safety concerns from a nonclinical perspective. We agree with the Applicant that a leachables study is not needed.

6. Clinical Pharmacology

6.1. Executive Summary

The Applicant submitted the present NDA for a proposed topical foam drug product containing 0.3% w/w (3 mg/g) roflumilast for the treatment of seborrheic dermatitis in patients 9 years of age and older. Roflumilast and its active metabolite, roflumilast *N*-oxide, are selective inhibitors of phosphodiesterase 4 (PDE4), a major metabolizing enzyme of cyclic 3',5'-adenosine monophosphate (cyclic AMP). Inhibition of PDE4 leads to the accumulation of intracellular cyclic AMP. Two other roflumilast-containing drug products have been approved in the United States and are summarized below. Note that the Applicant of Zoryve topical cream is the same as the Applicant seeking approval for the proposed roflumilast topical foam. This Applicant has obtained a right of reference from NDA 022522 DALIRESP Oral Tablets and, hence, this application will follow a 505(b)(1) regulatory pathway.

Table 3. Summary of Approved and Proposed Roflumilast-Containing Drug Products

Drug Product	Year of Approval	Indication	Dosage Form	Dosage Regimen
Daliresp (approved) NDA 022522	2011	To reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations	Oral tablets	500 mcg once daily
Zoryve (approved) NDA 215985	2022	For topical treatment of plaque psoriasis, including intertriginous areas, in patients 12 years of age and older	Topical cream, 0.3% (3 mg/g)	Apply once daily to affected areas
Zoryve (proposed) NDA 217242	Proposed	For topical treatment of seborrheic dermatitis in patients 9 years of age and older	Topical foam, 0.3% (3 mg/g)	Apply once daily to affected areas

Source: Approved labeling for DALIRESP [roflumilast] tablets and ZORYVE [roflumilast] cream; proposed labeling for 0.3% roflumilast foam

The clinical pharmacology program includes a maximal use study conducted in adult and pediatric subjects with moderate to severe seborrheic dermatitis (ARQ-154-116). PK and safety were evaluated following once daily (QD) application of the proposed roflumilast foam to affected areas for two weeks. This study enrolled 12 adults aged ≥ 18 years, and 10 pediatric subjects aged ≤ 16 years (pediatric age range: 11 to 16 years). The mean (SD) treated % body surface area was 5.5% (1.3%) (range: 5.0 to 9.0%) in pediatric subjects, and 6.5% (1.1%) (range: 5.0 to 9.0%) in adults.

Results from the maximal use study indicated that steady-state C_{max} for roflumilast and roflumilast *N*-oxide following oral administration are 3.3- and 2.0-fold higher, respectively, compared to topical administration of 0.3% roflumilast foam under maximal use conditions in subjects with seborrheic dermatitis. Similarly, the steady-state AUC_{0-24} for roflumilast and

roflumilast *N*-oxide following oral administration was 1.1- and 1.9-fold higher, respectively, compared to topical administration under maximal use conditions.

In addition, roflumilast and roflumilast *N*-oxide exposure following topical application was lower in pediatric subjects relative to adult subjects. Although the treated % BSA was comparable between pediatric and adult subjects, the theoretical predicted dose administered is lower for pediatric subjects due to the overall lower total BSA. The smaller body surface area, and thus lower administered dose, likely contributed to the lower observed concentrations in pediatric subjects relative to adults.

The PK of roflumilast and roflumilast *N*-oxide was also assessed in other studies. These include a Phase 2a efficacy study in adults with seborrheic dermatitis (ARQ-154-203) with long-term extension including pediatric subjects (ARQ-154-214), and a Phase 3 efficacy study in adult and pediatric subjects (down to 9 years of age) with seborrheic dermatitis (ARQ-154-304).

In Study ARQ-154-304, plasma exposure to roflumilast and roflumilast *N*-oxide was detectable at Weeks 4 and 8. The relationship of roflumilast and roflumilast *N*-oxide concentrations in pediatric subjects relative to adults was similar in Study ARQ-154-304 and in the maximal use study, ARQ-154-116. Overall, steady-state exposures were lower in Study ARQ-154-304 relative to Study ARQ-154-116, which is likely due to lower mean treated BSA and lower foam application rate. The data overall suggest that the amount of 0.3% roflumilast foam administered during actual clinical use is likely to be lower than that administered under maximal use conditions.

The Applicant intends to reference relevant nonclinical, clinical, and CMC data from oral roflumilast (Daliresp, NDA 022522). The Applicant provided a letter of authorization from AstraZeneca (the Applicant of NDA 022522) allowing them the right to reference such information. The Applicant did not conduct any studies to evaluate metabolism, drug-drug interactions, or the impact of renal or hepatic impairment on PK. The Applicant plans to rely on safety findings from Daliresp to inform the labeling of their product.

Recommendation

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology has reviewed the available data and found NDA 217242 acceptable for approval.

Postmarketing Requirements and Commitments

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacokinetics Under Maximal Use Conditions

The Applicant conducted a maximal use study to characterize the PK of roflumilast and roflumilast *N*-oxide following daily administration of 0.3% roflumilast foam for 2 weeks in adult

and pediatric subjects with seborrheic dermatitis. Subjects were required to have seborrheic dermatitis involving at least 5% BSA with maximum involvement of 20% BSA. The median (range) % body surface area involvement was 5.0 (5.0 to 9.0)% in pediatric subjects, and 6.0 (5.0 to 9.0)% in adults. All subjects had some scalp involvement, including 4 subjects with 100% scalp involvement. The youngest subjects in Study ARQ-154-116 were 11 years of age. Study ARQ-154-116 was conducted using the to-be-marketed formulation.

PK data in adults based on richer sampling indicates that roflumilast and roflumilast *N*-oxide concentrations remain relatively flat with little change over 24 hours. The peak-to-trough ratios for roflumilast and roflumilast *N*-oxide were 1.68 and 1.62, respectively. At steady state, mean (SD) T_{max} for roflumilast and roflumilast *N*-oxide was 5.0 (7.3) h and 8.4 (11) h, respectively. Based on predose data collected at Weeks 3, 4, and 5, the mean (SD) half-life for roflumilast and roflumilast *N*-oxide was 3.6 (2.2) days and 4.4 (1.7) days, respectively.

The mean (SD) Day 15 predose concentrations of roflumilast and roflumilast *N*-oxide in pediatric subjects were 0.943 (1.23) ng/mL and 10.5 (16.8) ng/mL, respectively. The mean (SD) Day 15 predose concentrations of roflumilast and roflumilast *N*-oxide in adult subjects were 1.95 (1.66) ng/mL and 12.7 (9.32) ng/mL, respectively. The data indicates that predose concentrations were in the range of lower to comparable in pediatric subjects relative to adult subjects. This conclusion is corroborated by the extrapolated AUC_{0-24} determined based on the predose concentrations. Although the treated BSA was comparable between pediatric and adult subjects, the theoretical predicted dose administered is lower for pediatric subjects due to the overall lower total % BSA the drug was applied to. The smaller body surface area, and thus lower administered dose, likely contributed to the lower observed roflumilast concentrations in pediatric subjects relative to adults.

Steady-state exposures to roflumilast and roflumilast *N*-oxide were compared following daily administration of 0.3% roflumilast foam under maximal use conditions in subjects with seborrheic dermatitis and following daily administration of 500 mcg oral roflumilast in healthy subjects. The PK data of oral roflumilast in healthy subjects was derived from the original review for NDA 022522. Results indicate that the steady-state C_{max} for roflumilast and roflumilast *N*-oxide are 3.3- and 2.0-fold higher, respectively, following daily oral administration of 500 mcg roflumilast in healthy subjects relative to daily topical administration of 0.3% roflumilast foam under maximal use conditions in subjects with seborrheic dermatitis. Steady-state AUC_{0-24} for roflumilast and roflumilast *N*-oxide is 1.1- and 1.9-fold higher, respectively, in healthy subjects taking 500 mcg oral roflumilast compared to the values obtained following topical administration under maximal use conditions.

Pharmacokinetics in Phase 3

The Phase 3 study intended to characterize the PK, efficacy, and safety of roflumilast following daily administration of 0.3% roflumilast foam for 8 weeks in adult and pediatric subjects with seborrheic dermatitis. Subjects were required to have seborrheic dermatitis with maximum involvement of 20% BSA. The median (range) % body surface area involvement across all subjects was 2.2 (0.2 to 20.0)%. In this study, about 93% of subjects had some scalp

involvement. The youngest subjects in Study ARQ-154-304 were 9 years of age. Study ARQ-154-304 was conducted using the to-be-marketed formulation.

The mean Week 4 predose concentrations of roflumilast and roflumilast *N*-oxide in pediatric subjects were 0.717 (0.741) ng/mL and 7.19 (7.67) ng/mL, respectively. In adults, mean (SD) predose concentrations were 1.12 (1.06) ng/mL and 6.95 (6.58) ng/mL, respectively. Predose concentrations at Week 8 in pediatric subjects were overall lower than at Week 4, with values for roflumilast and roflumilast *N*-oxide of 0.440 (0.453) ng/mL and 3.51 (4.20) ng/mL, respectively. This may be partly due to variability attributed to low sample size and also the possibility of the change in the degree of drug absorption due to the resolution of the disease. In adults, Week 8 mean (SD) predose concentrations of roflumilast and roflumilast *N*-oxide were 0.986 (1.04) ng/mL and 5.59 (5.72) ng/mL, respectively. The mean Week 4 predose concentrations of roflumilast and roflumilast *N*-oxide were in the range of lower to comparable, respectively, in pediatric subjects relative to adult subjects, while at Week 8, concentrations in pediatric subjects for roflumilast and roflumilast *N*-oxide were both lower than in adults.

The relationship of roflumilast and roflumilast *N*-oxide concentrations in pediatric subjects relative to adults was similar in Study ARQ-154-304 and in the maximal use study, ARQ-154-116. Steady-state predose concentrations were lower in Study ARQ-154-304 compared to PK results from Study ARQ-154-116. This is likely due to the lower treated % BSA, lower foam application rate, and therefore, lower applied daily dose in Study ARQ-154-304. In Study ARQ-154-304, the mean (SD) treated % BSA in pediatric and adult subjects was 3.88 (1.86)% and 2.80 (2.05)%, respectively. In ARQ-154-116, the mean (SD) treated % BSA in pediatric and adult subjects was 5.50 (1.27)% and 6.50 (1.08)%, respectively. The mean (SD) daily dose of roflumilast applied in ARQ-154-304 was 8.37 (5.97) mg as compared with 12.4 (6.21) mg in ARQ-154-116. This suggests that the amount of the 0.3% roflumilast foam administered to subjects in the maximal use study is greater than what might be observed during actual clinical use. Thus, the maximal use study is acceptable and supportive as it was indeed conducted under maximal use conditions.

Metabolism

The metabolism of roflumilast was not evaluated in the present NDA. The Applicant is relying on information generated during the development of oral roflumilast (Daliresp, NDA 022522), for which the Applicant has right of reference.

Roflumilast is extensively metabolized via Phase I (cytochrome P450) and Phase II (conjugation) reactions. The *N*-oxide metabolite is the only active major metabolite observed in the plasma of humans. *In vitro* studies suggest that the biotransformation of roflumilast to its *N*-oxide metabolite is mediated by CYP1A2 and 3A4. Together, roflumilast and roflumilast *N*-oxide account for 87.5% of the total dose administered in plasma. In urine, roflumilast was not detectable while roflumilast *N*-oxide was only a trace metabolite (< 1%). Other conjugated metabolites such as roflumilast *N*-oxide glucuronide and 4-amino-3,5-dichloropyridine *N*-oxide were detected in urine.

In the maximal use study, ARQ-154-116, the roflumilast *N*-oxide metabolite appears to circulate at concentrations approximately 6.5-fold and 11-fold greater than the parent in adult and pediatric subjects, respectively. In the Phase 3 study, ARQ-154-304, the ratio of *N*-oxide metabolite to parent drug ranged from 5.7 to 6.2 in adults and from 8.0 to 10.0 in pediatric subjects. The labeling for Daliresp indicates that plasma AUC of roflumilast *N*-oxide is on average about 10-fold greater than that of roflumilast. The greater observed metabolism after oral dosing relative to topical application in adults may be due to the effects of first-pass metabolism after oral dosing. Meanwhile, the metabolite-to-parent ratio in pediatric subjects was greater than that in adults, which may suggest that there might be greater metabolism among the younger age group; however, concrete conclusions cannot be made due to low sample size.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant's proposed dosing regimen for 0.3% roflumilast foam is to apply once daily to affected areas. Currently, oral roflumilast (Daliresp) is only approved in adults, while the 0.3% roflumilast cream (Zoryve) is approved in pediatric patients and adults aged 12 years and older. Thus, roflumilast is not currently approved for use in patients younger than 12 years of age.

Two subjects younger than 11 years were enrolled in the Phase 3 study, ARQ-154-304. Exposure to roflumilast and roflumilast *N*-oxide in these subjects were either within the range of exposures observed among pediatric subjects across all clinical studies, or within the range of concentrations observed in adults in Study ARQ-154-304 and in pediatric and adult subjects in Study ARQ-154-116. However, conclusions are limited due to the small sample size of enrolled subjects aged younger than 12 years of age. See Section 8 of this Unireview for further information on efficacy and safety. We defer to the clinical review to determine whether the efficacy and safety of 0.3% roflumilast foam is adequate in the proposed patient population.

Therapeutic Individualization

The Applicant did not conduct any studies to assess whether therapeutic individualization is warranted for patients based on intrinsic or extrinsic factors, such as concomitant medications, renal impairment, and hepatic impairment. The Applicant plans to rely on findings from Daliresp to inform the labeling and provided a Letter of Authorization permitting right of reference.

No dosage adjustments are warranted for patients based on age, sex, race, ethnicity, renal impairment, or mild hepatic impairment (Child-Pugh A). Use is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C), which is consistent with the approved labeling for Daliresp (oral roflumilast) and Zoryve (0.3% roflumilast cream).

Roflumilast is metabolized by CYP3A4 and CYP1A2. Therefore, the coadministration of roflumilast with systemic CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and

CYP1A2 simultaneously may increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit.

The Applicant proposes to remove language regarding a possible DDI with oral contraceptives. This language is present in the current labeling for Daliresp (oral roflumilast) and in the labeling for Zoryve (0.3% roflumilast cream). Under clinical use conditions of 0.3% roflumilast foam, any increase in roflumilast systemic exposure expected in the presence of hormonal oral contraceptives is highly unlikely to exceed that which has been observed when co-administered with 500 mcg oral roflumilast. Thus, from a clinical pharmacology perspective, the proposed removal of language describing a potential DDI with hormonal oral contraceptives is acceptable.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Maximal Use PK Study ARQ-154-116

The proposed 0.3% roflumilast topical foam is being developed for the treatment of seborrheic dermatitis. The proposed dosage regimen is QD application to affected areas. To assess the PK, safety, and tolerability of the proposed product, the Applicant conducted a maximal use study in pediatric and adult subjects with moderate to severe seborrheic dermatitis involving at least 5% BSA.

The study was designed as an open-label, single-arm study in which all subjects applied the 0.3% roflumilast foam QD for two weeks. The protocol specified enrollment of pediatric subjects aged 9 to ≤16 years, and adults aged ≥18 years. All subjects were required to have a clinical diagnosis of seborrheic dermatitis of at least three months duration with stable disease for the past four weeks. Subjects were also required to have seborrheic dermatitis involving at least 5% BSA with maximum involvement of 20% BSA. Subjects with severe renal impairment (creatinine clearance < 30 mL/min), or moderate to severe hepatic impairment (Child-Pugh B or C) were excluded. Subjects were also excluded if they were not able to discontinue use of strong systemic cytochrome P450 inhibitors or inducers.

Disposition and Demographics

The study enrolled 22 subjects, including 10 pediatric subjects and 12 adults. A total of 20 subjects completed the study, with 2 adult subjects discontinuing prematurely due to subject withdrawal. All 20 subjects were included in the PK population, which included all subjects who were enrolled, treated with the roflumilast foam for at least 2 weeks, and had at least one PK sample analyzed.

The median (range) age of enrolled pediatric subjects was 14.0 (11 to 16) years. For the 12 adult subjects, median (range) age was 37.5 (22 to 81) years. Subjects were predominantly male (n=12, 54.5%), White (n=20, 90.9%), and of Hispanic or Latino ethnicity (n=13, 59.1%). Proportions were similar among pediatric and adult subjects. The median (range) % body surface area involvement was 5.0 (5.0 to 9.0)% in pediatric subjects, and 6.0 (5.0 to 9.0)% in adults. All subjects had baseline scalp involvement, and 72.7% (16/20) of subjects also had involvement of non-scalp locations, including face (n=13), ears (n=10), eyelids (n=5), and neck (n=4).

Dosing

Roflumilast foam was applied to all affected areas, including the scalp if lesions on the scalp were identified. All subjects in the maximal use study had some scalp involvement, and this includes 4 subjects with 100% scalp involvement.

The average daily weight of 0.3% roflumilast foam applied was determined by calculating the difference in weight between the returned product and dispensed product, and dividing by the total number of applications. Across all subjects, the overall mean (SD) weight of roflumilast foam applied per day was 4.13 (2.07) g, equivalent to a daily roflumilast dose of 12.4 (6.21) mg (Calculated as 4.13*3 as the product contains 3 mg of roflumilast per gram). Across age groups, the mean (SD) daily application was 3.33 (1.37) g in pediatric subjects and 4.81 (2.36) g in adult subjects, equivalent to a daily roflumilast dose of 10.0 (4.11) mg and 14.4 (7.08) mg, respectively.

Pharmacokinetic Sampling and Analysis

The primary objective of the study was to evaluate the systemic exposure and characterize the plasma PK profile of roflumilast foam 0.3%. Both roflumilast and its active metabolite roflumilast *N*-oxide were assessed. Plasma PK samples were collected from all subjects at predose on Day 15. In adult subjects only, additional PK samples were collected post-dose on Day 15 at hours 1, 2, 4, 8, and 24. Additional predose samples were collected in adults at Weeks 3, 4, and 5.

PK data analysis was conducted using Phoenix WinNonlin software. Data in adult subjects indicated that plasma concentration-time profiles were flat over 24 hours. Thus, values of $AUC_{0\text{-}24}$ were extrapolated by multiplying the predose concentration value by 24. Predose concentrations found to be below the limit of quantitation (0.10 ng/mL) were ignored for the extrapolation.

The 0.3% roflumilast foam was administered at an application rate of approximately 3 mg/cm^2. Calculations of a theoretical target dose was determined based on a theoretical total BSA of 17,100 cm^2 for adults, and 15,800 cm^2 for pediatric patients 9 to 16 years of age. The estimated amount of foam was determined by multiplying the treated BSA (calculated as total BSA multiplied by the percent total BSA treated) by the application rate of 3 mg/cm^2. The theoretical amount of roflumilast delivered is calculated as the amount of foam multiplied by 0.003 (0.3% = 0.003 mg roflumilast per mg of foam).

Pharmacokinetic Results

PK data on Day 15 in adults only following daily administration of 0.3% roflumilast foam is shown in Table 4 and Figure 1. PK parameters could be calculated in adults due to richer sample collection. The data indicate that roflumilast and roflumilast *N*-oxide concentrations remained relatively flat with little change over 24 hours. The steady-state, peak-to-trough ratios for roflumilast and roflumilast *N*-oxide were calculated as the ratio of C_{max} to C_{min} over the dosing interval on Day 15. The mean peak-to-trough ratios for roflumilast and roflumilast *N*-oxide were 1.68 and 1.62, respectively (data derived from the Applicant's response to labeling comments dated October 30, 2023). The data indicate that there is a less than 2-fold change in roflumilast and roflumilast *N*-oxide concentrations over the dosing interval at steady state.

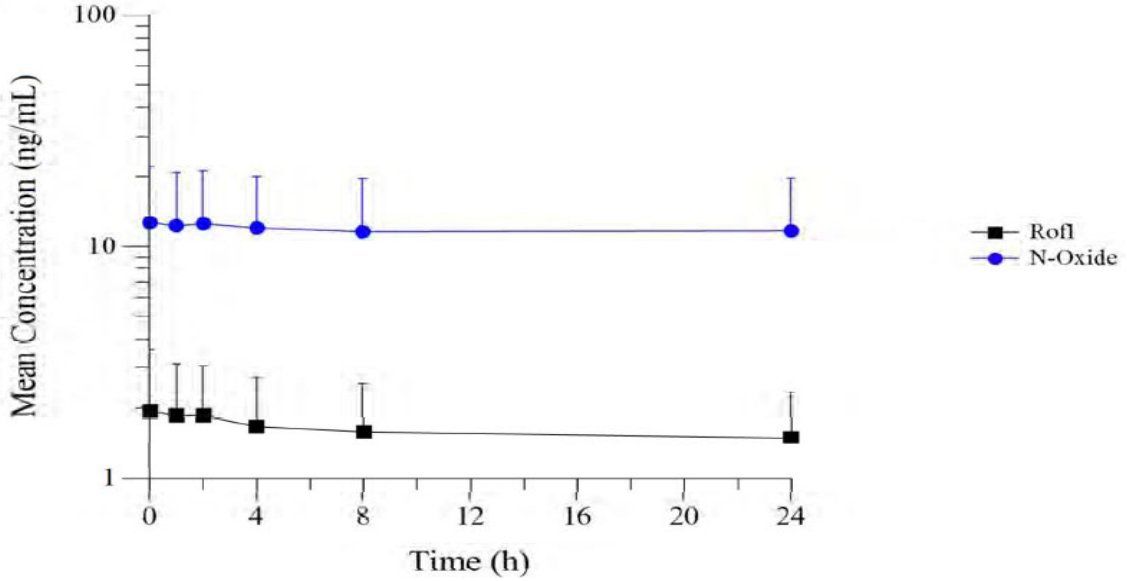
Drug concentrations were at steady state by Day 15. At steady state, mean (SD) T_{max} for roflumilast and roflumilast *N*-oxide was 5.0 (7.3) h and 8.4 (11) h, respectively. Based on predose data collected at Weeks 3, 4, and 5 (Figure 2), the mean (SD) half-life for roflumilast and roflumilast *N*-oxide was 3.6 (2.2) days and 4.4 (1.7) days, respectively. These half-life values are consistent with those reported in the approved labeling for Zoryve (roflumilast topical cream, 0.3%) of 4.0 and 4.6 days for roflumilast and roflumilast *N*-oxide, respectively.

Table 4. Mean ± SD Roflumilast and Roflumilast N-Oxide PK Parameters in Adults Following Daily Administration of 0.3% Roflumilast Foam in Study ARQ-154-116

Analyte	N	Treated BSA (%)	Predicted Dose (mg)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (days)
Roflumilast	10	6.50±1.08	10.0±1.66	5.0±7.3	2.21±1.62	36.6±23.7	3.6±2.2
N-Oxide				8.4±11	13.8±8.96	261±190	4.4±1.7

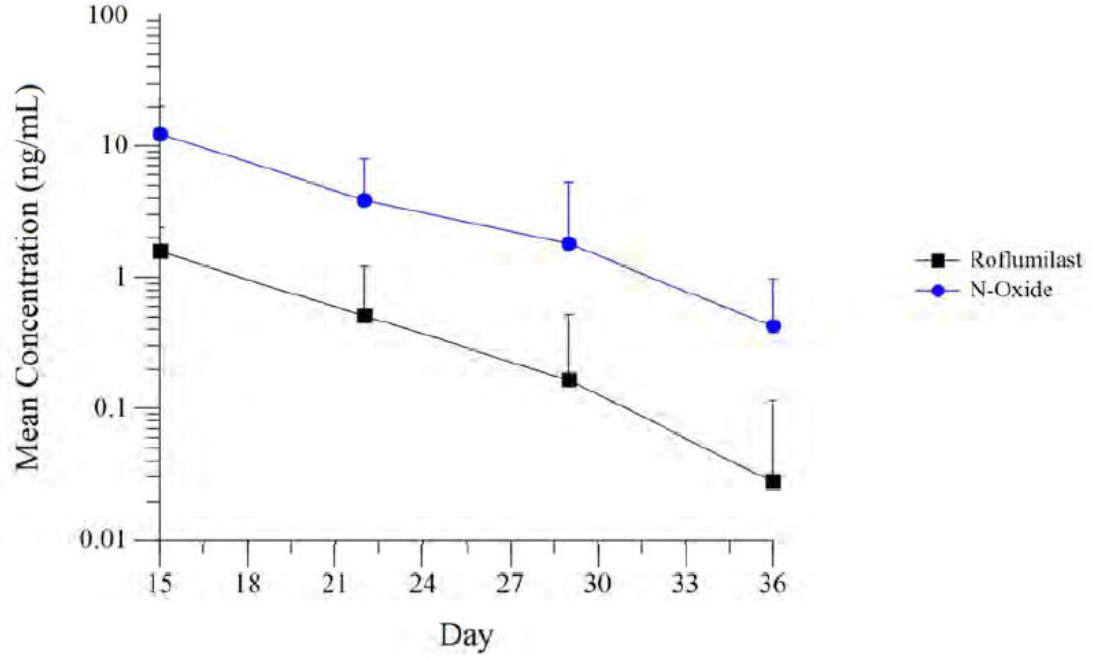
Source: Table B, Clinical Study Report for ARQ-154-116, Appendix 16.1.13.2.
Abbreviations: AUC_{0-24}, area under the plasma concentration-time curve from time zero to 24 hours; BSA, body surface area; C_{max}, maximum concentration; $t_{1/2}$, half-life; T_{max}, time to maximum concentration; SD, standard deviation

Figure 1. Plasma Concentration-Time Profiles Over 24 Hours for Roflumilast and Roflumilast N-Oxide on Day 15 in Adults in Study ARQ-154-116



Source: Figure 2, Clinical Study Report for ARQ-154-116, Appendix 16.1.13.2.
Note: The error bars represent standard deviation.

Figure 2. Plasma Concentration-Time Profiles for Roflumilast and Roflumilast N-Oxide After Administration of the Last Dose on Day 15 in Adults in Study ARQ-154-116



Source: Figure 3, Clinical Study Report for ARQ-154-116, Appendix 16.1.13.2.
Note: The error bars represent standard deviation.

A comparison of PK results in pediatric and adult subjects on Day 15 following daily administration of 0.3% roflumilast foam is shown in Table 5 and Figure 3. Predose roflumilast concentrations were quantifiable in all but two subjects (one pediatric subject and one adult subject). Predose roflumilast *N*-oxide concentrations were quantifiable in all subjects. The mean

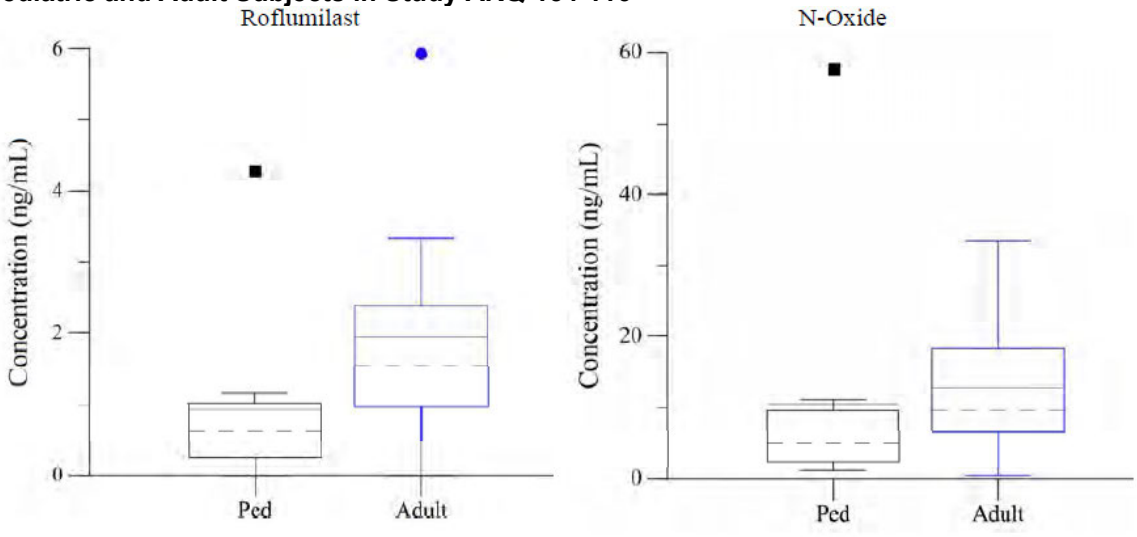
Day 15 predose concentrations of roflumilast and roflumilast *N*-oxide were lower and comparable, respectively, in pediatric subjects relative to adult subjects. Although the data suggest that mean concentrations of roflumilast *N*-oxide are comparable between pediatric and adult subjects, boxplots comparing pediatric and adult concentrations indicate that the overall distribution is lower in pediatric subjects. The extrapolated AUC_{0-24} determined based on the predose concentrations also indicate that exposure to roflumilast and roflumilast *N*-oxide is lower in pediatric subjects relative to adults. Note that the mean (SD) AUC_{0-24} in adults for roflumilast and roflumilast *N*-oxide extrapolated using predose concentrations (51.9 (38.4) ng*h/mL and 305 (224) ng*h/mL, respectively) appears to overestimate values calculated based on observed data collected over the 24-hour period (36.6 (23.7) ng*h/mL and 261 (190) ng*h/mL, respectively). Nevertheless, when accounting for variability, the values are approximately comparable.

Table 5. Summary of Roflumilast and Roflumilast N-Oxide PK on Day 15 in Pediatric and Adult Subjects in Study ARQ-154-116

		Mean (SD)				
Analyte Age group	N	Treated BSA (%)	Predicted Dose (mg)	Concentration (ng/mL)	Dose-normalized Concentration (ng/mg)	Extrapolated AUC_{0-24}[a] (h·ng/mL)
Roflumilast						
Pediatric	10	5.50 (1.27)	7.82 (1.80)	0.943 (1.23)	0.123 (0.173)	25.1 (30.2)[b]
Adult	10	6.50 (1.08)	10.0 (1.66)	1.95 (1.66)	0.191 (0.148)	51.9 (38.4)[b]
Roflumilast N-oxide						
Pediatric	10	5.50 (1.27)	7.82 (1.80)	10.5 (16.8)	1.41 (2.38)	253 (404)
Adult	10	6.50 (1.08)	10.0 (1.66)	12.7 (9.32)	1.27 (0.881)	305 (224)

Source: Table 3, Summary of Clinical Pharmacology, Module 2.7.2.
[a.] Because of the flat nature of the plasma concentration-time profile, AUC_{0-24} was extrapolated by multiplying the predose concentration value by 24.
[b.] n = 9
Abbreviations: AUC_{0-24}, area under the plasma concentration-time curve from time zero to 24 hours; BSA, body surface area; SD, standard deviation

Figure 3. Boxplots of Day 15 Predose Concentrations of Roflumilast and Roflumilast N-Oxide in Pediatric and Adult Subjects in Study ARQ-154-116



Source: Figure 1, Clinical Study Report for ARQ-154-116, Appendix 16.1.13.2.
Note: The dashed lines indicate the median, while the solid lines indicate the arithmetic mean.

Overall, roflumilast and roflumilast *N*-oxide exposure was lower in pediatric subjects relative to adult subjects. Although the treated % BSA was comparable between pediatric and adult subjects, the theoretical predicted dose administered is lower for pediatric subjects due to the overall lower total BSA. The smaller body surface area, and thus lower administered dose, likely contributed to the lower observed concentrations in pediatric subjects relative to adults.

Summary of Safety

Throughout the study, there were no SAEs, deaths, or TEAEs leading to discontinuation.

One pediatric subject (10%) reported a TEAE of eczema on Day 5 that was resolved by Day 7. This TEAE was judged to be of mild severity and related to treatment.

Four adult subjects (33%) reported at least one TEAE of either mild (n = 2) or moderate (n = 2) severity. One adult subject experienced a mild TEAE of headache beginning on Day 5 and resolved on Day 6. This was judged as related to treatment. All other TEAEs, including palpitations, nausea, herpes zoster, otitis externa, and headache were judged as unrelated to treatment.

Refer to Section 8 of this Unireview for complete safety results.

Comparison to Oral Roflumilast

Steady-state exposures to roflumilast and roflumilast *N*-oxide were compared following daily administration of 0.3% roflumilast foam under maximal use conditions in subjects with seborrheic dermatitis and following daily administration of 500 mcg oral roflumilast in healthy subjects (Table 6). PK data of oral roflumilast in healthy subjects was derived from the original review for NDA 022522. Data in subjects with COPD was estimated based on the same review.

Results indicate that the steady-state C_{max} for roflumilast and roflumilast *N*-oxide are 3.3- and 2.0-fold higher, respectively, following daily oral administration of 500 mcg roflumilast in healthy subjects relative to daily topical administration of 0.3% roflumilast foam under maximal use conditions in subjects with seborrheic dermatitis. Steady-state AUC_{0-24} for roflumilast and roflumilast *N*-oxide is 1.1- and 1.9-fold higher, respectively, in healthy subjects taking 500 mcg oral roflumilast.

Table 6. Summary of Steady-State Geometric Mean C_{max} and AUC_{0-24} of Roflumilast and Roflumilast N-Oxide in Adults Following Daily Administration of 500 mcg Oral Roflumilast or 0.3% Roflumilast Topical Foam

			Roflumilast		Roflumilast *N*-oxide	
Dose	ROA	Population	C_{max} (ng/mL)	AUC_{0-24} (ng*h/mL)	C_{max} (ng/mL)	AUC_{0-24} (ng*h/mL)
500 mcg	Oral	Healthy[a]	6.01	33.7	21.7	375
500 mcg	Oral	COPD[b]	6.37	53.9	29.7	488
0.3% (5 to 9% BSA)	Topical	SD[c]	1.8 (77.7)[d]	29.8 (80.4)[d]	11.0 (96.1)[d]	196 (115)[d]

Source: Reviewer-generated table using data adapted from Table 2 Summary of Clinical Pharmacology, Module 2.7.2; and the original review of NDA 022522, page 36.

[a.] PK data of oral roflumilast in healthy subjects is derived from the original review for NDA 022522

[b.] The original review for NDA 022522 notes that the AUC for roflumilast and roflumilast N-oxide are about 60% and 30% higher, respectively, in COPD patients compared to healthy subjects, while the C_{max} is about 6% and 37% higher, respectively. Values reported are calculated from data in healthy subjects by multiplying AUC by 1.6 or 1.3 and C_{max} by 1.06 or 1.37.

[c.] PK data of topical roflumilast in subjects with seborrheic dermatitis are derived from the maximal use study, ARQ-154-116. C_{max} and AUC_{0-24} are based on observed data and are not extrapolated.

[d.] Values reported as geometric mean (CV%)

Abbreviations: AUC_{0-24}, area under the plasma concentration-time curve from time 0 to 24 hours; BSA, body surface area; C_{max}, maximum concentration; COPD, chronic obstructive pulmonary disease; ROA, route of administration; SD, seborrheic dermatitis

Cross-Study Comparison With 0.3% Roflumilast Cream (Zoryve)

This Applicant also has another topical roflumilast product (Zoryve, 0.3% roflumilast cream), which was approved in 2022 for the topical treatment of plaque psoriasis, including intertriginous areas, in patients 12 years of age and older. The PK of roflumilast and roflumilast *N*-oxide in adolescent and adult subjects with chronic plaque psoriasis following administration of 0.3% roflumilast cream was evaluated in the maximal use study, ARQ-151-107 (study report submitted under NDA 215985). For additional details on study design and PK analysis, refer to the review for NDA 215985 (DARRTS date: July 28, 2022; Reference ID: 5020282).

Predose roflumilast and roflumilast *N*-oxide concentrations and exposures on Day 15 in pediatric and adult subjects following administration of either 0.3% roflumilast foam (ARQ-154 116, seborrheic dermatitis) or 0.3% roflumilast cream (ARQ-151-107, plaque psoriasis) are shown in Table 7. The observed predose roflumilast and roflumilast *N*-oxide concentrations in adult and pediatric subjects with seborrheic dermatitis is within the range of concentrations observed in adult and adolescent subjects with plaque psoriasis.

Notably, the treated BSA was higher for subjects with psoriasis in Study ARQ-151-107. However, the theoretical predicted dose of roflumilast administered does not scale proportionally with the treated BSA. This is because the drug product application rate differed between the two studies: 3 mg/cm^2 of roflumilast foam in Study ARQ-154-116 versus 2 mg/cm^2 of roflumilast cream in Study ARQ-151-107. It is also important to note that there may be

differences in systemic absorption based on both the formulation (i.e., foam vs. cream) and the indication (i.e., seborrheic dermatitis vs. plaque psoriasis). This thus precludes a meaningful comparison of exposures across the two studies.

Table 7. Summary of Roflumilast and Roflumilast N-Oxide Concentrations on Day 15 in Pediatric and Adult Subjects in Studies ARQ-154-116 and ARQ-154-107

			Mean (SD)			
Study	Age Group	N	Treated BSA (%)	Predicted Dose (mg)	Concentration (ng/mL)	Dose-Normalized Concentration (ng/mg)
Roflumilast						
ARQ-154-116	Pediatric	10	5.50 (1.27)	7.82 (1.80)	0.943 (1.23)	0.123 (0.173)
	Adult	10	6.50 (1.08)	10.0 (1.66)	1.95 (1.66)	0.191 (0.148)
ARQ-151-107	Adolescent	5	13.6 (3.65)	12.9 (3.46)	0.902 (1.14)	0.0699
	Adult	18	26.8 (6.80)	27.5 (6.98)	3.03 (2.32)[a]	0.110
Roflumilast N-oxide						
ARQ-154-116	Pediatric	10	5.50 (1.27)	7.82 (1.80)	10.5 (16.8)	1.41 (2.38)
	Adult	10	6.50 (1.08)	10.0 (1.66)	12.7 (9.32)	1.27 (0.881)
ARQ-151-107	Adolescent	6	13.0 (3.58)	12.3 (3.39)	5.52 (6.70)	0.449
	Adult	18	26.8 (6.80)	27.5 (6.98)	25.8 (26.3)	0.938

Source: Table 15, Summary of Clinical Pharmacology, Module 2.7.2.
Note: The application rate was 3 mg/cm^2 in ARQ-154-116 and 2 mg/cm^2 in ARQ-151-107.
[a] n = 19
Abbreviations: BSA, body surface area; SD, standard deviation

Phase 3 Study ARQ-154-304

The PK of 0.3% roflumilast foam was also evaluated in the Phase 3 study, ARQ-154-304, a randomized, double-blind, vehicle-controlled, parallel-group safety and efficacy study conducted in subjects aged 9 years and older with seborrheic dermatitis affecting up to 20% BSA. Subjects were randomized 2:1 to apply either 0.3% roflumilast foam or vehicle foam QD for 8 weeks. All subjects were required to have a clinical diagnosis of seborrheic dermatitis of at least 3 months duration with stable disease for the past 4 weeks. Subjects with severe renal impairment (creatinine clearance < 30 mL/min), or moderate to severe hepatic impairment (Child-Pugh B or C) were excluded. Subjects were also excluded if they were not able to discontinue use of strong systemic cytochrome P450 inhibitors.

Disposition and Demographics

The study enrolled a total of 457 subjects, including 304 subjects in the roflumilast group, and 153 subjects in the vehicle group. Overall, 414 subjects (90.6%) completed the study, including

276 subjects (90.8%) in the roflumilast group and 138 subjects (90.2%) in the vehicle group. The most common reason for discontinuation was being lost to follow-up and withdrawal by subject. The PK population included all subjects who received at least one confirmed dose of product and provided at least one PK sample. The PK population was comprised of 293/304 subjects (96.4%) in the roflumilast group and 148/153 subjects (96.7%) in the vehicle group.

The median (range) age of enrolled subjects was 42.0 (9 to 87) years. This included 32 subjects aged 9 to 17 years, 17 of whom were randomized to the roflumilast group. Subjects were predominantly female (n = 229, 50.1%), White (n = 356, 77.9%), and not of Hispanic or Latino ethnicity (n = 360, 78.8%). Proportions were similar among the roflumilast and control groups. The median (range) % body surface area involvement across all subjects was 2.2 (0.2 to 20.0)%. 93.4% of subjects had baseline scalp involvement (n = 427). Some subjects also had involvement of non-scalp locations, including face (n = 284), ears (n = 225), eyelids (n = 42), neck (n = 46), trunk (n = 46), and other body regions (n = 15).

Dosing

Roflumilast foam was applied to all affected areas, including the scalp if lesions on the scalp were identified. In this study, about 93% of subjects had baseline scalp involvement.

The average daily weight of 0.3% roflumilast foam applied was determined by calculating the difference in weight between the returned product and dispensed product, and dividing by the total number of applications. Across all subjects, the overall mean (SD) weight of roflumilast foam applied per day was 2.79 (1.99) g, equivalent to a daily roflumilast dose of 8.37 (5.97) mg.

Pharmacokinetic Sampling and Analysis

Pharmacokinetics were only assessed in subjects who were randomized to the roflumilast group, which included 17 pediatric subjects 9 to 17 years of age, and 276 adult subjects. Notably, the pediatric PK population included one subject 9 years of age (5.0% treated BSA) and one subject 10 years of age (2.0% treated BSA). Both roflumilast and its active metabolite roflumilast *N*-oxide were assessed. Plasma PK samples were collected from all subjects at predose on Day 28 (Week 4) and Day 56 (Week 8).

PK data analysis was conducted using Phoenix WinNonlin software. Values of AUC_{0-24} were extrapolated by multiplying the predose concentration value by 24. Predose concentrations found to be below the limit of quantitation (0.10 ng/mL) were ignored for the extrapolation.

The 0.3% roflumilast foam was administered at an application rate of approximately 2 mg/cm^2. Calculations of a theoretical target dose was determined based on a theoretical total BSA of 17,100 cm^2 for adults, and 15,800 cm^2 for pediatric patients 9 to 17 years of age. The estimated amount of foam was determined by multiplying the treated BSA (calculated as total BSA multiplied by the percent total BSA treated) by the application rate of 2 mg/cm^2. The theoretical amount of roflumilast delivered is calculated as the amount of foam multiplied by 0.003 (0.3% = 0.003 mg roflumilast per mg of foam).

Pharmacokinetic Results

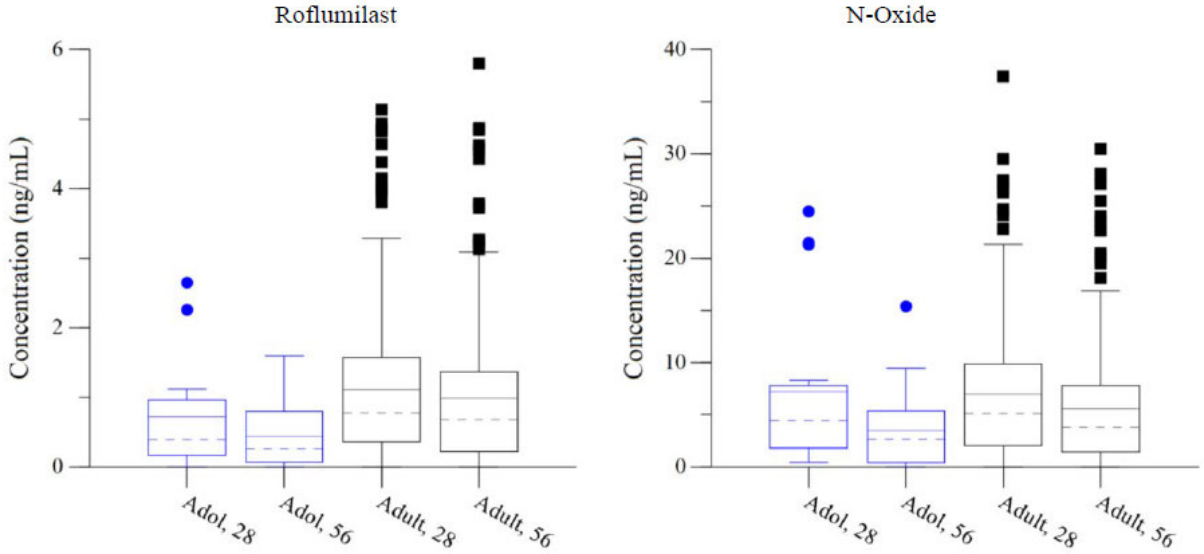
A comparison of predose PK in pediatric and adult subjects at Weeks 4 and 8 following daily administration of 0.3% roflumilast foam is shown in Table 8 and Figure 4. The mean Week 4 predose concentrations of roflumilast and roflumilast *N*-oxide were lower and comparable, respectively, in pediatric subjects relative to adult subjects. Predose concentrations at Week 8 in pediatric subjects were overall lower than at Week 4, which may be due to variability attributed to low sample size. At Week 8, concentrations in pediatric subjects for both roflumilast and roflumilast *N*-oxide were lower than in adults. This may have been due to resolution of the disease, which can impact the degree of drug absorption. The boxplot distributions corroborate that predose concentrations are lower in pediatric subjects. The extrapolated AUC_{0-24} determined based on the predose concentrations also indicate that exposure to roflumilast and roflumilast *N*-oxide is lower in pediatric subjects relative to adults, despite higher treated BSA and, therefore, higher theoretical predicted dose.

Table 8. Summary of Roflumilast and Roflumilast N-Oxide PK at Weeks 4 and 8 in Pediatric and Adult Subjects in Study ARQ-154-304

			Mean (SD)				
Analyte Age Group	N	Study Visit	Treated BSA (%)	Predicted Dose (mg)	Concentration (ng/mL)	Dose-normalized Concentration (ng/mg)	Extrapolated AUC_{0-24}[a] (h·ng/mL)
Roflumilast							
Pediatric	17	Week 4	3.88 (1.76)	3.68 (1.67)	0.717 (0.741)	0.222 (0.228)	18.3 (17.8)
	17	Week 8	3.88 (1.76)	3.68 (1.67)	0.440 (0.453)	0.138 (0.138)	13.8 (10.4)
Adult	265	Week 4	2.80 (2.05)	2.87 (2.11)	1.12 (1.06)	0.579 (0.775)	29.2 (25.2)
	257	Week 8	2.76 (2.06)	2.87 (2.11)	0.986 (1.04)	0.482 (0.582)	26.9 (24.8)
Roflumilast N-oxide							
Pediatric	17	Week 4	3.88 (1.76)	3.68 (1.67)	7.19 (7.67)	2.22 (2.31)	172 (184)
	17	Week 8	3.88 (1.76)	3.68 (1.67)	3.51 (4.20)	1.08 (1.17)	102 (103)
Adult	265	Week 4	2.80 (2.05)	2.87 (2.11)	6.95 (6.58)	3.50 (4.51)	173 (158)
	257	Week 8	2.76 (2.06)	2.83 (2.11)	5.59 (5.72)	2.74 (3.23)	141 (137)

Source: Table 4, Summary of Clinical Pharmacology, Module 2.7.2.
[a] Because of the flat nature of the plasma concentration-time profile, AUC_{0-24} was extrapolated by multiplying the predose concentration value by 24.
Abbreviations: AUC_{0-24}, area under the plasma concentration-time curve from time zero to 24 hours; BSA, body surface area; SD, standard deviation.

Figure 4. Boxplots of Week 4 and 8 Predose Concentrations of Roflumilast and Roflumilast N-Oxide in Pediatric and Adult Subjects in Study ARQ-154-304



Source: Figure 1, Clinical Study Report for ARQ-154-304, Appendix 16.1.13.2.
Note: The dashed lines indicate the median, while the solid lines indicate the arithmetic mean.

Comparison to Study ARQ-154-116

The relationship of roflumilast and roflumilast *N*-oxide concentrations in pediatric subjects relative to adults was similar in Study ARQ-154-304 and in the maximal use study, ARQ-154-116. Steady-state predose concentrations and extrapolated AUC_{0-24} was lower in Study ARQ-154-304 compared to PK results from Study ARQ-154-116. This is likely due to the lower treated BSA and foam application rate in Study ARQ-154-304. In Study ARQ-154-304, the mean (SD) treated % BSA in pediatric and adult subjects was 3.88 (1.86)% and 2.80 (2.05)%, respectively. In ARQ-154-116, the mean (SD) treated % BSA in pediatric and adult subjects was 5.50 (1.27)% and 6.50 (1.08)%, respectively. The foam application rate in ARQ-154-304 was 2 mg/cm^2 as compared with 3 mg/cm^2 in ARQ-154-116.

The reduction in dosage in Study ARQ-154-304 is also reflected in the observed weights of roflumilast foam applied per day in each study. In the maximal use study, ARQ-154-116, the mean (SD) weight of foam applied was 4.13 (2.07) g, equivalent to a daily roflumilast dose of 12.4 (6.21) mg. Meanwhile, in Study ARQ-154-304, the mean (SD) weight of foam applied was 2.79 (1.99) g, equivalent to a daily roflumilast dose of 8.37 (5.97) mg. Thus, the average daily dose applied in the maximal use study was approximately 1.5-fold greater than that in the Phase 3 study.

These differences are expected given that the maximal use study, ARQ-154-116, was designed to maximize the amount of roflumilast foam administered. Enrolled subjects were required to have seborrheic dermatitis with a minimum of 5% BSA involved, whereas a minimum BSA involvement was not specified for Study ARQ-154-304. Study ARQ-154-304 was designed as the pivotal study and enrolled a larger sample size with the mean (SD) BSA involvement among all enrolled subjects equal to 2.92 (2.22)%. This suggests that the amount of the 0.3% roflumilast

foam administered to subjects in the maximal use study is greater than what might be observed during actual clinical use. Thus, the maximal use study, ARQ-154-116, is acceptable and supportive as it was indeed conducted under maximal use conditions.

Phase 2a Study ARQ-154-203 and Extension Study ARQ-154-214

The PK of 0.3% roflumilast foam was also evaluated in the Phase 2a study, ARQ-154-203. This study had a similar study design to the Phase 3 study, ARQ-154-304, but only enrolled adult subjects. Pediatric subjects were not enrolled. Subjects were randomized 2:1 to apply either 0.3% roflumilast foam or vehicle foam QD for 8 weeks. At Week 8, subjects meeting eligibility requirements were given the option to roll over into Study ARQ-154-214, an open-label, single-arm, long-term safety extension study of daily administration of 0.3% roflumilast foam. Study ARQ-154-214 enrolled subjects who rolled over from studies ARQ-154-203 and ARQ-154-116, including adolescent subjects aged ≥ 9 years. The study also enrolled subjects who may not have participated in a prior clinical study of 0.3% roflumilast foam.

Disposition and Demographics

Study ARQ-154-203 enrolled a total of 226 subjects, including 154 subjects in the roflumilast group, and 72 subjects in the vehicle group. Overall, 208 subjects (92.0%) completed the study, including 141 subjects (91.6%) in the roflumilast group and 67 subjects (93.1%) in the vehicle group. The most common reason for discontinuation was being lost to follow-up and withdrawal by subject. The PK population included all subjects who received active drug and had a PK draw at Baseline Day 0 visit. The PK population was comprised of 153/154 subjects (99.4%), all in the roflumilast group.

The median (range) age of enrolled subjects was 41.0 (18 to 85) years. Subjects were predominantly male (n = 116, 51.3%), White (n = 185, 81.9%), and not of Hispanic or Latino ethnicity (n = 181, 80.1%). The median (range) body surface area involvement across all subjects was 3.0 (0.1 to 16.0)%.

In Study ARQ-154-214, PK was evaluated in three *de novo* pediatric subjects who did not roll over from a prior clinical study of 0.3% roflumilast foam. The ages of these three subjects were 13, 14, and 14. The percent treated BSA in all subjects was 5.0%.

Dosing

The average daily weight of 0.3% roflumilast foam applied was determined by calculating the difference in weight between the returned product and dispensed product, and dividing by the total number of applications. Across all subjects, the overall mean (SD) weight of roflumilast foam applied per day was 3.01 (3.20) g, equivalent to a daily roflumilast dose of 9.03 (9.60) mg.

Pharmacokinetic Sampling and Analysis

In Study ARQ-154-203, plasma PK samples were collected from all subjects at predose on Day 28 (Week 4) and Day 56 (Week 8).

In Study ARQ-154-214, a predose sample was collected from all subjects at Week 4. Values of AUC_{0-24} were extrapolated by multiplying the predose concentration value by 24.

For both studies, both roflumilast and its active metabolite roflumilast *N*-oxide were assessed. PK data analysis was conducted using Phoenix WinNonlin software.

Pharmacokinetic Results

A comparison of predose PK in adult subjects at Weeks 4 and 8 following daily administration of 0.3% roflumilast foam in ARQ-154-203 is shown in Table 9. The observed mean predose concentrations for roflumilast and roflumilast *N*-oxide at Weeks 4 and 8 are comparable to the observed mean predose concentrations in adults in the Phase 3 study, ARQ-154-304. In addition, the percent treated BSA was similar between the adult populations in ARQ-154-203 and ARQ-154-304.

Table 9. Summary of Roflumilast and Roflumilast N-Oxide PK at Weeks 4 and 8 in Adult Subjects in Study ARQ-154-203

	Week 4		Week 8	
	Treated BSA (%)	Concentration (ng/mL)	Treated BSA (%)	Concentration (ng/mL)
Roflumilast				
N	143	143	140	140
Mean (SD)	3.26 (2.52)	1.23 (1.48)	3.26 (2.51)	1.20 (1.75)
CV%	77.2	120	77.0	145
Median (min, max)	3.00 (0.100, 16.0)	0.965 (0.000100, 13.9)	3.00 (0.100, 16.0)	0.765 (0.000100, 16.7)
Geometric mean (geometric SD)	2.38 (2.41)	0.426 (15.8)	2.39 (2.40)	0.325 (20.5)
Geometric CV%	108	4490	107	9540
Roflumilast N-oxide				
N	143	143	140	140
Mean (SD)	3.26 (2.52)	7.89 (9.19)	3.26 (2.51)	7.34 (8.79)
CV%	77.2	116	77.0	120
Median (min, max)	3.00 (0.100, 16.0)	5.70 (0.000100, 70.4)	3.00 (0.100, 16.0)	5.02 (0.000100, 57.5)
Geometric mean (geometric SD)	2.38 (2.41)	3.38 (11.0)	2.39 (2.40)	2.87 (11.7)
Geometric CV%	108	1780	107	2040

Source: Table 5, Summary of Clinical Pharmacology, Module 2.7.2.
Note: To calculate geometric mean, all values were increased by 0.0001 ng/mL
Abbreviations: BSA, body surface area; CV, coefficient of variation; SD, standard deviation

For the three pediatric subjects in Study ARQ-154-214, the mean (range) Week 4 predose concentrations for roflumilast and roflumilast *N*-oxide were 0.858 (0.249, 1.33) ng/mL and 7.13 (1.52, 10.5) ng/mL, respectively. Based on these predose concentrations, the mean (range) extrapolated AUC_{0-24} values for roflumilast and roflumilast *N*-oxide were 20.6 (5.98, 31.9) ng*h/mL and 171 (36.5, 252) ng*h/mL, respectively. These values are within the range

observed in pediatric subjects in the maximal use study, ARQ-154-116, and Phase 3 study, ARQ-154-304.

Metabolism

The metabolism of roflumilast was not evaluated in the present NDA. Rather, the Applicant is relying on information generated during the development of oral roflumilast (Daliresp, NDA 022522), for which the Applicant has right of reference. Roflumilast metabolism was characterized during this program. The following information on roflumilast metabolism is derived from the current approved labeling for Daliresp.

Roflumilast is extensively metabolized via Phase I (cytochrome P450) and Phase II (conjugation) reactions. The *N*-oxide metabolite is the only major metabolite observed in the plasma of humans. *In vitro* studies suggest that the biotransformation of roflumilast to its *N*-oxide metabolite is mediated by CYP1A2 and 3A4. Together, roflumilast and roflumilast *N*-oxide account for 87.5% of the total dose administered in plasma. In urine, roflumilast was not detectable while roflumilast *N*-oxide was only a trace metabolite (< 1%). Other conjugated metabolites such as roflumilast *N*-oxide glucuronide and 4-amino-3,5-dichloropyridine *N*-oxide were detected in urine.

Following multiple topical applications of 0.3% roflumilast foam in the maximal use study, ARQ-154-116, the roflumilast *N*-oxide metabolite appears to circulate at concentrations approximately 6.5-fold and 11-fold greater than the parent in adult and pediatric subjects, respectively. In the Phase 3 study, ARQ-154-304, the ratio of *N*-oxide metabolite to parent drug ranged from 5.7 to 6.2 in adults and from 8.0 to 10 in pediatric subjects. The labeling for Daliresp indicates that plasma AUC of roflumilast *N*-oxide is on average about 10-fold greater than that of roflumilast. The greater observed metabolism after oral dosing relative to topical application in adults may be due to the effects of first-pass metabolism after oral dosing. Meanwhile, the metabolite-to-parent ratio in pediatric subjects was greater than that in adults, which may suggest that there is greater metabolism among the younger age group; however, definitive conclusions cannot be made due to the small sample size of pediatric subjects.

6.3.2. Clinical Pharmacology Questions

Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

No. The clinical pharmacology program assessed the systemic exposure to roflumilast and metabolite roflumilast *N*-oxide following daily topical administration of the proposed foam drug product. PK assessed under maximal use conditions supports systemic safety and does not provide supportive evidence of effectiveness. See Section 8 of this Unireview for efficacy results.

Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication is Being Sought?

The Applicant is proposing once daily topical application of 0.3% roflumilast foam in patients with seborrheic dermatitis aged 9 years and older. Currently, oral roflumilast (Daliresp) is only approved in adults, while the 0.3% roflumilast cream (Zoryve) is approved in pediatric patients and adults aged 12 years and older. Thus, roflumilast is not currently approved for use in patients younger than 12 years of age.

The youngest subjects enrolled in the maximal use study, ARQ-154-116, were 11 years of age. Subjects younger than 11 years were enrolled in the Phase 3 study, ARQ-154-304, including one subject 9 years of age (5.0% treated BSA) and one subject 10 years of age (2.0% treated BSA). In these subjects, the predose concentrations and extrapolated AUC_{0-24} for roflumilast and roflumilast *N*-oxide at Weeks 4 and 8 are shown in Table 10. For the subject aged 10 years, roflumilast and roflumilast *N*-oxide exposures are within the range observed among pediatric subjects across all clinical studies. Similarly, for the subject aged 9 years, exposure to both roflumilast and roflumilast *N*-oxide at Week 4 is within exposures observed in other pediatric subjects across all studies. At Week 8, this subject presented with the highest concentrations for both species among pediatric subjects in Study ARQ-154-304. However, these values are within the range of concentrations observed in adults in Study ARQ-154-304, and in pediatric and adult subjects in Study ARQ-154-116.

Table 10. Summary of Roflumilast and Roflumilast N-Oxide PK at Weeks 4 and 8 in Two Pediatric Subjects Aged 9 and 10 Years in Study ARQ-154-304

				Roflumilast		Roflumilast *N*-oxide	
Subject	Age	Treated BSA (%)	Day	Concentration (ng/mL)	AUC_{0-24}[a] (ng*h/mL)	Concentration (ng/mL)	AUC_{0-24}[a] (ng*h/mL)
(b) (6)	9	5.0	28	1.12	26.9	21.3	511
			56	1.60	38.4	15.4	370
	10	2.0	28	0.335	8.04	3.28	78.7
			56	0.365	8.76	2.68	64.3

Source: Reviewer-generated table adapted from Table 2, Clinical Study Report for ARQ-154-304, Appendix 16.1.13.2.
[a.] Because of the flat nature of the plasma concentration-time profile, AUC_{0-24} was extrapolated by multiplying the predose concentration value by 24.
Abbreviations: AUC_{0-24}, area under the plasma concentration-time curve from time zero to 24 hours; BSA, body surface area

Conclusions are limited due to the small sample size of enrolled subjects aged younger than 12 years. We defer to the clinical reviewer to determine whether the efficacy and safety of 0.3% roflumilast foam is adequate in the proposed pediatric patient population.

Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

An alternative dosing regimen is not required for subpopulations based on intrinsic patient factors. Using data from the Phase 3 study, ARQ-154-304, the Applicant analyzed predose roflumilast and roflumilast *N*-oxide concentrations by age (Table 11), sex (Table 12), race (Table

13), and ethnicity (Table 14). In all analyses, concentrations from Week 4 and Week 8 were combined as steady state is achieved prior to Week 4.

Analyses by age indicate that predose concentrations of roflumilast and roflumilast *N*-oxide were 1.7- and 1.5-fold greater, respectively in subjects aged ≥ 65 years relative to subjects aged 18 to < 65 years. The increase in exposure may be partly explained by the larger percent treated BSA for subjects aged ≥ 65 years.

Table 11. Summary of Roflumilast and Roflumilast N-Oxide Steady State Predose Concentrations by Age Group in Adult Subjects From Study ARQ-154-304

		Mean (SD)		
Age Group	N	Treated BSA (%)	Roflumilast (ng/mL)	Roflumilast N-oxide (ng/mL)
≥65 years	73	3.42 (3.12)	1.61 (1.61)	8.85 (8.31)
18 to <65 years	449	2.68 (1.81)	0.962 (0.900)	5.86 (5.69)

Source: Table 6, Summary of Clinical Pharmacology, Module 2.7.2.
Abbreviations: BSA, body surface area; SD, standard deviation

Analyses by sex indicate that predose concentrations of roflumilast and roflumilast *N*-oxide were 1.7- and 1.4-fold greater, respectively in male subjects relative to female subjects. These differences by sex are consistent with observations following administration of 0.3% roflumilast cream in subjects with plaque psoriasis (refer to the original review for NDA 215985, DARRTS date: July 28, 2022; Reference ID: 5020282).

Table 12. Summary of Roflumilast and Roflumilast N-Oxide Steady State Predose Concentrations by Sex in Adult Subjects From Study ARQ-154-304

		Mean (SD)		
Age Group	N	Treated BSA (%)	Roflumilast (ng/mL)	Roflumilast N-oxide (ng/mL)
Men	271	2.92 (2.21)	1.32 (1.21)	7.37 (6.49)
Women	251	2.63 (1.86)	0.767 (0.755)	5.10 (5.65)

Source: Table 7, Summary of Clinical Pharmacology, Module 2.7.2.
Abbreviations: BSA, body surface area; SD, standard deviation

Predose concentrations of roflumilast and roflumilast *N*-oxide were generally comparable by race. The largest difference in roflumilast concentration (1.6-fold) was between American Indian or Alaska Native subjects and Black or African American subjects. The largest difference in roflumilast *N*-oxide concentration (2.0-fold) was between American Indian or Alaska Native subjects and White subjects. The differences observed in American Indian or Alaska Native subjects and in those identifying as Other may be due to low sample size.

Table 13. Summary of Roflumilast and Roflumilast N-Oxide Steady-State Predose Concentrations by Race in Adult Subjects From Study ARQ-154-304

		Mean (SD)		
Age Group	N	Treated BSA (%)	Roflumilast (ng/mL)	Roflumilast N-oxide (ng/mL)
American Indian or Alaska Native	8	2.13 (1.33)	1.44 (1.20)	12.1 (11.3)
Asian	30	2.73 (2.17)	1.04 (0.892)	6.73 (5.65)
Black or African American	54	2.99 (1.56)	0.915 (0.866)	7.21 (6.54)
Other race	18	3.02 (4.49)	1.10 (0.748)	7.03 (5.03)
More than 1 race	2	2.00	0.512	3.39
White	410	2.76 (1.96)	1.06 (1.09)	5.99 (6.08)

Source: Table 8, Summary of Clinical Pharmacology, Module 2.7.2.
Abbreviations: BSA, body surface area; SD, standard deviation

There were no meaningful differences in predose concentrations of roflumilast and roflumilast *N*-oxide between ethnicities.

Table 14. Summary of Roflumilast and Roflumilast N-Oxide Steady-State Predose Concentrations by Ethnicity in Adult Subjects From Study ARQ-154-304

		Mean (SD)		
Age Group	N	Treated BSA (%)	Roflumilast (ng/mL)	Roflumilast N-oxide (ng/mL)
Hispanic or Latino	118	2.97 (2.15)	1.02 (1.07)	6.06 (6.19)
Not Hispanic or Latino	404	2.73 (2.02)	1.06 (1.04)	6.34 (6.21)

Source: Table 9, Summary of Clinical Pharmacology, Module 2.7.2.
Abbreviations: BSA, body surface area; SD, standard deviation

Renal Impairment

The Applicant did not conduct any dedicated studies to evaluate the impact of renal impairment on the PK of roflumilast following administration of the 0.3% roflumilast foam. The Applicant intends to rely on findings for Daliresp, roflumilast oral tablets (NDA 022522) for which the Applicant has a letter of authorization permitting right of reference. During the development program for oral roflumilast, a dedicated renal impairment study was conducted. Per the approved labeling for Daliresp, in twelve subjects with severe renal impairment administered a single dose of 500 mcg roflumilast, roflumilast and roflumilast *N*-oxide AUCs were decreased by 21% and 7%, respectively and C_{max} were reduced by 16% and 12%, respectively. Thus, the labeling indicates that no dosage adjustment is necessary for patients with renal impairment. Similarly, in the approved labeling for Zoryve (0.3% roflumilast cream), no dosage adjustments are recommended for patients with renal impairment as the topical dose is applied directly to the target site (skin).

In the maximal use study, ARQ-154-116, and Phase 3 study, ARQ-154-304, subjects with severe renal impairment (creatinine clearance < 30 mL/min) were excluded. An analysis of steady-state

predose roflumilast and roflumilast *N*-oxide concentrations was conducted among subjects with moderate renal impairment in Study ARQ-154-304 (creatinine clearance < 60 mL/min; n = 9) (Table 15). Relative to all adult subjects in Study ARQ-154-304 (Table 8), predose roflumilast and roflumilast *N*-oxide concentrations were 1.8- to 1.9-fold greater and 1.5- to 1.7-fold greater, respectively, in subjects with moderate renal impairment. This may be partly explained by the higher percent treated BSA in subjects with moderate renal impairment. Although exposure increased in subjects with moderate renal impairment, the observed concentrations are comparable to those observed in adults in the maximal use study, ARQ-154-116 (Table 5). In addition, steady-state exposure to roflumilast and roflumilast *N*-oxide in adults under maximal use conditions in subjects with seborrheic dermatitis is in the range of comparable to lower than that in healthy subjects and subjects with COPD following daily administration of 500 mcg oral roflumilast (Table 6). Lastly, all subjects with moderate renal impairment were over 65 years of age (range: 67 to 87 years). The increases in exposure observed among subjects with renal impairment are consistent with those observed in subjects aged ≥ 65 years relative to subjects aged 18 to 65 years (Table 11).

Table 15. Summary of Mean (SD) Roflumilast and Roflumilast N-Oxide Predose Concentrations at Weeks 4 and 8 in Subjects With Moderate Renal Impairment in Study ARQ-154-304

			Roflumilast		Roflumilast *N*-oxide	
N	Treated BSA (%)	Day	Concentration (ng/mL)	AUC_{0-24}[a] (ng*h/mL)	Concentration (ng/mL)	AUC_{0-24}[a] (ng*h/mL)
9	4.1 (4.3)	28	2.0 (1.9)	48.0	11.7 (10.9)	281
		56	1.9 (2.1)	45.6	8.6 (9.1)	206

Source: Reviewer-generated table adapted from adpc, adsl, and adlb datasets from Study ARQ-154-304.
[a.] Because of the flat nature of the plasma concentration-time profile, AUC_{0-24} was extrapolated by multiplying the predose concentration value by 24.
Abbreviations: AUC_{0-24}, area under the plasma concentration-time curve from time zero to 24 hours; BSA, body surface area

Overall, differences in exposure due to renal impairment are not clinically meaningful. Therefore, no dosage adjustments are recommended for patients with renal impairment using 0.3% roflumilast foam.

Hepatic Impairment

The Applicant did not conduct any dedicated studies to evaluate the impact of hepatic impairment on the PK of roflumilast following administration of the 0.3% roflumilast foam. The Applicant intends to rely on findings for Daliresp. During the development program for oral roflumilast, a dedicated hepatic impairment study was conducted. Per the approved labeling for Daliresp, roflumilast 250 mcg once daily for 14 days was studied in subjects with mild to moderate hepatic impairment (Child-Pugh A and B; n = 8/group). The AUC of roflumilast and roflumilast *N*-oxide were increased by 51% and 24%, respectively in Child-Pugh A subjects and by 92% and 41%, respectively, in Child-Pugh B subjects, as compared to age-, weight-, and gender-matched healthy subjects. The C_{max} of roflumilast and roflumilast *N*-oxide were increased by 3% and 26%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects.

Thus, the labeling for oral roflumilast indicates that clinicians should consider the risk-benefit of administering roflumilast to patients who have mild liver impairment (Child-Pugh A), while it is contraindicated for use in patients with moderate or severe liver impairment (Child-Pugh B or C). In the approved labeling for Zoryve (0.3% roflumilast cream), use is contraindicated in patients with moderate to severe liver impairment. No consideration of risk-benefit is recommended for patients with mild liver impairment.

As shown in Table 6, steady-state exposure to roflumilast and roflumilast *N*-oxide was in the range of comparable to lower in subjects with seborrheic dermatitis applying 0.3% roflumilast foam under maximal use conditions relative to that observed in healthy subjects and predicted in subjects with COPD following oral doses of 500 mcg. In addition, as previously noted, the amount of roflumilast foam administered to subjects in the maximal use study, ARQ-154-116, is likely to be greater than what might be observed during actual clinical use. This was corroborated by the difference in percent treated BSA among subjects in Study ARQ-154-116 and the Phase 3 study, ARQ-154-304.

Therefore, similar to what is recommended in the approved labeling for Zoryve 0.3% roflumilast cream, it is acceptable to contraindicate use in patients with moderate to severe liver impairment (Child-Pugh B or C). Use of 0.3% roflumilast foam in subjects with mild liver impairment (Child-Pugh A) is acceptable and no dosage adjustments are recommended.

Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What is the Appropriate Management Strategy?

The proposed foam drug product is intended for topical administration. Thus, food-drug interactions are not expected.

The Applicant did not conduct any drug-drug interaction studies with the roflumilast foam. Rather, the Applicant intends to rely on findings for Daliresp, roflumilast oral tablets (NDA 022522) for which the Applicant has a letter of authorization permitting right of reference. The approved labeling for Daliresp describes evaluations of drug-drug interactions for roflumilast.

Perpetrator of CYP Inhibition

Per the approved labeling for Daliresp, *in vitro* results in human liver microsomes indicated that therapeutic plasma concentrations of roflumilast and roflumilast *N*-oxide do not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, or 4A9/11. Therefore, there is a low probability of relevant interactions with substances metabolized by these P450 enzymes. In addition, *in vitro* studies demonstrated no induction of the CYP 1A2, 2A6, 2C9, 2C19, or 3A4/5 and only a weak induction of CYP2B6 by roflumilast. In a clinical drug-drug interaction study conducted with 500 mcg oral roflumilast and midazolam, a CYP3A4 substrate, showed no effect on midazolam exposure.

To determine whether data generated for oral roflumilast are applicable to the proposed 0.3% roflumilast foam with respect to drug-drug interactions mediated via CYP inhibition, exposure data in adults was compared (Table 6). The steady-state C_{max} and AUC_{0-24} for roflumilast and

roflumilast *N*-oxide are in the range of comparable to higher following daily oral administration of 500 mcg roflumilast in healthy subjects and subjects with COPD, relative to daily topical administration of 0.3% roflumilast foam under maximal use conditions in subjects with seborrheic dermatitis. As it was previously determined that roflumilast following oral administration does not mediate drug-drug interactions via CYP inhibition, the data are also applicable to the proposed 0.3% roflumilast foam.

Victim of CYP Inhibition

Per the approved labeling for oral roflumilast (Daliresp), coadministration of roflumilast with systemic CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously (e.g., erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) may increase roflumilast systemic exposure and may result in increased adverse reactions. Clinical drug-drug interaction studies with oral roflumilast (500 mcg) have been conducted with various CYP inhibitors, including erythromycin (CYP3A4), ketoconazole (CYP3A4), fluvoxamine (CYP3A4/1A2), enoxacin (CYP3A4/1A2), and cimetidine (CYP3A4/1A2). Across all studies, the C_{max} of roflumilast increased by 12 to 46%, while AUC increased by 56 to 99%. The C_{max} of roflumilast *N*-oxide decreased by 4 to 210%, while AUC increased by 3 to 52%. Therefore, the labeling for oral roflumilast cautions that the risk of concurrent use should be weighed carefully against benefit. The approved labeling for Zoryve (0.3% roflumilast topical cream) is aligned with that of Daliresp with respect to co-administration with CYP3A4 and CYP3A4/1A2 inhibitors.

Thus, in the proposed labeling for 0.3% roflumilast foam, it is acceptable to caution patients on the potential for increased adverse reactions when co-administered with CYP3A4 inhibitors or dual inhibitors of CYP3A4 and CYP1A2.

Victim of CYP Induction

Metabolism of roflumilast to roflumilast *N*-oxide is primarily mediated via CYP3A4 and CYP1A2. Under NDA 022522, an open-label, three-period, fixed-sequence clinical drug-drug interaction study was conducted in healthy subjects with rifampicin, an inducer of CYP3A4. Per the approved labeling for Daliresp, coadministration of rifampicin (600 mg once daily for 11 days) with a single 500 mcg oral dose of roflumilast resulted in reduction of roflumilast C_{max} and AUC by 68% and 79%, respectively; and an increase of roflumilast *N*-oxide C_{max} by 30% and reduced roflumilast *N*-oxide AUC by 56%. As strong P450 enzyme inducers can decrease roflumilast systemic exposure and reduce the therapeutic effectiveness of Daliresp, the use of strong cytochrome P450 inducers with Daliresp is not recommended.

For the proposed topical 0.3% roflumilast foam, roflumilast is administered locally, directly to the site of action (i.e., skin). Therefore, systemic exposure to roflumilast is not linked to efficacy in seborrheic dermatitis. Thus, a reduction in systemic exposure to roflumilast and roflumilast *N*-oxide mediated via CYP induction is unlikely to impact efficacy or yield any safety concerns. Thus, co-administration of 0.3% roflumilast foam with CYP inducers is acceptable. This is corroborated by the approved labeling for Zoryve (0.3% roflumilast topical cream), which does not recommend against co-administration with strong CYP inducers.

Oral Contraceptives

Under NDA 022522, roflumilast was also evaluated as a victim of drug-drug interactions when co-administered with oral contraceptives containing gestodene and ethinyl estradiol. Per the approved labeling for Daliresp, in an open-label crossover study in 20 healthy adult volunteers, coadministration of a single oral dose of 500 mcg roflumilast with repeated doses of a fixed combination oral contraceptive containing 0.075 mg gestodene and 0.03 mg ethinyl estradiol to steady state caused a 38% increase and 12% decrease in C_{max} of roflumilast and roflumilast *N*-oxide, respectively. Roflumilast and roflumilast *N*-oxide AUCs were increased by 51% and 14%, respectively.

The labeling for Daliresp therefore includes a warning that co-administration of oral roflumilast with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully against benefit. The approved labeling for Zoryve (0.3% roflumilast cream) is aligned with the Daliresp labeling and contains the same language regarding interactions with oral contraceptives containing gestodene and ethinyl estradiol. For the proposed product, the Applicant proposes to remove language regarding a possible DDI with oral contraceptives.

To support this change in the labeling, the Applicant assessed whether concomitant use of combination oral contraceptives comprised of an estrogen and a progestin results in elevated plasma concentrations of roflumilast and roflumilast *N*-oxide. A retrospective analysis was conducted in women of childbearing potential with plaque psoriasis or seborrheic dermatitis who participated in Phase 2 and Phase 3 studies of 0.3% roflumilast cream or roflumilast foam, respectively. Steady-state predose roflumilast and roflumilast *N*-oxide plasma concentrations in women of childbearing potential on various contraceptive methods and separated by roflumilast product (i.e., 0.3% cream or 0.3% foam) are summarized in Table 16.

Among subjects using the proposed 0.3% roflumilast foam, 3 were identified who were taking combination oral contraceptives. Data indicate that these subjects had the lowest concentrations of roflumilast and roflumilast *N*-oxide relative to subjects on other forms of contraception. These subjects had a lower mean percent treated BSA and this may have contributed to the observed lower concentrations. Overall, conclusions from this analysis are limited due to the small sample size.

Table 16. Mean ± SD Steady-State Roflumilast and Roflumilast N-Oxide Predose Plasma Concentrations in Women of Childbearing Potential on Various Contraceptive Methods and Separated by Roflumilast Product

Roflumilast Drug Product	Group	N	BSA (%)	Target Dose (mg)	Roflumilast		N-Oxide	
					Conc (ng/mL)	DN Conc (ng/mL/mg)	Conc (ng/mL)	DN Conc (ng/mL/mg)
0.3% Cream	NH	67	5.38±4.30	5.52±4.41	1.47±3.11	0.278±0.522	10.5±21.5	2.06±4.16
	Combination	16	5.39±2.94	5.53±3.02	1.50±1.08	0.278±0.185	10.2±6.86	1.80±0.840
	Other	25	5.43±4.19	5.57±4.30	1.09±1.05	0.257±0.261	6.57±5.89	1.58±1.48
0.3% Foam	NH	87	2.84±1.69	2.91±1.73	0.719±0.626	0.358±0.381	5.28±4.92	2.52±2.73
	Combination	3	1.17±0.764	1.20±0.784	0.174±0.159	0.272±0.310	1.13±1.05	1.77±2.06
	Other	53	2.17±1.64	2.23±1.68	0.750±0.532	0.522±0.568	4.82±3.63	3.32±3.52
Foam and Cream Combined	NH	154	3.94±3.34	4.04±3.43	1.04±2.13	0.323±0.448	7.56±14.8	2.32±3.42
	Combination	19	4.72±3.12	4.84±3.21	1.29±1.10	0.277±0.198	8.76±7.13	1.80±1.03
	Other	78	3.22±3.10	3.30±3.19	0.861±0.749	0.437±0.505	5.39±4.51	2.76±3.12

Source: Table 1, Response to Clin Pharm IR, June 23, 2023.
Abbreviations: BSA, body surface area; Combination, combination oral contraception; NH, non-hormonal contraception; Other, other hormonal forms of contraception; SD, standard deviation

However, as previously established, under clinical use conditions (i.e., as was evaluated in Phase 3 study, ARQ-154-304), exposure to roflumilast and roflumilast *N*-oxide was lower than that observed in the maximal use study. In addition, steady-state exposure to roflumilast and roflumilast *N*-oxide in adults under maximal use conditions in subjects with seborrheic dermatitis is comparable to lower than that in healthy subjects and subjects with COPD following daily administration of 500 mcg oral roflumilast (Table 6). Thus, under clinical use conditions of 0.3% roflumilast foam, any increase in roflumilast systemic exposure expected in the presence of hormonal oral contraceptives is highly unlikely to exceed that which has been observed when co-administered with 500 mcg oral roflumilast (up to 51% increase in roflumilast AUC).

Thus, from a clinical pharmacology perspective, the proposed removal of language describing a potential DDI with hormonal oral contraceptives is acceptable.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The development program for roflumilast foam, 0.3% for the treatment of Seborrheic Dermatitis included the following 4 studies:

1. ARQ-154-116 (N=22): A Phase 1, Maximal Use, PK/safety (MuST) study
2. ARQ-154-203 (N=226): A Phase 2a, R (2:1), DB, PC, PK/safety/efficacy trial
3. ARQ-154-214 (N=408): A Phase 2, open-label, long-term safety (LTS) study
4. ARQ-154-304 (N=457): A Phase 3, R (2:1), DB, PC, PK/safety/efficacy trial

Table 17. Listing of Clinical Trials Relevant to NDA 217242

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
ARQ-154-304 (STRATUM)	NCT 04973228	Phase 3, multicenter, randomized (2:1) , double-blind, vehicle-controlled, parallel-group	Roflumilast foam, 0.3% or vehicle foam applied topically once a day	Efficacy endpoints: Primary: -IGA success (IGA score of Clear (0) or Almost Clear (1) and a ≥2-point improvement from baseline) at Week 8 Secondary: -Worst Itch-Numerical Rating Scale (WI-NRS) success (≥4-point improvement from baseline in subjects with a baseline WI-NRS score ≥4) at Week 8 -WI-NRS Success at Week 4 -WI-NRS Success at Week 2 -IGA Success at Week 4 -Achievement of an Overall Assessment of Scaling (0-3) score of 0 at Week 8 -Achievement of an Overall Assessment of Erythema (0-3) score of 0 at Week 8 -IGA score of 0 at Week 8 -IGA Success at Week 2	8 Weeks	N=457	≥9 years of age Seborrheic Dermatitis (SD)-affected BSA < 20% Baseline IGA) ≥ 3 (moderate)	50 sites in the US and Canada

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. of Centers and Countries
ARQ-154-203	NCT 04091646	Phase 2a, multicenter, randomized (2:1) , double-blind, vehicle-controlled, parallel-group	Same as for Study ARQ-154-304	Efficacy endpoints: <u>Primary:</u> -IGA success at Week 8 <u>Secondary:</u> -IGA success at Weeks 4, 2 - Change from baseline (CFB) in Erythema score at W 2, 4, 8 - CFB in Scaling score at W 2, 4, 8 -Erythema success (score of 0/1 and ≥2-point improvement from baseline) at Weeks 2, 4, 8 -Scaling success (score of 0/1 and ≥2-point improvement from baseline) at Weeks 2, 4, 8 -CFB in WI-NRS score at Weeks 2, 4, and 8 -WI-NRS success (in subjects with a baseline WI-NRS score ≥4) at Weeks 2, 4, 8	8 Weeks	N=226	≥18 years of age SD-affected BSA < 20% Baseline IGA) ≥ 3 (moderate)	24 sites in the US and Canada
Studies to Support Safety								
ARQ-154-214		Phase 2, open-label, long-term safety study	Roflumilast foam, 0.3% or vehicle foam applied topically once a day	<u>Primary (Safety endpoint):</u> TEAEs, SAEs, application site reactions, laboratory measurements, PHQ8/-A, CDI-2, C-SSRS <u>Secondary (efficacy endpoints) over time:</u> -IGA = 0 or 1	26 weeks, extended to 52 Weeks	N= 408	<u>Cohort 1 (n=83):</u> ≥9 years of age Rolled-over from Phase 1, 2 studies ARQ-154-203/-116 <u>Cohort 2 (n=325):</u> -De novo subjects ≥12 years of age; or	40 sites in the US and Canada

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. of Centers and Countries
				-IGA success -Duration of IGA success -Duration of IGA=0 - CFB, %CFB in Scalpdex -CFB, %CFB on erythema and scaling scores -Erythema/scaling success -CFB, %CFB of SD-BSA -CFB, %CFB in WI-NRS -WI-NRS success -WI-NRS= 0/1 post-baseline			-Rolled-over from ARQ-154-203 with a treatment gap and SD BSA ≤ 20%	
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)								
ARQ-154-116		Phase 1, open-label, single-arm, Maximal Use, PK	Roflumilast foam, 0.3% foam applied topically once a day	Primary (PK): Roflumilast and N-oxide C_{max}, AUC_{last}, T_{max} Secondary (safety): TEAEs, application site reactions, vital signs, ECG, laboratory measurements, C-SSRS, PHQ-8/-A, CDI-2	2 Weeks	N= 22	9 to ≤16 years of age or ≥18 years of age SD-BSA = 5% to 20% SD- IGA ≥ 3 (moderate) Erythema score ≥2 (moderate) Scaling score≥2 (moderate)	7 sites in the US

7.2. Review Strategy

Data Sources

The data sources used for the evaluation of the efficacy and safety of roflumilast foam, 0.3% included the Applicant's CSRs, datasets, clinical summaries, and proposed labeling. The submission was submitted in electronic common technical document format and was entirely electronic. Both Study Data Tabulation Model (SDTM) and analysis datasets (ADaM) were submitted. The analysis datasets used in this review are archived under NDA 217242, SDN1/eCTD1 (Arcutis Biotherapeutics 2023).

Data and Analysis Quality

A consultation for review of data fitness was obtained from CDER Office of Computational Sciences (OCS) on 2/24/2023. The OCS Clinical Services team performed exploratory safety analysis and data fitness analysis for Trials ARQ-154-203, ARQ-154-214, ARQ-154-304, and the ISS for this NDA and found the data quality acceptable. In collaboration with the OCS Clinical Services team, the Statistical and Clinical reviewers held the following meetings:

- 2/24/2023: Annotated Core DF assessment
- 3/15/2023: ISS overview assessment
- 3/16/2023: SDTM to ADaM traceability assessment
- 3/17/2023: ISS traceability assessment
- 3/20/2023: Exploratory Safety Analysis Bundles Assessment- Disposition/AE/labs

Assessments evaluated the data fitness, whether certain common analyses could be performed, and other data quality metrics including:

- Availability of appropriate variables
- Variables populated by expected data points
- Appropriate use of standard terminology
- Data well described by metadata

In general, the data submitted by the Applicant to support the efficacy and safety of roflumilast foam, 0.3% for the proposed indication appeared adequate.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial ARQ-154-304

Trial Design

Trial ARQ-154-304 (Trial 304) is a randomized, double-blind, vehicle-controlled trial in subjects with seborrheic dermatitis. The trial enrolled subjects 9 years of age and older with moderate to severe seborrheic dermatitis. Subjects were to have up to 20% body surface area (BSA) involvement with involvement of the scalp and/or face and/or trunk and/or intertriginous areas. Subjects were also to have overall assessment of erythema and scaling of at least moderate at baseline. The trial was designed to enroll approximately 450 subjects in a 2:1 ratio to roflumilast foam or vehicle foam. Subjects were to apply treatment once daily for 8 weeks. Randomization was stratified by study site and baseline investigator's global assessment (IGA) [IGA=3 (moderate) or IGA=4 (severe)].

Study Endpoints

The primary endpoint and key secondary endpoints were based on the IGA scale, the Worst Itch Numeric Rating Scale (WI-NRS), the Overall Assessment of Scaling, and the Overall Assessment of Erythema. The IGA, Erythema, and Scaling assessment scales are listed below. The WI-NRS had subjects report the "highest intensity during the previous 24-hour period" from 0 to 10 (no itch to worst imaginable itch).

Table 18. Investigator Global Assessment of Disease (IGA)

Score	Description
0	Clear: No erythema, no scaling (hypo-hyperpigmentation can be present)
1	Almost clear: Slight erythema and/or trace (barely perceptible) amounts of scaling
2	Mild: Pink to red color and/or slight scaling
3	Moderate: Distinct erythema (redness) and/or clearly visible scaling
4	Severe: Severe erythema (intense, fiery red) and/or severe scaling (coarse, thick scales with flaking onto clothes or skin)

Source: Page 41 of protocol (Arcutis Biotherapeutics 2022).

Table 19. Overall Assessment of Erythema and Overall Assessment of Scaling

Score	Erythema	Scaling
0	None: No evidence of erythema	None: No scaling evident of lesions
1	Mild: Barely perceptible erythema which is faint of patchy	Mild: Barely detectable, scattered, small flaking scales
2	Moderate: Distinct erythema	Moderate: Scales clearly visible and prominent
3	Severe: Intense (fiery red) erythema	Severe: Coarse, thick scales, with flaking into clothes or skin

Source: Pages 41-42 of protocol (Arcutis Biotherapeutics 2022).

The primary efficacy endpoint was IGA success at Week 8, where success was defined as score of 'clear' or 'almost clear' plus at least 2-point improvement at Week 8.

The secondary endpoints were

- WI-NRS success at Week 8, where WI-NRS success is defined as achievement of at least a 4-point improvement in WI-NRS among subjects with an average weekly baseline WI-NRS ≥4
- WI-NRS success at Week 4
- WI-NRS success at Week 2
- IGA Success at Week 4
- IGA Success at Week 2
- Overall Scaling Score of '0' at Week 8
- Overall Erythema Score of '0' at Week 8
- IGA score of 'clear' at Week 8

Statistical Analysis Plan

The primary analysis population was the intent-to-treat (ITT) population, defined as all randomized subjects. The protocol also defined a modified ITT (mITT) population, defined as all randomized subjects except those who missed the Week 8 IGA assessment due to COVID-19 disruption. However, in Study 304 the mITT population was the same as the ITT population. The PRU4-ITT population was defined as all randomized subjects with a baseline WI-NRS ≥4 The primary endpoint was analyzed with the Cochran-Mantel-Haenszel test stratified by baseline IGA score and pooled study site. The intercurrent events of discontinuation due to lack of efficacy or adverse events were handled with non-responder imputation. Missing data were handled with multiple imputation.

Reviewer Comment: *Two subjects had discrepancies between the IGA score that was entered into the randomization system for stratification and the IGA score that was recorded in the case report form (CRF) as the baseline score. For one subject on each treatment arm, the subject was randomized using a baseline IGA score of moderate, but recorded as severe in the CRF. The statistical analysis plan (SAP) did not provide instructions regarding which values to use in the analyses. The Applicant used the value entered into the randomization system (stratum value) as the covariate in the analyses. As only two subjects had discrepancies, the impact was minimal.*

The trial was designed to test the efficacy endpoints using an overall α=0.01, as the Applicant intended to use Study 304 as the primary support for effectiveness. Multiplicity was controlled across the secondary endpoints by organizing the secondary endpoints into two families and using the fallback method between families and the sequential method within families. Family 1 included the WI-NRS success endpoints at Week 8, 4, and 2 and these endpoints were analyzed sequentially in that order. Initially α=0.0033 was allocated to Family 1. If all 3 WI-NRS endpoints were statistically significant then the α=0.0033 was passed to Family 2 and the Family 2

endpoints were analyzed at α=0.01, otherwise the endpoints in Family 2 were analyzed using α=0.0067. Family 2 contained the endpoints of IGA success at Weeks 4 and 2, Scaling=0 at Week 8, Erythema=0 at Week 8, and IGA=0 at Week 8, analyzed in that order. The secondary endpoints were analyzed using the same methods as the primary endpoint.

Protocol Amendments

Protocol 304 was amended one time after subjects began enrollment. In Protocol Amendment 2 dated 5/5/2022, the exclusion criteria related to suicidal ideation or behavior was clarified to be exclusionary and the multiplicity control strategy related to the secondary endpoints was updated to include use of the fallback method, and allowing unused α to pass from Family 1 to Family 2.

8.1.2. Study Results for Trial ARQ-1540-304

Compliance with Good Clinical Practices

The Applicant states that the trial was 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

See Section 15.2 of this Unireview.

Patient Disposition

Study 304 enrolled 457 subjects with 304 randomized to roflumilast and 153 randomized to vehicle. Nine percent of subjects withdrew from the study. The most common reason for study discontinuation were lost to follow-up and withdrawal by subject. Approximately 4% of roflumilast and 3% of vehicle subjects discontinued the trial for each of these 2 reasons.

Table 20. Subject Disposition in Study ARQ-154-304

Disposition	Roflumilast Foam 0.3%	Vehicle	Overall
Number of participants randomized	304	153	457
ITT Population	304	153	457
mITT Population	304	153	457
Completed study, n (%)	276 (90.8%)	138 (90.2%)	414 (90.6%)
Prematurely withdrawn from study, n (%)	28 (9.2%)	15 (9.8%)	43 (9.4%)
Lost To Follow-Up	12 (3.9%)	4 (2.6%)	16 (3.5%)
Withdrawal By Subject	11 (3.6%)	4 (2.6%)	15 (3.3%)

Disposition	Roflumilast Foam 0.3%	Vehicle	Overall
Adverse Event	2 (0.7%)	3 (2%)	5 (1.1%)
Lack Of Efficacy	1 (0.3%)	3 (2%)	4 (0.9%)
Other	2 (0.7%)	1 (0.7%)	3 (0.7%)

Source: Statistical Analyst; adsl.xpt.
Note:

- The ITT population includes all randomized subjects.
- The mITT population includes all randomized subjects with the exception of subjects who missed the Week 8 IGA assessment specifically due to COVID-19 disruption.
- Percentages are based on ITT population (primary analysis population).

Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat

Protocol Violations/Deviations

The incidence of protocol violations was similar on the two treatment arms with 62% of subjects on the roflumilast arm and 61% of subjects on the vehicle arm having protocol violations. The most common protocol violations were with the investigation product use (8% for roflumilast and 4% for vehicle) and visit window violations (3% for roflumilast and 5% for vehicle). Approximately 3% of subjects on each treatment arm had violations associated with COVID-19.

Table of Demographic Characteristics

The demographic characteristics were generally balanced across the two treatment arms, though more subjects less than 18 years of age were randomized to vehicle (10%) than to roflumilast (6%). Approximately 12% of subjects were 65 years of age or older. Approximately 78% of subjects were white, 11% were Black or African American, and 6% were Asian. The trial enrolled equal proportions of males and females. Approximately 21% of subjects were Hispanic or Latino.

Table 21. Demographic Characteristics in Study ARQ-154-304

Characteristic	Roflumilast Foam 0.3%	Vehicle	Overall
Number of participants randomized	304	153	457
ITT Population	304	153	457
mITT Population	304	153	457
Age (years)			
Mean (SD)	43.2 (16.81)	41.8 (17.47)	42.7 (17.03)
Median [Min, Max]	42 [9, 87]	40 [9, 83]	42 [9, 87]
Age group, years, n (%)			
9 – 17	17 (5.6%)	15 (9.8%)	32 (7%)
18 – 64	249 (81.9%)	119 (77.8%)	368 (80.5%)
>= 65	38 (12.5%)	19 (12.4%)	57 (12.5%)
Gender, n (%)			
M	153 (50.3%)	75 (49%)	228 (49.9%)
F	151 (49.7%)	78 (51%)	229 (50.1%)

Characteristic	Roflumilast Foam 0.3%	Vehicle	Overall
Ethnicity, n (%)			
Hispanic Or Latino	69 (22.7%)	28 (18.3%)	97 (21.2%)
Not Hispanic Or Latino	235 (77.3%)	125 (81.7%)	360 (78.8%)
Race, n (%)			
White	234 (77%)	122 (79.7%)	356 (77.9%)
Black Or African American	36 (11.8%)	15 (9.8%)	51 (11.2%)
Asian	18 (5.9%)	10 (6.5%)	28 (6.1%)
Other	11 (3.6%)	4 (2.6%)	15 (3.3%)
American Indian Or Alaska Native	4 (1.3%)	0	4 (0.9%)
Multiple	1 (0.3%)	1 (0.7%)	2 (0.4%)
Native Hawaiian Or Other Pacific Islander	0	1 (0.7%)	1 (0.2%)
BMI (kg/m²), n (%)			
Underweight: BMI <18.5	3 (1%)	6 (3.9%)	9 (2%)
Normal: 18.5 <= BMI <= 24.9	74 (24.3%)	40 (26.1%)	114 (24.9%)
Overweight: 25.0 <= BMI <= 29.9	104 (34.2%)	49 (32%)	153 (33.5%)
Obese: BMI >= 30.0	122 (40.1%)	58 (37.9%)	180 (39.4%)
NA	1 (0.3%)	0	1 (0.2%)

Source: Statistical Analyst; adsl.xpt.
Note:
- The ITT population includes all randomized subjects.
- The mITT population includes all randomized subjects with the exception of subjects who missed the Week 8 IGA assessment specifically due to COVID-19 disruption.
- Percentages are based on ITT population (primary analysis population).

Abbreviations: BMI, body mass, index; ITT, intent-to-treat; mITT, modified intent-to-treat

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

The majority of subjects (94%) had moderate disease at baseline, and the rate was similar on the two treatment arms.

Table 22. Baseline Disease Characteristics in Study ARQ-154-304

Characteristic	Roflumilast Foam 0.3%	Vehicle	Overall
Number of participants randomized	304	153	457
ITT Population	304	153	457
mITT Population	304	153	457
IGA Strata, n (%)			
Moderate	288 (94.7%)	142 (92.8%)	430 (94.1%)
Severe	16 (5.3%)	11 (7.2%)	27 (5.9%)

Characteristic	Roflumilast Foam 0.3%	Vehicle	Overall
Baseline IGA, n (%)			
Moderate	287 (94.4%)	141 (92.2%)	428 (93.7%)
Severe	17 (5.6%)	12 (7.8%)	29 (6.3%)

Source: Statistical Analyst; adsl.xpt.
Note:

- The ITT population includes all randomized subjects.
- The mITT population includes all randomized subjects with the exception of subjects who missed the Week 8 IGA assessment specifically due to COVID-19 disruption.
- Percentages are based on ITT population (primary analysis population).
- IGA Strata is based on the data collected in the web interactive web response system.

Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The compliance rate was similar on the two treatment arms, with a mean of 52 applications of study product on each arm. For 8 weeks of once daily treatment, the anticipated number of treatment applications was 56.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the proportion of subjects with an IGA score of clear or almost clear and at least 2-grades improvement from baseline at Week 8. The endpoint was analyzed with the Cochran-Mantel-Haenszel test stratified by baseline IGA strata and pooled study site. IGA success at Weeks 2 and 4 were secondary endpoints. The primary efficacy endpoint of IGA success at Week 8 was statistically significant ($p<0.0001$) with risk difference estimate of 21%. The results for the secondary endpoints of IGA success at Weeks 2 and 4 were also statistically significant under the prespecified multiplicity control scheme ($p<0.0001$).

Table 23. IGA Success (Clear or Almost Clear With at Least 2 Grades Reduction) by Visit in Study ARQ-154-304 (ITT)

IGA Status	Roflumilast Foam 0.3%	Vehicle
Number of participants randomized	304	153
ITT Population	304	153
Completed study, n (%)	276 (90.8%)	138 (90.2%)
Week 2		
IGA Success	43.0%	25.7%
Difference from Vehicle (95% CI)	19.0% (9.96, 28.07)	
p-value		< 0.0001
Week 4		
IGA Success	73.1%	47.1%
Difference from Vehicle (95% CI)		26.1% (16.39, 35.73)
p-value		< 0.0001

IGA Status	Roflumilast Foam 0.3%	Vehicle
Week 8		
IGA Success	79.5%	58.0%
Difference from Vehicle (95% CI)	20.6% (11.15, 30.04)	
p-value	< 0.0001	

Source: Statistical Analyst; adsl.xpt, admi.xpt.
Note:
- The ITT population includes all randomized subjects.
- IGA success is defined as an IGA score of "Clear" or "Almost Clear" plus a ≥2-grade improvement from baseline.
- The proportion difference and its p-value are obtained from CMH method stratified by pooled site and IGA strata.

Abbreviations: ITT, intent-to-treat

Approximately 9% of subjects on each arm did not have observed efficacy data at Week 8. The Applicant conducted a tipping point analysis that shifted the imputed IGA score for subjects with missing data by up to 2 units in either direction in the multiple imputation procedure relative to what would be imputed in a missing at random imputation. Under the worst-case scenario, where subjects on the roflumilast arm with missing data were shifted by increasing the imputed IGA by 2 units and subjects on the vehicle arm with missing data were shifted by decreasing the imputed IGA by 2 units, the tipping point analysis had a p-value 0.0070. Thus, the conclusions are robust to the handling of missing data.

The treatment effects for IGA success rates were generally consistent across the demographic subgroups, favoring roflumilast in each subgroup.

Table 24. IGA Success by Demographic Subgroups in Study ARQ-154-304 (ITT)

IGA Status by Subgroup	Roflumilast Foam 0.3%	Vehicle
Age Group		
9 – 17 (n=17, 15)		
IGA Success	76.5%	46.7%
Difference from Vehicle (95% CI)		NE (NE, NE)
p-value		NE
18 – 64 (n=249, 119)		
IGA Success	79.5%	58.6%
Difference from Vehicle (95% CI)		20.5% (9.69, 31.28)
p-value		0.0002
>= 65 (n=38, 19)		
IGA Success	80.8%	63.2%
Difference from Vehicle (95% CI)		23.6% (-8.30, 55.46)
p-value		0.1471
Sex		
Male (n=153, 75)		
IGA Success	79.5%	64.1%
Difference from Vehicle (95% CI)		12.0% (-1.91, 25.99)
p-value		0.0908
Female (n=151, 78)		
IGA Success	79.5%	52.1%
Difference from Vehicle (95% CI)		25.0% (11.04, 37.87)
p-value		0.0004

IGA Status by Subgroup	Roflumilast Foam 0.3%	Vehicle
Race		
White (n=234, 122)		
IGA Success	80.3%	57.2%
Difference from Vehicle (95% CI)		21.9% (11.19, 32.61)
p-value		< 0.0001
Black or African American (n=36, 15)		
IGA Success	71.5%	59.4%
Difference from Vehicle (95% CI)		29.0% (-7.11, 65.18)
p-value		0.1154
Other (n=34, 16)		
IGA Success	82.0%	62.5%
Difference from Vehicle (95% CI)		20.0% (-19.64, 59.72)
p-value		0.3223
Ethnicity		
Hispanic or Latino (n=69, 28)		
IGA Success	77.5%	70.8%
Difference from Vehicle (95% CI)		6.3% (-18.20, 30.78)
p-value		0.6148
Not Hispanic or Latino (n-235, 125)		
IGA Success	80.0%	55.1%
Difference from Vehicle (95% CI)		24.3% (13.79, 34.83)
p-value		< 0.0001
Baseline IGA Severity		
Moderate (n=288, 142)		
IGA Success	80.2%	59.4%
Difference from Vehicle (95% CI)		20.2% (10.59, 29.76)
p-value		< 0.0001
Severe (n=16, 11)		
IGA Success	66.5%	41.7%
Difference from Vehicle (95% CI)		40.7% (-15.51, 96.99)
p-value		0.1557

Source: Statistical Analyst; adsl.xpt, admi.xpt.
Note:

- The ITT population includes all randomized subjects.
- IGA success is defined as an IGA score of "Clear" or "Almost Clear" plus a ≥2-grade improvement from baseline.
- The proportion difference and its p-value are obtained from CMH method stratified by pooled site and IGA strata or unstratified if it was not estimable.

Abbreviations: ITT, intent-to-treat

Data Quality and Integrity

No issues with data quality or integrity were identified with Study 304.

Efficacy Results – Secondary and other relevant endpoints

The secondary endpoint results were supportive of the primary efficacy endpoints. The efficacy results for the secondary endpoints based on IGA success are discussed above. The WI-NRS success endpoints, where success is defined as ≥4-point improvement from baseline were statistically significant at Weeks 8, 4, and 2 ($p \leq 0.0005$). The risk difference estimates ranged from 18% to 26% at the three timepoints.

Table 25. WI-NRS Success (≥4-Point Improvement From Baseline) by Visit in Study ARQ-154-304 (PRU4-ITT)

WI-NRS Status	Roflumilast Foam 0.3%	Vehicle
Number of participants randomized	304	153
PRU4-ITT Population	206	98
Completed study, n (%)	187 (90.8%)	87 (88.8%)
Week 2		
WI-NRS Success	32.7%	15.5%
Difference from Vehicle (95% CI)	18.2% (7.92, 28.54)	
p-value		0.0005
Week 4		
WI-NRS Success	47.6%	29.1%
Difference from Vehicle (95% CI)		21.6% (9.90, 33.23)
p-value		0.0003
Week 8		
WI-NRS Success	62.8%	40.6%
Difference from Vehicle (95% CI)	25.7% (13.35, 38.10)	
p-value	< 0.0001	

Source: Statistical Analyst; adsl.xpt, admiwin.xpt.
Note:
- The ITT population includes subjects with average weekly WI-NRS pruritus score ≥4 at Baseline.
- WI-NRS success is defined as achievement of a ≥4-point improvement from baseline.
- The proportion difference and its p-value are obtained from CMH method stratified by pooled site and IGA strata.

Abbreviations: PRU, pruritus; ITT, intent-to-treat

The remaining secondary endpoints were defined as response rates based achieving a score of 0 on the scaling, erythema, and IGA scales. These endpoints were statistically significant under the multiplicity control scheme ($p<0.0001$). The risk difference estimates ranged from 21% to 27%.

Table 26. Additional Secondary Endpoints at Week 8 in Study ARQ-154-304 (ITT)

Secondary Endpoint	Roflumilast Foam 0.3%	Vehicle
Number of participants randomized	304	153
ITT Population	304	153
Completed study, n (%)	276 (90.8%)	138 (90.2%)

Secondary Endpoint	Roflumilast Foam 0.3%	Vehicle
Scaling		
Score of 0 at Week 8	58.1%	36.5%
Difference from Vehicle (95% CI)	20.9% (11.07, 30.82)	
p-value		< 0.0001
Erythema		
Score of 0 at Week 8	57.8%	32.0%
Difference from Vehicle (95% CI)		26.8% (17.36, 36.27)
p-value		< 0.0001
IGA		
Score of 0 at Week 8	50.6%	27.7%
Difference from Vehicle (95% CI)	22.5% (13.22, 31.83)	
p-value	< 0.0001	

Source: Statistical Analyst; adsl.xpt, admiscal.xpt, admiery.xpt, admi.xpt.
Note:
- The ITT population includes all randomized subjects.
- The proportion difference and its p-value are obtained from CMH method stratified by pooled site and IGA strata.

Abbreviations: ITT, intent-to-treat

Dose/Dose Response

The Applicant did not conduct a dose ranging study with roflumilast foam. The Applicant selected the same dose concentration as was used in roflumilast cream for the treatment of psoriasis.

8.1.3. Trial ARQ-154-203

Trial Design

Trial ARQ-154-203 (Trial 203) is a randomized, double-blind, vehicle-controlled trial in subjects with seborrheic dermatitis. The trial enrolled subjects 18 years of age and older with moderate to severe seborrheic dermatitis. Subjects were to have up to 20% body surface area (BSA) involvement with involvement of the scalp and/or face and/or trunk and/or intertriginous areas. The trial was designed to enroll approximately 184 subjects in a 2:1 ratio to roflumilast foam or vehicle foam. Subjects were to apply treatment once daily for 8 weeks. Randomization was stratified by study site and baseline investigator's global assessment (IGA) [IGA=3 (moderate) or IGA=4 (severe)].

Study Endpoints

The primary efficacy endpoint was IGA success at Week 8, where success was defined as score of 'clear' or 'almost clear' plus at least 2-point improvement at Week 8.

The secondary endpoints were

- IGA Success at Weeks 2 and 4
- Change from baseline in Overall Scaling Score to Weeks 2, 4, and 8

- Change from baseline in Overall Erythema Score to Weeks 2, 4, and 8
- Overall Erythema success at Weeks 2, 4, and 8
- Change and percent change in WI-NRS at Weeks 2, 4, and 8
- WI-NRS success, where WI-NRS success is defined as achievement of at least a 4-point improvement in WI-NRS among subjects with an average weekly baseline WI-NRS ≥4, at Weeks 2, 4, and 8

Statistical Analysis Plan

The primary analysis population was the intent-to-treat (ITT) population, defined as all randomized subjects. Supportive analyses were based on the modified ITT (mITT) population, defined as all randomized subjects except those who missed the Week 8 IGA assessment due to COVID-19 disruption. The PRU4-ITT population was defined as all randomized subjects with a baseline WI-NRS ≥4 The primary endpoint was analyzed with the Cochran-Mantel-Haenszel test stratified by baseline IGA score and pooled study site. The protocol did not specify handling for any intercurrent events. All missing data for the primary endpoint was handled with multiple imputation. Secondary endpoints were analyzed with observed cases only.

No methods to control multiplicity across the secondary endpoints were planned. The secondary endpoints were analyzed using the same methods as the primary endpoint.

Protocol Amendments

Protocol 203 was amended one time after the trial was started (Amendment 2 dated 1/7/2020). The amendment increased the sample size to 184 subjects and clarified that subjects were to have scores of at least moderate for erythema and scaling at baseline. The sample size increase was not due to an interim analysis. The protocol also added a planned interim analysis for futility, but the Applicant decided not to conduct any interim analysis and completed the trial as initially planned, as noted in the statistical analysis plan. The statistical analysis plan also included the clarification that subjects who were unable to attend the Week 8 visit due to COVID-19 would be excluded from the efficacy analysis (mITT population). The ITT analysis was included as a sensitivity analysis.

8.1.4. Study Results for Trial ARQ-154-203

Compliance With Good Clinical Practices

The Applicant states that the trial was 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

See Section 15.2 of this Unireview.

Patient Disposition

Study 203 enrolled 226 subjects, randomized 2:1 to roflumilast or vehicle. The discontinuation rates were similar on the two arms with 8% of subjects discontinuing. The most common reason for discontinuation was loss to follow-up with 4% of subjects on the roflumilast arm and 3% on the vehicle arm discontinuing for this reason. The mITT population excluded subjects who missed their Week 8 visit due to COVID-19. One subject on each treatment arm was excluded from the mITT population.

Table 27. Subject Disposition in Study ARQ-154-203

Disposition	Roflumilast Foam 0.3%	Vehicle	Overall
Number of participants randomized	154	72	226
ITT Population	154	72	226
mITT Population	153	71	224
Completed study, n (%)	141 (92.2%)	66 (93%)	207 (92.4%)
Prematurely withdrawn from study, n (%)	12 (7.8%)	5 (7%)	17 (7.6%)
Lost To Follow-Up	6 (3.9%)	2 (2.8%)	8 (3.6%)
Subject Withdrawal Of Consent	3 (2%)	1 (1.4%)	4 (1.8%)
Adverse Event	2 (1.3%)	1 (1.4%)	3 (1.3%)
Other	1 (0.7%)	0	1 (0.4%)
Protocol Violation	0	1 (1.4%)	1 (0.4%)

Source: Statistical Analyst; adsl.xpt.
Note:
- The ITT population includes all randomized subjects.
- The mITT population includes all randomized subjects with the exception of subjects who missed the Week 8 IGA assessment specifically due to COVID-19 disruption.
- Percentages are based on mITT population (primary analysis population).

Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat

Protocol Violations/Deviations

A greater proportion of subjects on the vehicle arm had protocol violations than on the roflumilast arm (56% vs. 45%). The most common protocol violations were with informed consent (5% for roflumilast and 11% for vehicle), study intervention (4% for roflumilast and 10% for vehicle) and visit window violations (4% for roflumilast and 4% for vehicle).

Table of Demographic Characteristics

Demographic characteristics were generally balanced across the two treatment arms. Study 203 enrolled adults 18 years of age and older. Eighteen percent of subjects were 65 years of age and older. The study enrolled similar proportions of male and female subjects. Approximately 82% of subjects were white, 10% were Black or African American, and 3% were Asian. Approximately 20% of subjects were Hispanic or Latino.

Table 28. Baseline Demographics in Study ARQ-154-203

Characteristic	Roflumilast Foam 0.3%	Vehicle	Overall
Number of participants randomized	154	72	226
ITT Population	154	72	226
mITT Population	153	71	224
Age (years)			
Mean (SD)	45.2 (17.06)	44.3 (16.39)	44.9 (16.82)
Median [Min, Max]	41 [19, 85]	41 [18, 85]	41 [18, 85]
Age group, years, n (%)			
18 – 64	125 (81.7%)	58 (81.7%)	125 (81.7%)
>= 65	28 (18.3%)	13 (18.3%)	41 (18.3%)
Gender, n (%)			
M	75 (49%)	40 (56.3%)	115 (51.3%)
F	78 (51%)	31 (43.7%)	109 (48.7%)
Ethnicity, n (%)			
Hispanic Or Latino	29 (19%)	16 (22.5%)	45 (20.1%)
Not Hispanic Or Latino	124 (81%)	55 (77.5%)	179 (79.9%)
Race, n (%)			
White	123 (80.4%)	61 (85.9%)	184 (82.1%)
Black Or African American	17 (11.1%)	6 (8.5%)	23 (10.3%)
Asian	6 (3.9%)	1 (1.4%)	7 (3.1%)
Multiple	5 (3.3%)	1 (1.4%)	6 (2.7%)
Other	1 (0.7%)	2 (2.8%)	3 (1.3%)
American Indian Or Alaska Native	1 (0.7%)	0	1 (0.4%)
BMI (years)			
Mean (SD)	30.7 (6.67)	29.5 (5.81)	30.3 (6.42)
Median [Min, Max]	29.6 [18.9, 54.6]	27.6 [20.3, 47.1]	29.4 [18.9, 54.6]

Source: Statistical Analyst; adsl.xpt.
Note:
- The ITT population includes all randomized subjects.
- The mITT population includes all randomized subjects with the exception of subjects who missed the Week 8 IGA assessment specifically due to COVID-19 disruption.
- Percentages are based on mITT population (primary analysis population).

Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

The majority of subjects had moderate disease at baseline (93%), with a slightly higher proportion of subjects on the roflumilast arm having severe disease (8% vs. 4%).

Table 29. Baseline Disease Characteristics in Study ARQ-154-203

Characteristic	Roflumilast Foam 0.3%	Vehicle	Overall
Number of participants randomized	154	72	226
ITT Population	154	72	226
mITT Population	153	71	224

Characteristic	Roflumilast Foam 0.3%	Vehicle	Overall
Baseline IGA, n (%)			
Moderate	140 (91.5%)	68 (95.8%)	208 (92.9%)
Severe	13 (8.5%)	3 (4.2%)	16 (7.1%)

Source: Statistical Analyst; adsl.xpt.
Note:
- The ITT population includes all randomized subjects
- The mITT population includes all randomized subjects with the exception of subjects who missed the Week 8 IGA assessment specifically due to COVID-19 disruption.
- Percentages are based on mITT population (primary analysis population).

Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The compliance rate was similar on the two treatment arms, with a mean of 53 applications of study product on each arm. For 8 weeks of once daily treatment, the anticipated number of treatment applications was 56.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the proportion of subjects with an IGA score of clear or almost clear and at least 2-grades improvement from baseline at Week 8. The endpoint was analyzed with the Cochran-Mantel-Haenszel test stratified by baseline IGA strata and pooled study site. IGA success at Weeks 2 and 4 were secondary endpoints. The primary efficacy endpoint of IGA success at Week 8 was statistically significant ($p<0.0001$) with risk difference estimate of 34%. The results for the mITT and ITT population were very similar, as the analysis differs only by the results of 2 subjects. Although the mITT population was specified as the primary analysis population, to account for all subjects in the analysis and for consistency with the results for Study 304, The protocol did not include a plan to control multiplicity across the secondary endpoints, thus they cannot be formally analyzed for statistical significance; however, the results are consistent with those observed in Study 304.

Table 30. IGA Success (Clear or Almost Clear With at Least 2 Grades Reduction) by Visit in Study ARQ-154-203 (mITT, ITT)

IGA Status	Roflumilast Foam 0.3%	Vehicle
Number of participants randomized	154	72
ITT Population	154	72
Completed study, n (%)	141 (91.2%)	67 (93.1%)
Week 2		
IGA Success	34.4%	14.4%
Difference from Vehicle (95% CI)		20.0% (8.62, 31.34)
p-value		0.0006
Week 4		
IGA Success	57.3%	30.3%
Difference from Vehicle (95% CI)		27.6% (14.35, 40.91)
p-value		< 0.0001

IGA Status	Roflumilast Foam 0.3%	Vehicle
Week 8		
IGA Success	73.1%	40.8%
Difference from Vehicle (95% CI)		33.8% (20.27, 47.38)
p-value		< 0.0001
mITT Population	153	71
Completed study, n (%)	141 (92.2%)	66 (93.0%)
Week 2		
IGA Success	34.2%	14.6%
Difference from Vehicle (95% CI)		19.8% (8.36, 31.25)
p-value		0.0007
Week 4		
IGA Success	57.2%	29.3%
Difference from Vehicle (95% CI)		28.8% (15.68, 41.97)
p-value		< 0.0001
Week 8		
IGA Success	73.1%	40.8%
Difference from Vehicle (95% CI)		34.3% (20.88, 47.75)
p-value		< 0.0001

Source: Statistical Analyst; adsl.xpt, admi.xpt.
Note:
- The ITT population includes all randomized subjects.
- The mITT population includes all randomized subjects with the exception of subjects who missed the Week 8 IGA assessment specifically due to COVID-19 disruption.
- IGA success is defined as an IGA score of "Clear" or "Almost Clear" plus a ≥2-grade improvement from baseline.
- The proportion difference and its p-value are obtained from CMH method stratified by pooled site and baseline IGA.

Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat

Approximately 8% of subjects on each arm did not have observed efficacy data at Week 8. In a 'worst case' analysis where subjects on the roflumilast arm with missing data were imputed as failures and subjects on the vehicle arm with missing data were imputed as responders, the IGA response rates would be 68% vs 45% with p<0.0001 for the mITT population under this 'worst case' imputation, rather that 73% vs 41% with p<0.0001 for the mITT population with protocol-specified missing data handling using multiple imputation. Thus the conclusions are robust to the handling of missing data.

The treatment effects for IGA success rates were generally consistent across the demographic subgroups, favoring roflumilast in each subgroup.

Table 31. IGA Success by Demographic Subgroups in Study ARQ-154-203 (ITT)

IGA Status by Subgroup	Roflumilast Foam 0.3%	Vehicle
Age Group		
18 – 64 (n=125, 58)		
IGA Success	72.3%	44.4%
Difference from Vehicle (95% CI)		29.0% (14.10, 43.82)
p-value		0.0001
>= 65 (n=28, 13)		

IGA Status by Subgroup	Roflumilast Foam 0.3%	Vehicle
IGA Success	76.7%	24.3%
Difference from Vehicle (95% CI)		63.5% (28.23, 98.81)
p-value		0.0004
Sex		
Male (n=76, 40)		
IGA Success	81.9%	45.7%
Difference from Vehicle (95% CI)		36.5% (17.37, 55.64)
p-value		0.0002
Female (n=78, 32)		
IGA Success	64.6%	34.3%
Difference from Vehicle (95% CI)		35.4% (14.78, 56.01)
p-value		0.0008
Race		
White (n=123, 62)		
IGA Success	73.3%	42.5%
Difference from Vehicle (95% CI)		34.2% (19.23, 49.22)
p-value		< 0.0001
Black or African American (n=17, 6)		
IGA Success	63.5%	33.3%
Difference from Vehicle (95% CI)		30.1% (-14.85, 75.15)
p-value		0.1891
Other (n=14, 4)		
IGA Success	83.9%	25.0%
Difference from Vehicle (95% CI)		37.5% (-27.25, 100.00%)
p-value		0.2563
Ethnicity		
Hispanic or Latino (n=29, 16)		
IGA Success	56.5%	41.5%
Difference from Vehicle (95% CI)		19.4% (-13.27, 52.15)
p-value		0.2442
Not Hispanic or Latino (n=125, 56)		
IGA Success	77.0%	40.6%
Difference from Vehicle (95% CI)		37.4% (21.92, 52.79)
p-value		< 0.0001
Baseline IGA Severity		
Moderate (n=141, 69)		
IGA Success	73.5%	42.4%
Difference from Vehicle (95% CI)		32.5% (18.94, 46.13)
p-value		< 0.0001
Severe (n=13, 3)		

IGA Status by Subgroup	Roflumilast Foam 0.3%	Vehicle
IGA Success	68.1%	3.5%
Difference from Vehicle (95% CI)		64.7% (27.60, 100.00)
p-value		0.0006

Source: Statistical Analyst; adsl.xpt, admi.xpt.
Note:

- The ITT population includes all randomized subjects.
- IGA success is defined as an IGA score of "Clear" or "Almost Clear" plus a ≥2-grade improvement from baseline.
- The proportion difference and its p-value are obtained from CMH method stratified by pooled site and IGA strata or unstratified if it was not estimable.

Abbreviations: ITT, intent-to-treat

Data Quality and Integrity

No issues related to data quality or integrity were identified in Study 203.

Efficacy Results – Secondary and other relevant endpoints

Because Study 203 was designed as Phase 2 trial, the protocol did not include multiplicity adjustments for the secondary endpoints. However, the results on the secondary endpoints that are consistent with those in Study 304 are supportive of the primary endpoint. Because the secondary endpoints were not adjusted for multiplicity, only the primary efficacy endpoint is appropriate for inclusion in labeling. IGA success at Weeks 2 and 4 is discussed above. The WI-NRS success endpoints, where success is defined as ≥4-point improvement from baseline had trends consistent with the treatment effect observed on the primary endpoint. The risk difference estimate was approximately 30% at each of the three timepoints. Thus, the findings on this endpoint are also supportive of the findings on the WI-NRS endpoint results in Study 304. Note that the protocol-specified analyses of these endpoints did not incorporate missing data handling.

Table 32. WI-NRS Success (≥4-Point Improvement) From Baseline by Visit in Study ARQ-154-203 (PRU4-mITT)

WI-NRS Status	Roflumilast Foam 0.3%	Vehicle
Number of participants randomized	154	72
PRU4-mITT Population	125	58
Week 2		
WI-NRS Success	52.8%	23.2%
Difference from Vehicle (95% CI)		28.4% (13.98, 42.89)
p-value		0.0007
Week 4		
WI-NRS Success	58.3%	28.3%
Difference from Vehicle (95% CI)		29.0% (13.22, 44.75)
p-value		0.0009

WI-NRS Status	Roflumilast Foam 0.3%	Vehicle
Week 8		
WI-NRS Success	64.6%	34.0%
Difference from Vehicle (95% CI)		29.9% (13.3, 46.4)
p-value		0.0007

Source: Statistical Analyst; adsl.xpt, admiwin.xpt
Note:
- The PRU4-mITT population includes subjects with average weekly WI-NRS pruritus score ≥4 at Baseline.
- WI-NRS success is defined as achievement of a ≥4-point improvement from baseline.
- The proportion difference and its p-value are obtained from CMH method stratified by pooled site and IGA strata.

Abbreviations: PRU, pruritus

8.1.5. Assessment of Efficacy Across Trials

Efficacy on the primary efficacy endpoint of IGA success at Week 8 was demonstrated in both Studies 304 and 203. The risk difference estimates in the two studies were 21% and 34%. Most of the difference in the treatment effects was due to a higher vehicle response rate in Study 304 relative to Study 203.

Table 33. IGA Success (Clear or Almost Clear With at Least 2 Grades Reduction) in Studies ARQ-154-304 and ARQ-154-203 (ITT)

	Study ARQ-154-304		Study ARQ-154-203	
IGA Status	Roflumilast Foam 0.3%	Vehicle	Roflumilast Foam 0.3%	Vehicle
ITT Population	304	153	154	72
IGA Success	79.5%	58.0%	73.1%	40.8%
Difference from Vehicle (95% CI)	20.6% (11.2, 30.0)		33.8% (20.3, 47.4)	
p-value	< 0.0001		< 0.0001	

Source: Statistical Analyst; adsl.xpt, admi.xpt.
Note:
- The ITT population includes all randomized subjects.
- IGA success is defined as an IGA score of "Clear" or "Almost Clear" plus a ≥2-grade improvement from baseline.
- The proportion difference and its p-value are obtained from CMH method stratified by pooled site and IGA strata.

Abbreviations: ITT, intent-to-treat

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety evaluation of roflumilast foam, 0.3% QD for topical treatment of subjects with seborrheic dermatitis (SD) relied on pooled safety data from one Phase 2 (ARQ-154-203) and one Phase 3 (ARQ-154-304) randomized ®, double-blind (DB), placebo-controlled (PC) trial which shared similar inclusion/exclusion criteria, study designs, dosing regimen, treatment durations (8 weeks), and primary and secondary efficacy endpoints; were included in the ISS integrated analysis and comprised the safety population for the pooled vehicle-controlled (VC) studies. TEAEs ongoing at the 8-week visit were followed to their resolution, or up to one month after last study drug application.

Additionally, the Applicant submitted supportive safety data (under individual study reports) from a Phase 2, open-label, long-term safety study (ARQ-154-214) of up to 26 weeks (extended to up to 52 weeks) duration, and a Phase 1 open-label, maximal use/PK study (MuST: ARQ-154-116) conducted for this drug product.

During 4 clinical studies ARQ-154-116/-203/-214/-304 in the roflumilast foam development program, 787 subjects were exposed to roflumilast foam, 0.3% at least once, including 329 subjects exposed for ≥24 weeks and 41 subjects exposed for ≥52 weeks. For the pooled VC studies, the mean number of drug applications were 52.5 for roflumilast group and 52.1 for the vehicle group.

To determine the safety profile of roflumilast foam, 0.3% QD for the treatment of SD, the review team analyzed the data for exposure, demographics, baseline characteristics, TEAEs [including severe TEAEs, SAEs, adverse events leading to discontinuation (AELD)], physical examinations, vital signs, weight, local tolerability assessments (LTA), pigmentation assessments, clinical laboratory parameters (hematology, chemistry, urinalysis), urine pregnancy tests for female subjects of child-bearing potential, and psychiatric assessments (PHQ-8/PHQ-A/CDI-2, C-SSRS). No Adverse events of special interest (AESI) were prespecified.

8.2.2. Review of the Safety Database

Overall Exposure

Overall exposure to roflumilast foam, 0.3% in terms of frequency, duration and target population was adequate for the evaluation of safety. In the pooled VC trials safety population, 417/458 (91.0%) subjects in the roflumilast group and 205/225 (91.1%) subjects in the vehicle group completed treatment with the study drug at Week 8.

Adverse Events Leading to Discontinuation from treatment (AELDs) were reported for 4/458 (0.9%) subjects in the roflumilast group and 5/225 (2.2%) subjects in the vehicle group during treatment period (Weeks 0-8).

The Demographic Characteristics of the safety population at baseline were well-balanced across treatment groups and representative of the target population. Refer to Section 8.1 of this Unireview for details of Subject Disposition.

Adequacy of the Safety Database

The safety database presented by the Applicant is adequate to characterize the safety profile of roflumilast foam for the treatment of subjects with moderate to severe seborrheic dermatitis. Safety assessments were reasonable and consistent with known adverse events for roflumilast in the target population:

- The size of safety database is adequate. A total of 787 subjects received at least one dose of roflumilast foam, 0.3% (including 683 subjects in the VC trials); of which 329 subjects were treated for ≥24 weeks and 41 subjects were treated for ≥52 weeks.

- The total subject exposure to roflumilast foam, 0.3% provides adequate data for the evaluation of safety. The Mean (SD) for the number of study drug applications were 52.5 (11.8) in the roflumilast group and 52.1 (13.2) in the vehicle group in the VC pool, and 154.5 (77.9) in the roflumilast group for the open-label, LTS study.
- The demographics of the study population are sufficiently representative of the target population as presented in Table 34.

Table 34. Demographic and Baseline Disease Characteristics: Roflumilast Foam, 0.3% Once a Day for Seborrheic Dermatitis (Safety Population)

	Vehicle-Controlled (VC) Studies Pool: ARQ-154-203 and ARQ-154-304		Open-label LTS Study: ARQ-154-214
Characteristic	**Roflumilast foam, 0.3% (n=458)**	**Vehicle foam (n=225)**	**Roflumilast foam, 0.3% (N=400)**
Age (years)			
Mean (SD)	43.9 (16.9)	42.6 (17.1)	43.4 (16.4)
Median (Min to Max)	42.0 (9, 87)	41.0 (9, 85)	40.0 (12, 85)
Age group (years), n (%)			
≥9 and ≤17	17 (3.7)	15 (6.7)	13 (3.3)
≥18 and ≤64	375 (81.9)	178 (79.1)	330 (82.5)
≥65	66 (14.4)	32 (14.2)	57 (14.3)
Sex, n(%)			
Male	229 (50.0)	115 (51.1)	197 (49.3)
Female	229 (50.0)	110 (48.9)	203 (50.8)
Race, n(%)			
American Indian or Alaska native	5 (1.1)	0	0
Asian	25 (5.5)	11 (4.9)	17 (4.3)
Black or African American	53 (11.6)	21 (9.3)	51 (12.8)
Native Hawaiian or other Pacific Islander	0	1 (0.4)	1 (0.3)
White	357 (77.9)	184 (81.8)	319 (79.8)
Other	12 (2.6)	6 (2.7)	6 (1.5)
Multiple	6 (1.3)	2 (0.9)	3 (0.8)
Missing	0	0	3 (0.8)
Ethnicity, n(%)			
Hispanic or Latino	98 (21.4)	44 (19.6)	115 (28.8)
Not Hispanic or Latino	360 (78.6)	181 (80.4)	283 (70.9)
Unknown/unreported	0	0	2 (0.5)
Weight (Kg)			
Mean (SD)	86.5 (21.4)	86.1 (23.9)	87.7 (23.0)
Median (Min to Max)	83.4 (30.6, 162.7)	82.8 (32.9, 203.1)	83.6 (38.6, 206.4)
BMI (Kg/m^2)			
Mean (SD)	29.9 (6.6)	29.5 (7.5)	30.2 (7.0)
Median (Min to Max)	29.0 (17.8, 54.6)	27.7 (16.9, 63.1)	28.7 (15.1, 59.4)
BSA(%) affected by SD			
Mean (SD)	3.0 (2.2)	3.0 (2.4)	3.3 (3.1)
Median (Min to Max)	2.5 (0.1, 16.0)	2.0 (0.2, 20.0)	2.3 (0.0, 20.0)

	Vehicle-Controlled (VC) Studies Pool: ARQ-154-203 and ARQ-154-304		Open-label LTS Study: ARQ-154-214
Characteristic	**Roflumilast foam, 0.3% (n=458)**	**Vehicle foam (n=225)**	**Roflumilast foam, 0.3% (N=400)**
Baseline IGA, n (%)			
Clear (0)	0	0	14 (3.5)
Almost Clear (1)	0	0	33 (8.3)
Mild (2)	0	0	20 (5.0)
Moderate (3)	428 (93.4)	210 (93.3)	296 (74.0)
Severe (4)	30 (6.6)	15 (6.7)	37 (9.3)

Source: Adapted from NDA 217242, M 2.7.4 (SCS) Section 1.3.1, Tables 8, 10 (Pages 35, 37). Consistent with Clinical Reviewer's JMP Clinical 8.1 analysis.
Abbreviations: BMI, body mass index, BSA, body surface area; IGA, Investigator Global Assessment; SD, standard deviation

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of data submitted is adequate to characterize the safety and efficacy of roflumilast foam, 0.3% for the treatment of moderate to severe seborrheic dermatitis. The review team discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

An AE was defined as any untoward medical occurrence, including illness, sign, symptoms, clinically significant laboratory abnormalities, or disease temporally associated with the use of the drug, in a subject administered the drug product. AEs did not necessarily have a causal relationship to the study drug. AEs that occur after the first application of study drug through the end of the study are recorded in the subject's medical record and the eCRF (as TEAEs). SAEs were recorded from the time the informed consent was signed. TEAEs and clinically significant abnormal laboratory test values were evaluated by the Investigators, treated and/or followed up for up to one month after the end of treatment, until the symptoms or values return to the subject's baseline value, or acceptable levels, as judged by the Investigator. TEAEs were documented at each study visit as observed by the investigators or reported by subjects.

Application site reactions, based on the protocol-specified Berger and Bowman Scoring Scale for skin irritation, were considered TEAEs if they required intervention, suspension, or discontinuation of study drug.

The investigators categorized AEs by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities version 24.1. The Applicant assessed TEAEs by the number of subjects reporting one or more adverse events. Each subject reporting a TEAE was counted once at each level of Medical Dictionary for Regulatory Activities summarization (PT or SOC). Both verbatim terms and preferred terms were included in the data files for Phase 2 and 3 trials, and there was good correlation between the verbatim and preferred terms used. No new safety signals emerged from the review of TEAEs.

Investigators categorized AEs for seriousness, causality, event name (diagnosis/signs and symptoms), duration, maximum intensity (severity), action taken regarding the study drug (including any treatment given), and outcome of AEs.

SAEs were any AE that resulted in death, was immediately life-threatening, required (or prolonged) hospitalization, resulted in persistent disability or incapacity, resulted in a congenital anomaly or birth defect, or a medically important event that may have required medical or surgical intervention to prevent one of the outcomes listed above.

Severity of AEs were assessed by investigators using the National Institutes of Health National Cancer Institute Common Terminology Criteria for Adverse Events (NIH NCI CTCAE) toxicity grading scale 5-point severity scale [Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), and Grade 5 (death)].

Causality of AEs (relationship to study drug as Unrelated, Unlikely, Possibly, Probably, or Likely) were assessed by investigators as "Suspected" or " Not Suspected"(related or unrelated) based on positive temporal relationship to the study drug, reasonable possibility of association of AE with underlying or concomitant illness or therapy, whether the AE was related to study procedures or lack of efficacy, and existence of a likely alternative etiology.

Adverse events of special interests were not prespecified in the Protocol. However, the Applicant reported the frequency of TEAEs associated with depression/suicidal ideation and behaviors and weight decrease (which are included in the Warnings and Precautions label of oral roflumilast (Daliresp) tablet) and gastrointestinal AEs (associated with the PDE-4 mechanism of action and reported as AEs for oral roflumilast and oral apremilast tablets).

The Applicant's assessment of adverse events conducted for the VC studies and the LTS study appears reasonable and appropriate. The Applicant reported accurate definitions of treatment emergent adverse events, serious adverse events, and severity of adverse events.

Routine Clinical Tests

The Applicant performed clinical laboratory evaluations (chemistry, hematology, urinalysis, and serum/urine pregnancy tests), physical examinations, vital signs measurements, psychiatric assessments (C-SSRS, PHQ-8, PHQ-A/CDI-2 (except in Study ARQ-154-203)), local tolerability assessment (LTA) by investigator/subject, and pigmentation assessments according to the schedules of activities during the VC trials and the LTS study. No ECGs were conducted during Phase 2 or Phase 3 trials.

8.2.4. Safety Results

Deaths

One death was reported in the roflumilast foam clinical development program for SD in an 81-year-old male (Subject (b) (6) in the LTS study, ARQ-154-214). The last roflumilast dose was on D 84. Subject was diagnosed with the SAE of malignant brain neoplasm on D 185 and died on D

192. The SAE/death was assessed as unrelated to study drug by the investigator. An autopsy was performed. However, no autopsy results or additional information was provided.

Serious Adverse Events

In the VC trials pool, one SAE was reported in 1/458 (0.2%) subject in the roflumilast group and 0 subjects in the vehicle group:

- Subject ARQ-154-304 (b) (6): SAE of Keratoacanthoma

A 75-year-old male subject with history of squamous cell carcinoma (SCC) was reported with SAE/severe AE of keratoacanthoma on the right forearm (not at drug application site) on D 20, assessed by the investigator as unrelated to study drug, and resolved on D 28. Study drug was continued and subject completed the study.

In the open-label LTs study, ARQ-154-214, SAEs were reported for the 7 subjects listed in Table 35.

Table 35. Serious Adverse Events (SAE) in Subjects Treated With Roflumilast Foam, 0.3% in the LTS Study ARQ-154-214 (Safety Population)

Subject ID/ Age (years)/Sex	PT(s)	Start Day/End Day	Severity (CTCAE Toxicity Grade	Relationship To roflumilast/ Outcome	Action taken
(b) (6) 81/M	Brain neoplasm malignant	185/192	5 death	Unrelated Fatal	Study drug withdrawn
(b) (6) 33/F	COVID-19 pneumonia	97/99	4 life-threatening	Unrelated Recovered/resolved	Not applicable
(b) (6) 61/M	Performance status decreased	116/126	3 severe	Unrelated Recovered/resolved	Dose not changed
(b) (6) 17/M	Hypertension	175/179	3 severe	Unrelated Recovered/resolved	Study drug interrupted
(b) (6) 42/M	Small intestinal obstruction	134/135	3 severe	Unrelated Recovered/resolved	Dose not changed
(b) (6) 52/M	Cerebrovascular accident	91/96	3 severe	Unrelated Recovered/resolved	Study drug interrupted
(b) (6) 47/F	Abdominal pain	131/132	3 severe	Unrelated Recovered/resolved	Study drug interrupted

Source: Adapted from NDA 217242, M. 2.7.4, Tables 14-15. Consistent with Clinical Reviewer's JMP Clinical 8.1 analysis.

Dropouts and/or Discontinuations Due to Adverse Effects

In the VC trials pool, 8 AELDs were reported in 4/458 (0.9%) subjects in the roflumilast group, compared to 6 AELDs in 5/225 (2.2%) subjects in the vehicle group (Application site pain(1), Application site dysaesthesia (1), Application site irritation (1), Depression (1), and Seborrheic dermatitis (2)). No AELD was an SAE.

In the open-label LTs study, ARQ-154-214, 8 AELDs were reported for 5/400 (crude incidence rate of 1.3%) subjects. The only AELD, also reported as an SAE, was the brain neoplasm

malignant reported under Deaths. The AELDs reported for the VC pool and the LTS study are summarized in the following table.

Table 36. Adverse Events Leading to Study Drug Discontinuations (AELD) in Subjects Treated With Roflumilast Foam, 0.3% in the VC Pool and the LTS Study (Safety Population)

(Study)/ Subject ID/ Age (years)/Sex	PT(s)	Start Day/End Day	Severity (CTCAE Toxicity Grade	Relationship To roflumilast	Outcome
VC pool					
ARQ-154-304/ (b) (6) /37/F	Abdominal pain	4/15	2 moderate	Probably related	Recovered/resolved
	Diarrhoea	5/12			
	Haematochezia	9/9	1 mild		
ARQ-154-304/ (b) (6) /51/M	Blood potassium decreased	45/87	3 severe	Unrelated	
ARQ-154-203/ (b) (6) /27/F	Application site pain	28/46	2 moderate	Possibly related	
	Migraine	28/55		Unlikely related	
ARQ-154-203/ (b) (6) /85/F	Dyspnoea	5/8	1 mild	Unrelated	
	Blepharitis	5/ ongoing			Not recovered/not resolved
LTS study ARQ-154-214					
(b) (6) /81/M	Brain neoplasm malignant	185/192	5 death	Unrelated	Fatal
(b) (6) /49/F	Diarrhoea	4/5	1 mild	Possibly related	Recovered/resolved
	Nausea				
	Vomiting				
	Headache				
(b) (6) 58/F	Lymphadenopathy	169/ ongoing	1 mild	Unrelated	Recovering/ resolving
(b) (6) 66/F	Diffuse alopecia	86/ ongoing	2 moderate	Possibly related	Not recovered/not resolved
(b) (6) 63/M	Ocular rosacea	105/ ongoing	2 moderate	Possibly related	Not recovered/not resolved

Source: Adapted from NDA 217242, M. 2.7.4, Tables 16-18. Consistent with Clinical Reviewer's JMP Clinical 8.1 analysis.

Significant Adverse Events

The Applicant proactively assessed the frequency of weight decrease, psychiatric AEs, and gastrointestinal AEs in clinical trials of roflumilast foam because oral PDE-4 inhibitors (roflumilast and apremilast) have been associated with increased frequency of psychiatric AEs (insomnia, anxiety, and depression), weight decrease, and gastrointestinal AEs.

Additionally, the Applicant proactively assessed the frequency of weight decrease, psychiatric AEs, and gastrointestinal AEs in clinical trials of roflumilast cream for psoriasis; and concluded

that roflumilast cream was not associated with depression and weight decrease while diarrhea and nausea were reported at significantly lower rates for roflumilast cream than for oral PDE-4 inhibitors.

The Applicant proposes Nausea (1.3%), Diarrhea and Insomnia (< 1% each) as Adverse Drug Reactions of the roflumilast foam for inclusion in Sec. 6.1 of the label.

Psychiatric AEs

Prespecified assessments of depression and suicidality (PHQ-8, modified PHQ-A, CDI-2, and C-SSRS) did not raise any safety concerns for any subjects in the clinical trials of roflumilast foam.

The VC Pool

TEAEs for the SOC of Psychiatric disorders were reported in 7 (1.5%) subjects in the roflumilast group compared to 6 (2.7%) subjects in the vehicle group. Insomnia was reported with equal frequency in 4 (0.9%) subjects in the roflumilast group compared to 2 (0.9%) of subjects in the vehicle group; and is the only AE in the SOC of Psychiatric disorders included in Sec. 6 of the label for roflumilast foam. Anxiety and Depression were reported in 3 (0.7%) and 0 subjects respectively in the roflumilast group, compared to 1 (0.4%) subject and 2 (0.9%) subjects in the vehicle group. Suicidal ideation (no suicidal behavior), attributed to the recent death of a friend, was reported in a 30-year-old female subject in the roflumilast group at the end of study (Week 8) visit. Subject declined referral for mental health evaluation.

The LTS Study

TEAEs of Anxiety for 2 subjects (0.5%) and generalised anxiety disorder (GAD) for 1 subject (0.3%) were reported as mild/moderate in severity and were not reported as AELDs. TEAEs of depression were reported in 4 subjects (1.0%), including:

- Subject (b) (6) was reported with severe depression that led to study drug interruption (not an AELD), causality as unrelated and outcome as resolved.
- Three subjects ((b) (6)) were reported with mild/moderate severity, not AELD, causality as unrelated, outcome as ongoing/ongoing/resolved respectively. Subject (b) (6), a 28-year-old female, was reported with depression of moderate severity at Week 8 and suicidal ideation (not suicidal behavior) at Week 12, was referred to a mental health counselor, was discontinued from treatment, and was lost to follow-up.

Gastrointestinal AEs

The VC Pool

TEAEs for the SOC of Gastrointestinal disorders were reported in 14 (3.1%) subjects in the roflumilast group compared to 1 (0.5%) subject in the vehicle group.

Nausea and diarrhea were reported with at a frequency of 6 (1.3%) and 4 (0.9%) subjects, respectively, in the roflumilast group compared to 0 subjects each in the vehicle group; and are the only AEs in the SOC of gastrointestinal disorders to be included in Sec. 6 of the label for roflumilast foam.

The LTS Study

Nausea and diarrhea were reported in 5 (1.3%) and 4 (1.0%) subjects, respectively.

For both the VC and LTS studies, the AEs of nausea and diarrhea were reported as mild or moderate in severity, non-serious, and included 1 AELD each. AEs of diarrhea occurred early during treatment.

Weight Decrease

The VC Pool

The mean (SD) change from baseline in weight at Week 8 was -3.40 (2.1) Kg in the roflumilast group compared with +2.9 (1.8) Kg in the vehicle group. In the LTS study, the mean (SD) change from baseline in weights were -0.5 (5.2) Kg at Week 36 and +0.5 (5.2) Kg at Week 52. In general, the mean changes from baseline in subjects' weights were not considered clinically significant.

In the VC pool, no AEs for the PT of "weight decreased" was reported for any subject.

One subject reported a weight loss ≥10% of baseline body weight at Week 8 as a result of intentional diet or lifestyle modifications. A clinically significantly weight loss (≥5% from baseline) was reported for 11 subjects (2.6%) in the roflumilast group (9/11 intentional) and 7 subjects (3.4%) in the vehicle group (3/7 intentional).

In the VC pool, a shift in the body-mass index (BMI) from borderline normal BMI (18.5 kg/cm^2) and a baseline weight of 57.2 kg to underweight BMI at Week 8 was reported for 1/458 (0.2%) subject in the roflumilast group (a 22-year-old man with a history of ulcerative colitis and ileostomy lost 1.7 kg (3.0% of weight) and completed the study without any TEAEs). This shift was not considered to be a clinically significant weight loss.

The LTS Study

At Week 24 of the LTS study, 5/341 (1.5%) subjects had lost ≥10% of body weight (4/5 intentional) and 23/341 (6.7%) of subjects had lost ≥5% of body weight (15/23 intentional). At Week 52, 3/46 (6.5%) subjects had lost ≥10% of body weight (3/3 intentional) and 5/46 (10.9%) of subjects had lost ≥5% of body weight (3/5 intentional).

In the LTS study, 4 subjects (1.0%) were reported with AEs of "weight decreased" of mild severity; the cause in 3 subjects was attributed to diet, exercise, or COVID-19 infection. The fourth subject had a -5.2% weight decreased from baseline with unknown cause. No AEs of "weight decreased" was reported as an AELD, and no subject's BMI shifted from normal to underweight category.

Of the 4 subjects reported with AE of "weight decreased" in the LTS study, one subject ((b) (6)), a 47-year-old female was also reported with AEs in the SOC of gastrointestinal disorders including moderate constipation and hemorrhoids and an SAE of severe abdominal pain (attributed to an abdominal mass of unknown etiology, assessed as unrelated to study drug). The AE of weight decreased started 4 weeks prior to the onset of gastrointestinal AEs which were not considered as the causes of weight decreased.

Pregnancy

No pregnancies were reported in studies of roflumilast foam.

Severe (Grade 3) AEs

In the VC pool, severe AEs were reported in 6/458 (1.3%) subjects in the roflumilast group compared to 2/225 (0.9%) subjects in the vehicle group. In the LTS study, severe AEs were reported in 9/400 (crude incidence of 2.3%) subjects in the roflumilast group.

Treatment Emergent Adverse Events and Adverse Reactions

For the VC Pool, the incidence of TEAEs were 107/458 (23.4%) in the roflumilast group, compared to 46/225 (20.4%) in the vehicle group. The PTs reported as TEAEs in ≥1% of subjects treated with roflumilast (and more frequently than in the vehicle group) included COVID-19, nasopharyngitis, nausea, dermatitis contact, and headache as summarized in the following table.

Table 37. TEAEs by PT Reported in ≥1% of Subjects in Roflumilast Group and at a Higher Frequency Compared to Vehicle Group in the VC Pool (Safety Population)

	VC Pool	
Preferred Term	Roflumilast Foam, 0.3% (N = 458) n (%)	Vehicle Foam (N = 225) n (%)
COVID-19	12 (2.6)	5 (2.2)
Nasopharyngitis	7 (1.5)	1 (0.4)
Nausea	6 (1.3)	0
Dermatitis contact	6 (1.3)	2 (0.9)
Headache	5 (1.1)	0

Source: NDA 217242 Submission (Module 2.7.4, Table 12, Page 40). AEs were coded using MedDRA version 24.1.
Note:
- Consistent with Clinical Reviewer's analysis by Analysis Studio, Safety Explorer.
- Filters: TRT01A = "Roflumilast Foam 0.3%" and SAFFL = "Y" (Roflumilast Foam 0.3%); TRT01A = "Vehicle" and SAFFL = "Y" (Vehicle); TRTEMFL = "Y" and STUDYID = "ARQ-154-203" or "ARQ-154-304" (Adverse Events).
- For the VC Pool, Incidence is based on the weighted average incidence from each study in the pool. Weight is the proportion of sample size in each study.

Abbreviations: PT, preferred term; TEAEs, treatment-emergent adverse events

The reported frequencies (crude incidence rates) during the LTS study for the AEs listed in the table above were consistent with those reported in the VC pool.

Contact Dermatitis

For the VC pool, contact dermatitis was reported at a frequency of 6/458 (1.3%) in the roflumilast group compared to 2/225 (0.9%) in the vehicle group. Of the 6 AEs of contact dermatitis in the roflumilast group, all were mild or moderate in severity and were attributed to allergic contact dermatitis (related to poison ivy) or irritant contact dermatitis (related to insect bites); none were at the study drug application site or deemed as related to the study drug, and none led to discontinuation from treatment.

Although the AEs of contact dermatitis reported in 2 of the 3 subjects in Trial ARQ-154-203 could not initially be ruled out as caused by roflumilast (because information on whether the AEs occurred at the study drug application site was not collected), a review of the verbatim terms for these AEs confirmed that contact dermatitis occurred on the subjects' extremities (not a protocol-specified site for study drug application). (b) (4)

For the LTS study, a similar pattern for the AE of contact dermatitis was reported in 3/400 subjects.

Adverse Drug Reactions

For the VC pool, adverse drug reactions (ADRs; defined as possibly, probably, or likely related to the study drug) occurred in 11/458 (2.4%) subjects in the roflumilast group, compared to 8/225 (3.6%) subjects in the vehicle group.

(b) (4)

Laboratory Findings

Specimens for laboratory tests, including hematology, chemistry, urinalysis, and serum/urine pregnancy tests were collected according to study Schedule of Activities.

For the VC pool, mean changes from baseline to Week 8 in hematology, chemistry, and urinalysis parameters were small, similar between roflumilast and vehicle groups, and not clinically significant. Similar results were reported for laboratory measurements in the LTS.

The proportion of subjects with shifts from normal to high was similar between roflumilast and vehicle treatment groups for ALT (roflumilast, 7.3%; vehicle, 6.9%) and AST (roflumilast, 4.1%; vehicle, 4.0%). The frequency of AEs of "ALT increased" (roflumilast, 0.2%; vehicle, 0.5%) and "AST increased" (roflumilast, 0.4%; vehicle, 0.5%) were also similar between treatment groups. No subject met Hy's law criteria for hepatotoxicity.

Vital Signs

For the VC pool, mean (SD) changes from baseline to Week 8 for roflumilast group compared to vehicle group were 0.3 (10.9) versus 0.5 (12.0) mm Hg in systolic blood pressure, -0.7 (7.9) versus 0.3 (8.4) mm Hg in diastolic blood pressure, 1.5 (10.5) versus 1.1 (10.1) beats per minute in heart rate, and 0 (0.3) versus 0 (0.4) (°C) in Temperature, respectively. The changes from baseline to Week 8 in vital signs were small and not clinically significant. Results for the LTS study was similar to results for VC pool.

Electrocardiograms (ECGs)

ECG data were collected only for the Phase 1 MUsT (ARQ-154-116) during roflumilast foam clinical development program; with no clinically significant changes in ECG parameters reported.

Of note, at the EOP2 meeting for roflumilast cream, 0.3% for the treatment of psoriasis (11/5/2019), the Agency had agreed that ECG data collection would not be required for the Phase 3 trials of roflumilast cream for psoriasis based on no evidence for an adverse effect on any ECG variable.

QT

The Agency waived the requirement for a thorough QT study for roflumilast foam, 0.3% in an Advice letter dated 1/12/2023, based on the TQT study previously conducted with oral roflumilast, the vast amount of nonclinical and clinical cardiovascular safety data that exist for the oral formulation, and the pharmacokinetics and safety profile to date of ARQ-154 foam.

Immunogenicity

Not applicable to roflumilast foam, 0.3% drug product.

8.2.5. Analysis of Submission-Specific Safety Issues

Refer to the Significant Adverse Events subsection of this review for a discussion of the safety assessments for the AEs typically associated with (oral) PDE-4 inhibitors class of drugs (weight decrease, psychiatric AEs, and gastrointestinal AEs).

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Local Safety and Tolerability Assessments

In general, both investigator and subject assessments of local safety and tolerability scores were low (favorable) and similar between the roflumilast and vehicle groups in the VC pool; with a similar trend reported for the LTS study.

Local safety and tolerability assessments (by investigator [Berger and Bowman Scoring Scale] and by subject [burning/stinging]) were conducted for subjects in the VC pool and the LTS

study. Local safety and tolerability assessments used the scoring scales described in Table 38 and Table 39.

Table 38. Investigator's (Berger and Bowman) Scoring Scale

Dermal Response Scoring		Other Effects Scoring	
Score	**Definition**	**Score**	**Definition**
0	No evidence of irritation	A	Slight glazed appearance
1	Minimal erythema; barely perceptible	B	Marked glazing
2	Definite erythema, readily visible; or minimal edema; or minimal papular response	C	Glazing with peeling and cracking
3	Erythema and papules	D	Glazing with fissures
4	Definite edema	E	Film of dried serous exudates
5	Erythema, edema, and papules	F	Small petechial erosions and/or scabs
6	Vesicular eruption	G	No other effect
7	Strong reaction spreading beyond test site		

Source: NDA 217242 Submission. Modified from Module 2.7.4 (Table 98).

Table 39. Subject Local Tolerability Assessment

Grade	Sensation Following Investigational Product Application
0 (none)	No sensation
1 (mild)	Slight warm, tingling sensation; not really bothersome
2(moderate)	Definite warm, tingling sensation that is somewhat bothersome
3 (severe)	Hot, tingling/stinging sensation that has caused definite discomfort

Source: NDA 217242 Submission. Modified from Module 2.7.4 (Table 99).

Local Safety Assessment by Investigators

For subjects in the VC pool, all subjects had a score of 0 and other effects (G) at baseline. At Week 4, roflumilast group reported 1 (0.2%) subject (score 1) and 4 (1.0%) subjects (score 2) and 10 (2.4%) with slight glazed appearance (A), compared to 1 (0.5%) subject (score 1) in the vehicle group and 2 (1.0%) with slight glazed appearance (A). At Week 8, all subjects in roflumilast group had a score of and 4 (1.0%) subjects had slight glazed appearance (A).

A similar trend was observed in the LTS study.

Local Tolerability Assessment by Subjects

For subjects in the VC pool, the proportion of subjects with a score (0) increased over time from baseline (48%) to Week 8 (63.7%) and were greater than the corresponding proportions for subjects in the vehicle group. A trend towards a decrease in the proportion of subjects with scores of 1, 2, or 3 at baseline from baseline to Week 8 was reported, which were lower than the percentages for the corresponding subjects in the vehicle group.

A similar trend was observed in the LTS study.

Hyperpigmentation and Hypopigmentation

Hypopigmentation and hyperpigmentation were assessed for subjects in the VC pool and the LTS study and scored individually using a grade (0-3) of none (0), mild (1), moderate (2), and severe (3). Hypopigmentation and hyperpigmentation were less frequent in white subjects, and most subjects reported improvement during the trials. New or worsening hypopigmentation and hyperpigmentation were uncommon.

Hypopigmentation

For the VC pool, the reported frequency of mild and moderate hypopigmentation improved from baseline to Week 8 for both roflumilast and vehicle groups. For roflumilast group, [mild: 13 (2.8%) to 8 (1.9%); moderate: 5 (1.1%) to 2 (0.5%)], and for vehicle group [mild: 11 (4.9%) to 2 (1.0%); moderate: 0]. New or worsening hypopigmentation each was reported for 1 (0.2%) subject in the roflumilast group at Week 8.

A similar trend was reported for the LTS study with the frequency of mild/moderate/severe hypopigmentation at baseline and Week 52, respectively, of 15 (3.8%)/18 (4.5%)/1 (0.3%) to 3 (6.5%)/1 (2.2%)/0.

Hyperpigmentation

For the VC pool, the reported frequency of mild and moderate hyperpigmentation improved from baseline to Week 8 for both roflumilast and vehicle groups. For roflumilast group, [mild: 15 (3.3%) to 8 (1.9%); moderate: 6 (1.3%) to 3 (0.7%)], and for vehicle group [mild: 6 (2.7%) to 4 (2.0%); moderate: 4 (1.8%) to 2 (1.0%)]. Severe new hyperpigmentation was reported for 1 (0.2%) subject in the roflumilast group and 1 (0.5%) subject in the vehicle group at Week 8.

Overall, the improvement in the frequency of subjects with any severity of hyperpigmentation from baseline to Week 8 in the roflumilast group (21 (4.6%) to 12 (2.8%)) was greater than the corresponding improvement in the vehicle group (10 (4.5%) to 7 (3.5%)).

A similar trend was reported for the LTS study with the frequency of mild/moderate/severe hyperpigmentation at baseline and Week 52, respectively, of 9 (2.3%)/18 (4.5%)/1 (0.3%) to 3 (6.5%)/0/0.

Dermal Safety Studies

Provocative dermal safety studies were not conducted for roflumilast foam, 0.3% in the seborrheic dermatitis clinical development program.

At the end of Phase 2 (EOP2) meeting (12/16/2020), FDA agreed that the results of dermal safety studies (ARQ-151-108/-109/-110/-111) conducted with ARQ-151 Cream, 0.3% in healthy subjects in psoriasis development program may be used to support dermal safety, and that distinct dermal safety studies in healthy subjects were not necessary with ARQ-154 foam, 0.3%.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant conducted safety analyses by intrinsic factors for demographic subgroups (age, sex, race, ethnicity) and for baseline disease characteristics (%BSA, IGA) subgroups; and reported no clinically significant differences in the AE profiles by subgroups in the VC pool or the LTS study.

The subgroup analyses were not powered for safety, and because of relatively small number of subjects in each subgroup, no meaningful conclusions may be drawn by comparing the incidence of AEs between corresponding subgroups of subjects in the roflumilast group compared to vehicle group. For all subgroups, most AEs were mild to moderate in severity, not related to study drug, and did not lead to discontinuation from treatment or from the study. A summary of the AE profiles for subjects in the VC pool and the LTS study are described below.

TEAEs by Age Group

For the VC pool, the following proportion of subjects in each age group were reported with a TEAE for the roflumilast group compared to the vehicle group, respectively:

- Age 9 to <18 years: 5/17 (29.4%) v. 1/15 (6.7%)
- Age 18 to <65 years: 85/375 (22.7%) v. 39/178 (21.9%)
- Age ≥65 years: 17/66 (25.7%) v. 6/32 (18.8%)

For the LTS study, the crude incidence of TEAEs by age group were slightly higher in subjects ≥65 years of age:

- Age 12 to <18 years: 4/13 (30.8%)
- Age 18 to <65 years: 105/330 (31.8%)
- Age ≥65 years: 21/57 (36.8%)

TEAEs by Gender

For the VC pool, the following proportion of subjects in each gender group were reported with a TEAE for the roflumilast group compared to the vehicle group, respectively:

- Male: 54/229 (23.6%) v. 13/115 (11.3%)
- Female: 53/229 (23.1%) v. 33/110 (29.8%)

For the LTS study, the crude incidence of TEAEs by gender was slightly higher in female subjects:

- Male: 57/197 (28.9%)
- Female: 73/203 (36.0%)

TEAEs by Race

For the VC pool, the following proportion of subjects in each race group were reported with a TEAE for the roflumilast group compared to the vehicle group, respectively:

- Black or African American: 9/53 (17.1%) v. 4/21 (19.0%)
- White: 87/357 (24.4%) versus 36/184 (19.5%)
- Other: 11/48 (23.0%) versus 6/20 (33.6%)

For the LTS study, the crude incidence of TEAEs by race were similar between races:

- Black or African American: 17/51 (33.3%)
- White: 103/319 (32.3%)
- Other: 9/27 (33.3%)

TEAEs by Ethnicity

For the VC pool, the following proportion of subjects in each ethnic group were reported with a TEAE for the roflumilast group compared to the vehicle group, respectively:

- Hispanic or Latino: 22/98 (22.2%) v. 9/44 (21.0%)
- Not Hispanic or Latino: 85/360 (23.6%) v. 37/181 (20.4%)

For the LTS study, the crude incidence of TEAEs by ethnicity were slightly higher in the Not Hispanic or Latino group:

- Hispanic or Latino: 29/115 (25.2%)
- Not Hispanic or Latino: 101/283 (35.7%)

TEAEs by Baseline IGA

The VC pool included 638 subjects with moderate (IGA =3), and 45 subjects with severe (IGA =4) at baseline. The following proportion of subjects in each IGA score group were reported with a TEAE for the roflumilast group compared to the vehicle group, respectively:

- Moderate (IGA =3): 100/428 (23.4) v. 43/210 (20.5)
- Severe (IGA =4): 7/30 (22.3) v. 3/15 (20.0)

For the LTS study, the frequency of AEs reported based on baseline IGA category [4/14 (28.6%) for clear (IGA =0), 9/33 (27.3%) for almost clear (IGA =1), 6/20 (30.0%) for Mild (IGA =2), 94/296 (31.8%) for moderate (IGA =3), and 17/37 (45.9%) for severe (IGA =4)] was slightly higher for subjects with severe (IGA=4) at baseline.

TEAEs by Baseline BSA

The VC pool included 547 subjects with BSA < 5% and 136 subjects with BSA>=5% affected by seborrheic dermatitis at baseline. The following proportion of subjects in each BSA group were reported with a TEAE for the roflumilast group compared to the vehicle group, respectively:

- BSA<5%: 91/370 (24.6%) v. 36/177 (20.3%)
- BSA>=5%: 16/88 (17.8%) v. 10/48 (21.0%)

For the LTS study, the frequency of AEs reported based on baseline BSA category [91/294 (31.0%) for BSA<5%, and 39/105 (37.1%) for BSA >=5%] was slightly higher for subjects with BSA>=5% at baseline.

Additional Subgroup Analyses

The Applicant conducted subgroup analyses of the TEAE frequency for the VC pool based on a history of inadequate response, intolerance, or contraindication to topical antifungals or topical corticosteroids for the roflumilast group compared to the vehicle group, respectively; and reported a similar frequency of AEs in the subgroups.

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable to roflumilast foam, 0.3% drug product.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable to roflumilast foam, 0.3% drug product.

Human Reproduction and Pregnancy

Not applicable to roflumilast foam, 0.3% drug product.

Pediatrics and Assessment of Effects on Growth

Not applicable to roflumilast foam, 0.3% drug product.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable to roflumilast foam, 0.3% drug product.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Roflumilast foam, 0.3% has not been marketed in any country, and there are no postmarketing

safety data available. No safety signals were identified based on the brief postmarketing experience with roflumilast cream 0.3% as of 28 October 2022.

Expectations on Safety in the Postmarket Setting

The comprehensive analysis of the roflumilast foam, 0.3% safety data identified no safety signals. There are no safety concerns that are expected to change the favorable risk/benefit assessment or lead to increased risk with administration of roflumilast foam, 0.3% in the Postmarket setting.

8.2.11. Integrated Assessment of Safety

The safety profile of roflumilast foam, 0.3% was adequately characterized during the drug development program. The primary review of safety of the drug product for topical treatment of moderate to severe seborrheic dermatitis relied on the evaluation of pooled safety data from 683 subjects enrolled in the vehicle-controlled trials (VC pool) including a Phase 3 trial (ARQ-154-304) a Phase 2 trial (ARQ-154-203); which were similar in design, trial population, dosing regimen, and key primary and secondary efficacy endpoints. Eligible subjects were randomized in a 2:1 ratio to receive roflumilast foam or vehicle foam once daily for 8 weeks.

Additionally, the Applicant submitted safety data from a (26 week, up to 52 weeks), Phase 2 open-label, long term safety study (ARQ-154-214) in subjects ≥9 years of age with SD, and safety data for subjects treated with roflumilast foam, 0.3% in a Phase 1, open-label, maximal use study (ARQ-154-116).

One death was reported during the LTS study -214 in an 81-year-old male subject diagnosed with malignant brain neoplasm and deemed as not related to the study drug by the investigator.

For VC pool, the following safety results were reported:

- SAEs were reported in 1/458 (0.2%) subject treated with roflumilast foam (deemed by the investigators as not related) compared to no subject treated with the vehicle foam.
- AELDs were reported at a lower frequency of 8 AELDs in 4/458 (0.9%) subjects treated with roflumilast foam, compared to 6 AELDs in 5/225 (2.2%) subjects treated with vehicle foam.
- TEAEs were reported in 107/458 (23.4%) subjects treated with roflumilast foam compared to 46/225 (20.4%) subjects treated with the vehicle foam. The PTs reported as TEAEs in ≥1% of subjects treated with roflumilast foam (and at a higher frequency than for vehicle foam) compared to the vehicle foam, respectively, included COVID-19 (2.6% v. 2.2%), nasopharyngitis (1.5% v. 0.4%), nausea (1.3% versus 0), contact dermatitis (1.3% v. 0.9%), and headache (1.1% versus 0).
- Severe AEs were reported in 6/458 (1.3%) subjects treated with roflumilast foam compared to 2/225 (0.9%) of subjects treated with the vehicle foam.

- ADRs: Adverse Drug Reactions (possibly, probably, or likely related to the study drug) were reported in 11/458 (2.4%) subjects treated with roflumilast foam compared to 8/225 (3.6%) of subjects treated with vehicle foam.
- PDE-4-related AEs: Psychiatric or Gastrointestinal-related AEs were reported at significantly lower frequencies for subjects treated with the roflumilast foam compared to subjects treated with oral PDE-4 inhibitors. Suicidal ideation (no suicidal behavior) was reported for one subject in the VC pool and 2 subjects in the LTS study. The mean weight decrease in subjects treated with roflumilast foam was not clinically significant.
- Local safety and tolerability assessments by investigators and by subjects demonstrated low scores and were similar in subjects treated with the roflumilast foam or the vehicle foam.

The available data from the clinical trials demonstrated that roflumilast foam, 0.3% was safe in the treatment of subjects ≥9 years of age with seborrheic dermatitis. Postmarketing risk management will include professional labeling and routine pharmacovigilance. No PMRs will be issued for roflumilast foam, 0.3%.

120-Day Safety Update

Per 21 CFR 314.50(d)(5)(vi)(b), the Applicant submitted a 120-Day Safety Update Report (SDN 3 dated 9 June 2023). The review team identified no new safety signals in the safety update report.

8.3. Statistical Issues

There were no significant statistical issues identified in the review of Studies 304 and 203. Study 203 was designed as a Phase 2 study; the trial was randomized, double-blind, vehicle-controlled and conducted under comparable conditions as the Phase 3 trial. However, Study 203 was not designed to control the multiplicity across the secondary endpoints. Thus, the secondary endpoints in Study 203 are not appropriate for inclusion in labeling. The Phase 3 trial was designed to control the type I error rate at two-sided α=0.01 to provide a stronger level of evidence than a trial conducted at α=0.05.

8.4. Conclusions and Recommendations

To establish the safety and efficacy of roflumilast foam, 0.3% in the treatment of seborrheic dermatitis, the Applicant submitted data from two similarly designed, adequate and well-controlled, randomized (2:1), double-blind, vehicle-controlled, parallel-group trials (Phase 2 trial, ARQ-154-203 and Phase 3 trial, ARQ-154-304). Subjects applied roflumilast foam, 0.3% once daily to affected areas for 8 weeks. The VC trials, -203/-304, enrolled a total of 683 subjects ≥9 years of age with moderate to severe seborrheic dermatitis (an IGA score of 3 (moderate) or 4 (severe) and BSA involvement of < 20%) at baseline. Trials -203/-304 evaluated the primary endpoint of “IGA success”, defined as an IGA score of 0 (“clear”) or 1 (“almost clear”) and a ≥2-point improvement from baseline, at Week 8.

Secondary efficacy endpoint (intended for labeling) in Trial -304 included WI-NRS success (defined as a ≥4-point improvement in WI-NRS score from baseline [in subjects with a baseline NRS ≥4 score]) at Week 8.

In both VC trials, roflumilast foam, 0.3%, was superior to the vehicle foam for the primary efficacy endpoint of IGA success at Week 8 (79.5% v. 58.0% [p-value <0.001], a treatment effect of 20.6% for Trial -304; and 73.1% versus 40.8% [p-value <0.001], a treatment effect of 33.8% for Trial -203). The result for the secondary efficacy endpoint of WI-NRS success at Week 8 for Trial -304 (62.8% v. 40.6% [p-value <0.0001], a treatment effect of 25.7%) was in alignment with the results for the primary efficacy endpoint. Efficacy data submitted by the Applicant demonstrated that roflumilast foam, 0.3%, is effective for its intended use in the target population.

To define the safety profile of roflumilast foam, 0.3%, the Applicant conducted a comprehensive assessment of the safety of the drug product in the target population. There were no drug- related deaths or SAEs. The size of the safety database, subject exposure, and safety assessments were adequate to characterize the safety profile of roflumilast foam, 0.3%.

The Applicant submitted safety data from 683 subjects who participated in the vehicle-controlled trials and 400 subjects who participated in the open-label, LTS safety Study -214 to support the safety of roflumilast foam, 0.3% for topical treatment of seborrheic dermatitis. In the VC safety pool, the most frequently reported adverse events were COVID-19 (2.6%), Nasopharyngitis (1.5%), Nausea (1.3%), Dermatitis contact (1.3%), and Headache (1.1%). The safety results reported in the open-label, LTS study -214 were consistent with the safety results reported for the VC trials.

The Applicant provided adequate efficacy and safety data to support the conclusion that the benefit-risk analysis is favorable for approval of NDA 217242. This reviewer recommends approval of roflumilast foam, 0.3%, applied topically once a day, for the treatment of moderate to severe seborrheic dermatitis in patients ≥ 9 years of age.

9. Advisory Committee Meeting and Other External Consultations

The Agency did not hold an Advisory Committee Meeting for this application, because there were no efficacy, safety, or novel/complex regulatory issues that required input from an Advisory Committee.

Additionally, roflumilast cream, 0.3% was approved in July 2022 for the indication of topical treatment of plaque psoriasis, including intertriginous areas, in patients >=12 years of age (Zoryve, NDA 215985); and roflumilast oral tablets (250 mcg, 500 mcg) were approved by the FDA in 2011 (Daliresp, NDA 022522) for the indication of "treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations", and the safety profile of oral roflumilast is well characterized.

10. Pediatrics

Because roflumilast foam, 0.3% is used for a new indication with a new dosage form and route of administration compared to the oral roflumilast tablets approved in 2011, it triggers the requirement under the PREA (21 USC 355c) for an assessment of its safety and effectiveness for the topical treatment of seborrheic dermatitis in pediatric patients unless this requirement is waived, deferred, or inapplicable.

In an Agreed iPSP letter of 6/2/2021, the Agency agreed with the Applicant's plan to request a waiver for pediatric subjects between ages of 0 to <9 years of age (because necessary studies are impossible or highly impracticable), no request for deferral of pediatric studies, and inclusion of pediatric subjects between ages of 9 to <18 years of age in the Phase 2, LTS study, ARQ-154-214, and Phase 3 clinical trial, ARQ-154-304.

The Applicant's PREA Waiver/Pediatric Plan and Assessment request was presented and discussed at the Pediatric Review Committee (PeRC) meeting on 10/10/2023. The PeRC agreed with the Division's recommendation to grant a partial waiver to subjects under 9 years of age, and pediatric assessment for subjects >= 9 years of age. The PeRC also agreed with the Division's recommendation for not issuing a PREA PMR for this product.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

The Applicant submitted proposed prescribing information (PI), patient package insert (PPI; also known as patient information), container labels and carton labeling for Zoryve (roflumilast) foam, 0.3%. The Office of Prescription Drug Promotion reviewed and provided comments regarding the PI, PPI, and the carton/container. These comments are reflected in final labeling.

Ruth Mayrosh, PharmD (Senior Patient Labeling Reviewer from the Division of Medical Policy Programs (DMPP)), and Montherson L. Saint Juste, PharmD, MS (Regulatory Review Officer from the Office of Prescription Drug Promotion (OPDP)) reviewed the Patient Package Insert (PPI) and Instructions for Use (IFU) and provided comments to convey to the Applicant (Review in DARRTS on 9/21/2023).

Montherson L Saint Juste, PharmD, MS (Regulatory Review Officer from the Office of Prescription Drug Promotion (OPDP)) reviewed the proposed Prescribing Information (PI) and provided comments to convey to the Applicant (Review in DARRTS on 9/29/2023).

Other Prescription Drug Labeling

The final labeling will reflect all recommendations from the review teams and will be appended to the Action Letter.

12. Risk Evaluation and Mitigation Strategies (REMS)

Based on the favorable safety profile of this product, risk mitigation measures beyond professional labeling and standard postmarketing surveillance are not warranted at this time.

13. Postmarketing Requirements and Commitment

The review team recommends that no PMRs be required for this product based on their review of the data submitted to this NDA.

14. Division Director (Clinical) Comments

I agree with the review team recommendation to approve Zoryve (roflumilast) foam, 0.3% for the treatment of seborrheic dermatitis in patients 9 years of age and older.

The Applicant provided sufficient efficacy and safety data to allow this determination. In support of efficacy claim the applicant submitted two well-controlled trials (Phase 3 and Phase 2) in subjects 9 years of age and older. Both trials succeeded in winning on primary endpoint.

The secondary endpoint results were supportive of the primary efficacy endpoint.

In addition, the data from 1 long-term extension trial and one phase 1 PK trial were submitted to support safety of the product.

Roflumilast cream, 0.3% was approved in 2022 with no significant safety concerns. This submission did not raise additional safety concerns, either.

15. Appendices

15.1. References

Arcutis Biotherapeutics, 2022, Protocol Amendment 2, Protocol Amendment 1, and Original Protocol: Roflumilast Foam 0.3%, Clinical Study Report ARQ-154-304, \\CDSESUB1\EVSPROD\nda217242\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\seborrheic-dermatitis\5351-stud-rep-contr\arq-154-304\1611-prot-amend.pdf.

Arcutis Biotherapeutics, 2023, NDA 217242 Zoryve (Roflumilast Foam, 0.3%) Submission: Data Sources Used in the Review of NDA 217242, Zoryve (Roflumilast Foam, 0.3%), Food and Drug Administration (FDA), \\CDSESUB1\evsprod\NDA217242\0001.

Naldi, L and A Rebora, 2009, Clinical practice. Seborrheic dermatitis, N Engl J Med, 360(4):387-396, https://www.ncbi.nlm.nih.gov/pubmed/19164189.

Sasseville, D, JE Fowler, and CE Rosamaria, 2023a, UpToDate: Seborrheic Dermatitis in Adolescents and Adults, Wolters Kluwer Health, accessed August, 2023, https://www.uptodate.com/contents/seborrheic-dermatitis-in-adolescents-and-adults.

Sasseville, D, LLE Moise, and CE Rosamaria, 2023b, UpToDate: Cradle Cap and Seborrheic Dermatitis in Infants, Wolters Kluwer Health, accessed August, 2023, https://www.uptodate.com/contents/cradle-cap-and-seborrheic-dermatitis-in-infants.

15.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical studies for roflumilast foam. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4 (a)(3) (i-iv).

The covered clinical studies as defined in 21 CFR 54.2 (e) were Trials ARQ-154-203/-304, which provided the primary data to establish effectiveness and safety of this product. Refer to Section 8 of this review for the trial designs. The Applicant provided the following disclosures for significant payments of other sorts from the Applicant of the covered study [21 CFR 54.4 (a)(3) (ii), 54.2 (f)]:

(b) (6), participated as a clinical investigator in studies ARQ-154-203, and ARQ-154-214. (b) (6) holds financial interests that are required to be disclosed. (b) (6) reported a positive financial interest of equity in Arcutis Biotherapeutics, Inc. on his financial disclosure forms. The details of the positive financial interest are provided below for each study he participated in as a clinical investigator.

Table 40. Clinical Investigator Financial Interests

Study Number	Number of Shares[a]	Stock Price	Value
ARQ-154-203	99,964	$32.59	$3,258,826
ARQ-154-214	99,964	$33.79	$3,378,783

[a.] Series A preferred stock held in a revocable trust.

The following steps were taken as a result of the financial disclosure and to minimize the potential for bias:

1. The following language was added to informed consent forms at the request of the IRB:

   "Your Study Doctor owns significant stock with the Sponsor of this study."

2. The Arcutis team including the CMO, VP of Clinical Development, VP of Clinical Operations, VP of Regulatory Affairs and VP of Biometrics reviewed the disclosure and determined to monitor the site's data in the manner as other sites on the study. After enrollment of the 10th and 20th subjects, accrual was to be paused at the site in order for Arcutis to review the data for trends/issues and to decide if further enrollment would be allowed. Neither of these thresholds were reached as (b) (6) enrolled (b) (6) subjects in ARQ-154-203 and (b) (6) subjects in ARQ-154-214.

Covered Clinical Study: ARQ-154-203

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: 24		
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): 1		
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 Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 24		
Is an attachment provided with the reason:	Yes X	No ☐ (Request explanation from Applicant)

Covered Clinical Study: ARQ-154-304

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: 52		
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 Sponsor of covered study: 1		
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 X	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 52		
Is an attachment provided with the reason:	Yes X	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

15.3.1. Calculations for Multiples of Human Exposure

The Applicant deviated from the Daliresp label by using AUC comparison for all reproductive toxicology studies, based on AUC values extrapolated from other studies. Further, during calculation of the multiples, the Applicant appeared to have used the human exposure data from the clinical study using roflumilast cream 0.3% (ARQ-151-107 under NDA 215958) instead of the pivotal Phase 3 study using roflumilast foam, 0.3%. Per Clinical Pharmacology within the Agency, for topical products, the maximum recommended human dose (MRHD) is defined as the mean dose used in Phase 3 trials. These aforementioned factors may explain why in this review different multiples of human exposures are derived as compared to those provided in the Applicant-proposed labeling.

Per the Daliresp labelling, roflumilast is three times more potent than roflumilast N-oxide against the PDE4 enzyme activity in vitro, and the plasma AUC of roflumilast N-oxide on average is about 10-fold higher than that of roflumilast in humans. The Applicant proposed to calculate a total PDE-4 load value for exposure comparison to account for the difference in potency of roflumilast and roflumilast N-oxide. This proposed approach appears reasonable from a Pharm/Tox perspective.

Data in the following table are used in determining the multiples of human exposures in the labeling of ZORYVE Foam, and adjustment factors are calculated based on comparisons with the Daliresp labelling.

Table 41. Calculation of Adjustment Factors Based on PK Data in Pivotal Phase 3 Studies

PK Data		DALIRESP	ZORYVE Foam (Day 28 PK Data in One Phase 3 Study)
MRHD (mg/day)		0.5	8.37
$AUC_{0\text{-}24hr}$ (ng*hr/mL)	Roflumilast	33.7	29.2
	N-oxide	375	173
	PDE-4 load	154[a]	84.7[b]
Adjustment factor based on mg/m^2 comparison		--	1.0[c]
Adjustment factor based on AUC comparison		--	1.8[d]

Source: Daliresp labeling and study ARQ-154-304

[a.] 33.7 + ((375 ÷ 419.22) * 403.22)/3 = 154 ng*hr/mL

[b.] 29.2 + ((173 ÷ 419.22) * 403.22)/3 = 84.7 ng*hr/mL

[c.] (0.5 x 80%)/(8.37 x 5%) = 1.0. Oral bioavailability of roflumilast is 80%, and 5% is the assumed dermal absorption rate of roflumilast in topical products.

[d.] 154/84.7 = 1.8

Based on the adjustment factors provided in the table above, multiples of human exposure for ZORYVE Foam are calculated and presented in the following table. For the 2-year mouse dermal carcinogenicity study, the AUC values from the 13-week dermal mouse toxicity study at the dose strength of 1% cream are used for calculation of the multiples. The sex-combined $AUC_{0\text{-}24hr}$ values for roflumilast and roflumilast N-oxide were 194 and 1277 ng·hr/mL, respectively. When

normalized to PDE-4 load, the combined $AUC_{0\text{-}24hr}$ of roflumilast and roflumilast N-oxide is equivalent to 603 ng•hr/mL of roflumilast, which is 7-times the human exposure at MRHD.

Table 42. Multiples of Human Exposure for Nonclinical Studies

Study Type	Route	Dose (mg/kg/day)	Multiples in Daliresp Labeling[$]	Multiples in ZORYVE Foam Labeling
Male rat fertility study[a]	Oral	0.6 (NOAEL)	10	10
Female rat fertility study[a]	Oral	1.5 (NOAEL)	24	24
Rat embryo-fetal development study[a]	Oral	0.2 (NOAEL) 1.8	3 30	3 30
Rat fertility and embryofetal development study[a]	Oral	0.6 1.8	10 29	10 29
Rabbit embryo-fetal development study[a]	Oral	0.8 (NOAEL)	26	26
Mouse pre- and postnatal development study[a]	Oral	2 6 12	16 49 97	16 49 97
2-year hamster carcinogenicity study[b]	Oral	8	11	20
2-year mouse carcinogenicity study[b]	Oral	F: 12 (NOAEL) M: 18 (NOAEL)	10 15	18 27
2-year mouse dermal carcinogenicity study[b]	Dermal	20 (NOAEL)	--	7[c]

Source: Daliresp labeling and studies submitted to this NDA
[a.] Calculations are based on mg/m^2 dose comparison.
[b.] Calculations are based on AUC comparison.
[c.] 603/84.7 = 7.

15.3.2. Nonclinical Labeling

Recommended changes to nonclinical information in Highlights of Prescribing Information and Sections 8.1, 8.2, 12.1 and 13.1 of the Applicant's proposed labeling are provided below. The pharmacologic class for roflumilast is phosphodiesterase 4 (PDE4) inhibitor.

15.3.2.1. FDA Reviewer-Recommended Deletions and Additions to Nonclinical Sections of the PI

Below, reviewer-recommended deletions and additions are indicated by "~~strike through~~" and "<u>underlined</u>" text, respectively.

(b) (4)

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

15.4. OCP Appendices (Technical documents supporting OCP recommendations)

15.4.1. Bioanalytical Methods

For all studies submitted (ARQ-154-116, ARQ-154-203, ARQ-154-214, and ARQ-154-304), concentrations of roflumilast and metabolite roflumilast *N*-oxide were quantified in K_2EDTA human plasma using turbo ion spray liquid chromatography-tandem mass spectrometry (LC/MS/MS). The method uses a protein-precipitation extraction procedure to isolate roflumilast, roflumilast *N*-oxide, and corresponding internal standards. The LLOQ of the assay is 0.100 ng/mL and the calibration range is 0.100 to 100 ng/mL.

Method validation report 171410VEMB_ARCMC_R1 was previously submitted under NDA 215985 for the 0.3% w/w roflumilast topical cream (same Applicant as present NDA, approved 2022). The method used to quantitate roflumilast and roflumilast *N*-oxide samples in studies

submitted to the current NDA is the same as that used on samples from studies submitted under NDA 215985. Bioanalytical method validation was previously found to be acceptable. Refer to the review for NDA 215985 (DARRTS date: July 28, 2022; Reference ID: 5020282). In-study bioanalytical performance is summarized below.

Table 43. Bioanalytical Method Performance in Study ARQ-154-116

Method performance in Study ARQ-154-116		
Assay passing rate	• 4/4 runs met the method acceptance criteria for both roflumilast and roflumilast *N*-oxide	Acceptable
Standard curve performance	• At least three-fourths of all standard curve samples across all runs fell within ± 15% of the nominal value (± 20% for the LLOQ) Roflumilast • Cumulative accuracy (% bias) range: -2.2 to 1.5% • Cumulative precision (% CV): ≤ 7.2% Roflumilast *N*-oxide • Cumulative accuracy (% bias) range: -2.6 to 2.0% • Cumulative precision (% CV): ≤ 5.4%	Acceptable
QC performance	• Across all runs, QC performance met acceptance criteria based on at least two-thirds of samples falling within ± 15% of the nominal values, and at least half of the QC samples at each level (high, medium, and low) falling within ± 15% of the nominal value. Roflumilast • Cumulative accuracy (% bias) range: -0.3 to 2.5% • Cumulative precision (% CV): ≤ 6.1% Roflumilast *N*-oxide • Cumulative accuracy (% bias) range: 2.3 to 4.5% • Cumulative precision (% CV): ≤ 3.8%	Acceptable
Method reproducibility	• Incurred sample reanalysis was performed for 40/104 samples (38.5%) for roflumilast and roflumilast *N*-oxide. • 36/40 samples (90.0%) for roflumilast and 35/40 samples (87.5%) for roflumilast *N*-oxide met acceptance criteria based on percent difference ≤ 20% of the mean.	Acceptable
Repeat analysis	Repeat analysis of samples was conducted as part of incurred sample reanalysis. The Sponsor notes that ISR was repeated and results from the reanalysis are reported. The original ISR passing rates were 72.5% and 70.0%, respectively for roflumilast and roflumilast *N*-oxide. The Sponsor indicates that the passing rates were abnormally low, and they suspect there may have been issues related to thawing and improper mixing of samples prior to extraction. As the original ISR passing rates would have still met acceptance criteria (at least two-thirds of samples with percent difference ≤ 20% of the mean), this is acceptable.	Acceptable

Method performance in Study ARQ-154-116	
Study sample analysis/ stability	All samples were stored at -70 °C until analysis. All samples were analyzed between June 16, 2021 (earliest collection date), and January 13, 2022 (last analysis date) (total time = 211 days). All samples were analyzed within the established stability of 671 days at -70 °C.

Source: ARQ-154-116 Bioanalytical Report

Table 44. Bioanalytical Method Performance in Study ARQ-154-203

Method performance in Study ARQ-154-203		

Assay passing rate	• 7/8 runs met the method acceptance criteria for roflumilast
	  ○ 1 run was rejected due to failure of QCs to meet criteria
	  ○ Another run was conducted for roflumilast only
	• 7/7 runs met the method acceptance criteria for roflumilast *N*-oxide
		Acceptable

Standard curve performance	• At least three-fourths of all standard curve samples across all runs fell within ± 15% of the nominal value (± 20% for the LLOQ) <u>Roflumilast</u> • Cumulative accuracy (% bias) range: -1.8 to 2.2% • Cumulative precision (% CV): ≤ 6.0% <u>Roflumilast *N*-oxide</u> • Cumulative accuracy (% bias) range: -1.5 to 2.2% • Cumulative precision (% CV): ≤ 4.7%	Acceptable
QC performance	• Across all runs, QC performance met acceptance criteria based on at least two-thirds of samples falling within ± 15% of the nominal values, and at least half of the QC samples at each level (high, medium, and low) falling within ± 15% of the nominal value. <u>Roflumilast</u> • Cumulative accuracy (% bias) range: -2.7 to 2.0% • Cumulative precision (% CV): ≤ 11.9% <u>Roflumilast *N*-oxide</u> • Cumulative accuracy (% bias) range: -1.7 to 3.3% • Cumulative precision (% CV): ≤ 13.5%	Acceptable
Method reproducibility	• Incurred sample reanalysis was performed for 46/436 samples (10.6%) for roflumilast and roflumilast *N*-oxide. • 43/46 samples (93.5%) for roflumilast and 43/46 samples (93.5%) for roflumilast *N*-oxide met acceptance criteria based on percent difference ≤ 20% of the mean.	Acceptable
Repeat analysis	Repeat analysis of samples was conducted as part of incurred sample reanalysis. Two samples were re-assayed for roflumilast and one sample was re-assayed for roflumilast *N*-oxide. For all samples, the listed reason for re-analysis was “Reanalysis requested (PK outlier)”	Acceptable

Method performance in Study ARQ-154-203	
Study sample analysis/ stability	All samples were stored at -70 °C until analysis. All samples were analyzed between December 4, 2019 (earliest collection date), and September 17, 2020 (last analysis date) (total time = 288 days). All samples were analyzed within the established stability of 671 days at -70 °C.

Source: ARQ-154-203 Bioanalytical Report

Table 45. Bioanalytical Method Performance in Study ARQ-154-304

Method performance in Study ARQ-154-304		

Assay passing rate	• 9/10 runs met the method acceptance criteria for both roflumilast and roflumilast *N*-oxide
	  ○ 1 run was rejected due to failure of QCs to meet criteria
	  ○ This run was repeated and subsequently passed
	• Sponsor indicates that carryover > 20.0% of the mean LLOQ was observed in Run 3 for roflumilast *N*-oxide. Sample-by-sample carryover assessments indicated that no samples had potential carryover contribution > 2.0% from the preceding sample.
		Acceptable

Standard curve performance	• At least three-fourths of all standard curve samples across all runs fell within ± 15% of the nominal value (± 20% for the LLOQ) <u>Roflumilast</u> • Cumulative accuracy (% bias) range: -4.5 to 2.0% • Cumulative precision (% CV): ≤ 5.3% <u>Roflumilast *N*-oxide</u> • Cumulative accuracy (% bias) range: -3.0 to 2.0% • Cumulative precision (% CV): ≤ 6.5%	Acceptable
QC performance	• Across all runs, QC performance met acceptance criteria based on at least two-thirds of samples falling within ± 15% of the nominal values, and at least half of the QC samples at each level (high, medium, and low) falling within ± 15% of the nominal value. <u>Roflumilast</u> • Cumulative accuracy (% bias) range: -0.3 to 5.0% • Cumulative precision (% CV): ≤ 6.4% <u>Roflumilast *N*-oxide</u> • Cumulative accuracy (% bias) range: -0.3 to 4.7% • Cumulative precision (% CV): ≤ 6.1%	Acceptable
Method reproducibility	• Incurred sample reanalysis was performed for 60/567 samples (10.6%) for roflumilast and roflumilast *N*-oxide. • 55/60 samples (91.7%) for roflumilast and 57/60 samples (95.0%) for roflumilast *N*-oxide met acceptance criteria based on percent difference ≤ 20% of the mean.	Acceptable

Method performance in Study ARQ-154-304		
Repeat analysis	Repeat analysis of samples was conducted as part of incurred sample reanalysis. One sample was re-assayed for both roflumilast and roflumilast *N*-oxide. The listed reason for re-analysis was "IS [internal standard] outlier".	Acceptable
Study sample analysis/ stability	All samples were stored at -70 °C until analysis. All samples were analyzed between August 5, 2021 (earliest collection date), and June 6, 2022 (last analysis date) (total time = 305 days). All samples were analyzed within the established stability of 671 days at -70 °C.	

Source: ARQ-154-304 Bioanalytical Report

Overall, the bioanalytical performance for quantitation of roflumilast and roflumilast *N*-oxide in human plasma samples is acceptable in studies ARQ-154-116, ARQ-154-203, and ARQ-154-304.

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/

DAVID L KETTL
12/14/2023 12:45:33 PM

TATIANA OUSSOVA
12/14/2023 03:38:56 PM