NDA Multi-Disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	NDA 217242/S-005
Priority or Standard	Standard
Submit Date(s)	July 19, 2024
Received Date(s)	July 22, 2024
PDUFA Goal Date	May 22, 2025
Division/Office	Division of Dermatology and Dentistry/ Office of Immunology and Inflammation
Review Completion Date	May 20, 2025
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 plaque psoriasis of the scalp and body in patients 12 years of age and older
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Plaque psoriasis (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	plaque psoriasis of the scalp and body in adult and pediatric patients 12 years of age and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Plaque psoriasis (disorder)
Recommended Dosing Regimen	Apply once daily to affected areas

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Sascha Randolph
Nonclinical Reviewer	
Nonclinical Team Leader	
Office of Clinical Pharmacology Reviewer(s)	Sriram Gunda, Ph.D.
Office of Clinical Pharmacology Team Leader(s)	Chinmay Shukla, Ph.D.
Clinical Reviewer	Hamid Tabatabai, MD
Clinical Team Leader	Hamid Tabatabai, MD
Statistical Reviewer	Daeyoung Lim, PhD
Statistical Team Leader	Kathleen Fritsch, PhD
Cross-Disciplinary Team Leader	Hamid Tabatabai, MD
Division Director (DHOT)	
Division Director (OCP)	
Division Director (OB)	
Division Director (OHOP)	
Office Director (or designated signatory authority)	

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

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Sriram Gunda, Ph.D.	OCP/DIIP	Sections: 6, 13	Select one: ___x Authored ___ Approved
	Signature: Sriram Gunda -S Digitally signed by Sriram Gunda -S Date: 2025.05.21 14:54:56 -04'00'			
Clinical Pharmacology Team Leader	Chinmay Shukla, Ph.D.	OCP/DIIP	Sections: 6, 13	Select one: ___ Authored _x_ Approved
	Signature: Chinmay Shukla -S Digitally signed by Chinmay Shukla -S Date: 2025.05.21 14:58:48 -04'00'			
Clinical Reviewer	Hamid Tabatabai, MD	OII/DDD	Sections: 1, 2, 3, 4.1, 7, 8.2, 8.4, 9, 10, 11, 12, 13, 19	Select one: __x_ Authored __ Approved
	Signature: HAMID TABATABAI -S Digitally signed by HAMID TABATABAI -S Date: 2025.05.21 16:14:33 -04'00'			
Clinical Team Leader	Hamid Tabatabai, MD	OII/DDD	Sections: 1, 2, 3, 4.1, 7, 8.2, 8.4, 9, 10, 11, 12, 13, 19	Select one: ___ Authored __x_ Approved
	Signature: HAMID TABATABAI -S Digitally signed by HAMID TABATABAI -S Date: 2025.05.21 16:17:52 -04'00'			
Deputy Division Director (Clinical)	Tatiana Oussova, MD	OII/DDD	Sections: All	Select one: ___ Authored __x_ Approved
	Signature: Tatiana Oussova -S Digitally signed by Tatiana Oussova -S Date: 2025.05.21 17:19:49 -04'00'			
Statistical Reviewer	Daeyoung Lim, PhD	DB III	Sections: 8.1, 8.3	Select one: __X_ Authored ___ Approved
	Signature: Daeyoung Lim -S Digitally signed by Daeyoung Lim -S Date: 2025.05.21 17:41:58 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Team Leader	Kathleen Fritsch, PhD	DB III	Sections: 8.1, 8.3	**Select one:** ___ Authored __X_ Approved
	Signature:	KATHLEEN S. FRITSCH -S Digitally signed by KATHLEEN S. FRITSCH -S Date: 2025.05.21 21:37:09 -04'00'		

Glossary

ADaM	Analysis Data Model
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AELD	adverse event leading to discontinuation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BLA	biologics license application
BMI	body mass index
BSA	body surface area
B-IGA	Body–Investigator Global Assessment
CDER	Center for Drug Evaluation and Research
CFB	change from baseline
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CSR	clinical study report
CYP	cytochrome P450
C-SSRS	Columbia-Suicide Severity Rating Scale
DB	double-blind
DHOT	Division of Hematology Oncology Toxicology
DILI	drug-induced liver injury
ECG	electrocardiogram
FDA	Food and Drug Administration
ICE	intercurrent event
IFU	instructions for use
IGA	Investigator Global Assessment
IL	interleukin
IND	investigational new drug
IP	investigational product
iPSP	initial pediatric study plan
ISE	integrated summary of effectiveness
ISR	incurred sample reanalysis
ISS	integrated summary of safety
ITT	intent-to-treat
MI	multiple imputation

mITT	modified intent to treat
MUSE	maximal usage systemic exposure
MUsT	maximal use study
NDA	new drug application
OB	Office of Biostatistics
OCP	Office of Clinical Pharmacology
OCS	Office of Computational Science
PASI	Psoriasis Area and Severity Index
PASI-75	≥75% reduction from baseline in Psoriasis Area and Severity Index
PC	placebo-controlled
PDE-4	phosphodiesterase-4
PeRC	Pediatric Review Committee
PHQ-A	modified Patient Health Questionnaire-9 for adolescents
PHQ-8	eight-item Patient Health Questionnaire
PI	prescribing information
PK	pharmacokinetic
PMR	postmarketing requirement
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRU4-ITT	Pruritus Intent-to-Treat
PSD	Psoriasis Symptoms Diary
PSSI	Psoriasis Scalp Severity Index
PT	preferred term
P3	phase 3
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SI-NRS	Scalp Itch Numerical Rating Scale
sNDA	supplemental new drug application
SOC	system organ class
SPRU4-ITT	Scalp Pruritus Intent-to-Treat
S-IGA	Scalp–Investigator Global Assessment
TCS	topical corticosteroids
TEAE	treatment emergent adverse event
ULN	upper limit of normal
USPI	U.S. prescribing information
VC	vehicle-controlled
WI-NRS	Worst Itch Numerical Rating Scale

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 plaque psoriasis of the scalp and body.

ZORYVE foam, 0.3% was approved on December 15, 2023, for the topical treatment of seborrheic dermatitis in patients 9 years of age and older.

ZORYVE cream, 0.3% was approved on July 29, 2022, for the topical treatment of plaque psoriasis, including intertriginous areas, in patients 12 years of age and older.

Supplement NDA 215985-002 was approved on October 5, 2023. This supplement expanded the age group for the use of ZORYVE cream, 0.3% to patients 6 years of age and older with plaque psoriasis.

ZORYVE cream, 0.15% was approved under supplement NDA 215985-007 on July 9, 2024, for the topical treatment of mild to moderate atopic dermatitis in patients 6 years of age and older.

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 [chronic obstructive pulmonary disease] 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 had submitted NDA 215985 and NDA 217242 under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for marketing ZORYVE for above indications.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from two adequate and well-controlled trials, ARQ-154-309 and ARQ-154-204 (Trials -309 and -204), which provided evidence of the effectiveness of roflumilast foam, 0.3% for the topical treatment of plaque psoriasis of the scalp and body in the target population. Both trials assessed Investigator Global Assessment (IGA) for the scalp (S-IGA) and IGA for the body (B-IGA) success (defined as achievement of a score of clear (0) or almost clear (1) plus a 2-grade improvement from their baseline) compared to vehicle at Week 8 [as the primary and secondary efficacy endpoints in Trial -204; and as the co-primary efficacy endpoints in Trial -309].

Roflumilast foam, 0.3% was statistically superior to vehicle on the primary or co-primary efficacy endpoints in their respective 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

Psoriasis is a chronic, inflammatory disease that primarily affects the skin and is characterized by erythematous, scaly plaques and affects quality of life (Refer to Section 2 of this review for a discussion of plaque psoriasis and available topical treatment options). The Applicant proposes ZORYVE (roflumilast) foam, 0.3% applied daily for the topical treatment of subjects (≥12 years of age) with plaque psoriasis 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-154-204) and one phase 3 (ARQ-154-309) randomized, double-blind, vehicle-controlled trials. The Applicant did not conduct a long-term safety study for roflumilast foam, 0.3% once daily (QD) for the indication of treatment of psoriasis of the scalp and body and proposed to use the long-term safety data accrued in the roflumilast cream, 0.3% QD in the psoriasis development program to support the long-term safety of roflumilast foam in this patient population.

Efficacy:

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

1. For the efficacy endpoint of Scalp–Investigator Global Assessment (S-IGA) success (S-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 66.4% vs. 27.8% (p-value<0.001) [a treatment effect of 37.1%] in Trial ARQ-154-309, and 56.7% vs. 11.0% (p-value<0.001) [a treatment effect of 47.7%] in Trial ARQ-154-204.
2. For the efficacy endpoint of Body-Investigator Global Assessment (B-IGA) success (B-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 45.5% vs. 20.1% (p-value<0.001) [a treatment effect of 24.8%] in Trial ARQ-154-309, and 39.0% vs. 7.4% (p-value<0.001) [a treatment effect of 32.4%] in Trial ARQ-154-204.
3. For subjects with baseline Scalp Itch Numerical Rating Scale (SI-NRS) ≥4, the secondary efficacy endpoint of scalp itch (SI-NRS) success (≥4-points improvement from baseline) at week 8, the roflumilast group, compared to the vehicle group, achieved a response of 65.3% vs. 30.3% [a treatment effect of 35.4%] in Trial ARQ-154-309 (p-value<0.001); and a response of 67.3% vs. 20.7% (p<0.001), [a treatment effect of 43.6%] in Trial ARQ-154-204 (p-value<0.001). In Trial ARQ-154-204, SI-NRS was only assessed at study visits, rather than through a daily diary assessment.

4. For subjects with baseline Worst Itch NRS (WI-NRS) score ≥4, the secondary efficacy endpoint [in Trial -309] of the whole-body itch (WI-NRS) success (≥4-points improvement from baseline) at week 8, the roflumilast group, compared to the vehicle group, achieved a response of 63.1% vs. 30.1% ($p<0.001$), [a treatment effect of 32.8%]. In Trial -204, the secondary endpoint based on the WI-NRS was not multiplicity-controlled.

Safety:

Analysis of the vehicle-controlled (VC) safety database (Trials ARQ-154-309/-204) did not identify any significant safety signals and was adequate to characterize the safety profile of roflumilast foam, 0.3% for the treatment of (mild to severe) plaque psoriasis of the scalp and body.

Adverse events reported through Week 8 in ≥1% of subjects treated with roflumilast foam (and more frequently than subjects receiving vehicle foam) included headache (3.1%), diarrhea (2.5%), nausea (1.7%), and nasopharyngitis (1.3%); and are proposed by the Applicant for inclusion in Sec. 6.1 of the label as adverse drug reactions.

Roflumilast foam, 0.3% offers an alternative treatment option to a number of FDA-approved products and has an acceptable risk-benefit profile for the treatment of (mild to severe) plaque psoriasis of the scalp and body. None of the FDA-approved 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 plaque psoriasis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Psoriasis is a common, chronic, inflammatory multi-system disorder which primarily affects the skin and joints and is associated with impairment of quality of life. The prevalence of psoriasis in the United States is approximately 2-3%, of which an estimated 80 percent have mild to moderate disease, while 20% have moderate to severe disease affecting more than 5 percent of the body surface area. One third of patients have concomitant arthritis. Other comorbidities include depression/suicide, autoimmune disease, cardiovascular disease, and metabolic syndrome (Menter et al. 2008).	Plaque Psoriasis can be a serious disease because of its chronicity, impact on quality of life, and co-morbidities.
Current Treatment Options	Available treatment options for the treatment of (mild to moderate) plaque psoriasis include targeted phototherapy (e.g., excimer light therapy with UV-B at a wavelength of 308 nm), off-label use of topical calcineurin inhibitors tacrolimus or pimecrolimus (not FDA-approved for psoriasis); and the following FDA-approved topical treatments for psoriasis: ☐ Multiple classes/strengths/formulations of topical corticosteroids (TCS) approved for the indication of "treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses (CSRD)" ☐ Vitamin D analogues (e.g., calcipotriene) ☐ Keratolytic/Retinoid (e.g., tazarotene) ☐ Combination topical therapies [TCS/vitamin D analogue, TCS/retinoid] ☐ Aryl hydrocarbon receptor (AhR) modulating agonist (e.g., tapinarof)	There are several FDA-approved products with an acceptable benefit-risk profile for the treatment of plaque psoriasis. Although the efficacy varies, no product produces a response in all patients or provides a permanent cure. Phototherapy and photochemotherapy may be impractical due to office-based administration requirements. All the systemic products may have one or more serious adverse reactions, including malignancy, serious infections, teratogenicity, depression, nephrotoxicity, hepatotoxicity, and bone marrow suppression (Menter et al. 2008).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Approved products for the systemic treatment of (moderate to severe) plaque psoriasis include anti-metabolites (methotrexate), tumor necrosis factor inhibitors (etanercept, adalimumab and infliximab), interleukin (IL)-12/23 blockers (ustekinumab), IL-17A blockers (secukinumab and ixekizumab), an IL-17A receptor antagonist (brodalumab), IL-23 blockers (guselkumab and tildrakizumab), a T cell inhibitor (cyclosporine), retinoids (acitretin) and phosphodiesterase-4 inhibitors (apremilast [for mild to severe psoriasis]). Other treatment options include phototherapy with either PUVA (UV-A light combined with methoxsalen) or UV-B light (narrow or broadband). Approved therapeutic options may be associated with the risk of serious adverse reactions or administration challenges. The use of phototherapy and photochemotherapy are limited by the need for office administration and additional photoprotection. Teratogenicity and hyperlipidemia are labeled risks with acitretin. Depression and weight loss are safety concerns with apremilast. The primary risks of cyclosporine use are nephrotoxicity and hypertension. Methotrexate has teratogenic, hepatotoxic, and nephrotoxic effects and may cause bone marrow toxicity and pulmonary fibrosis. Other systemic products may cause immunosuppression, serious infections and malignancy. All biologic products may be associated with loss of effect and serious hypersensitivity 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	For the vehicle-controlled trials [phase 3 trial (ARQ-154-309) and phase 2 trial (ARQ-154-204)], the (co)-primary efficacy endpoint Scalp–Investigator Global Assessment (S-IGA) success [defined as S-IGA =0 or 1 and ≥2-point improvement from baseline] at Week 8 and the (co)-primary/secondary efficacy endpoint of Body-Investigator Global Assessment (B-IGA) success (defined as B-IGA =0 or 1 and ≥2-point improvement from baseline) at Week 8 in the intent-to-treat (ITT) population; roflumilast foam, 0.3% was statistically superior to vehicle foam and achieved the following response rates compared to the vehicle foam, respectively: 1. For the efficacy endpoint of S-IGA success at week 8, a response of 66.4% vs. 27.8% (p-value<0.001) [a treatment effect of 37.1%] in Trial ARQ-154-309, and 56.7% vs. 11.0% (p-value<0.001) [a treatment effect of 47.7%] in Trial ARQ-154-204. 2. For the efficacy endpoint of B-IGA success at week 8, a response of 45.5% vs. 20.1% (p-value<0.001) [a treatment effect of 24.8%] in Trial ARQ-154-309, and 39.0% vs. 7.4% (p-value<0.001) [a treatment effect of 32.4%] in Trial ARQ-154-204. 3. For the secondary efficacy endpoint of scalp itch (Scalp Itch Numerical Rating Scale [SI-NRS]) success (≥4-points improvement from baseline) at week 8, a response of 65.3% vs. 30.3% (p<0.001), [a treatment effect of 35.4%] in Trial ARQ-154-309 (p-value<0.001); and a response of 67.3% vs. 20.7% (p<0.001), [a treatment effect of 43.6%] in Trial ARQ-154-204 (p-value<0.001). In Trial ARQ-154-204, SI-NRS was only assessed at study visits, rather than through a daily diary assessment.	The data submitted by the Applicant met the evidentiary standard for provision of substantial evidence of effectiveness [as two adequate and well-controlled trials] under the proposed conditions of use. Trials ARQ-154-309/-204 were adequate and well-controlled and the results are persuasive.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	4. For the secondary efficacy endpoint [in Trial -309] of the whole-body itch (Worst Itch NRS [WI-NRS]) success (≥4-points improvement from baseline) at week 8, a response of 63.1% vs. 30.1% (p<0.001), [a treatment effect of 32.8%]. For all secondary efficacy endpoints intended for labeling, roflumilast foam, 0.3% was statistically superior to the vehicle foam for the ITT population.	
Risk and Risk Management	The primary safety database consisted of 734 subjects from the vehicle-controlled (VC) trials (a phase 3 trial [ARQ-154-309] and a phase 2 trial [ARQ-154-204]) treated once daily for 8 weeks. The safety database is adequate to characterize the safety profile of ZORYVE foam, 0.3%. During the VC trials (ARQ-151-301/-302), serious adverse events (SAEs) were reported for 3/479 (0.6%) subjects in the ZORYVE foam group (1 SAE possibly related to study drug), and 1/255(0.4%) subjects in the vehicle group. Adverse drug reactions (possibly, probably, or likely related to study drug) were reported for 24/479 (5.0%) of subjects in the ZORYVE foam group, compared to 12/255 (4.7%) subjects in the vehicle group. The most common (reported for ≥1% of subjects) adverse events (treatment-emergent adverse events [TEAEs]) reported in the ZORYVE foam group, and more frequent than the vehicle foam group, were headache (3.1%), diarrhea (2.5%), nausea (1.7%), and nasopharyngitis (1.3%). The effects of ZORYVE Foam on pregnant or lactating women are unknown.	The safety profile of ZORYVE foam, 0.3% has been adequately characterized by the premarket safety data for psoriasis. 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 (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		
		x	Patient reported outcome (PRO)	SI-NRS, WI-NRS, PSD Score, PSSI-75, subject-rated local tolerability score, C-SSRS, PHQ-8/PHQ-A, DLQI/CDLQI
		☐	Observer reported outcome (ObsRO)	
		x	Clinician reported outcome (ClinRO)	IGA (S-IGA and B-IGA), PASI, Investigator-rated local tolerability score
		☐	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		
	x	Patient-focused drug development or other stakeholder meeting summary reports		The Voice of the Patient: the U.S. FDA's Patient-Focused Drug Development Initiative Psoriasis (Public Meeting: March 17, 2016; Report Date: November 2016)

	☐	Observational survey studies designed to capture patient experience data	
	☐	Other: (Please specify):	
☐	**Patient experience data was not submitted as part of this application.**		

Abbreviations: B-IGA, Body-Investigator Global Assessment; BSA, Body Surface Area Affected by Plaque Psoriasis of the Scalp and Body; CDLQI, Children's Dermatology Life Quality Index; C-SSRS, Columbia- Suicide Severity Rating Scale; DLQI, Dermatology Life Quality Index; FDA, Food and Drug Administration; IGA, Investigator Global Assessment; IP, investigational product; PASI, Psoriasis Area and Severity Index; PHQ-8, Patient Health Questionnaire depression scale; PHQ-A, modified Patient Health Questionnaire-9 for adolescents; PSD, Psoriasis Symptom Diary; PSSI, Psoriasis Scalp Severity Index; PSSI-75, Achievement of a 75% reduction in PSSI from baseline in Psoriasis Scalp Severity Index; Scalpdex questionnaire; S-IGA, Scalp-Investigator Global Assessment; SI-NRS, Scalp Itch Numerical Rating Scale; WI-NRS, Worst Itch Numerical Rating Scale

2 Therapeutic Context

2.1. Analysis of Condition

Psoriasis is a common, chronic, immune-mediated skin disorder. The characteristic lesion is a sharply demarcated erythematous plaque with micaceous scale, and the plaques may be localized or widespread in distribution (Feldman 2015). Psoriasis is a complex autoimmune inflammatory disease that occurs in genetically susceptible individuals. The pathophysiology of psoriasis involves the activation of innate immune cells in the skin, which produce proinflammatory cytokines which trigger and perpetuate the inflammatory cascade (Blauvelt and Ehst 2015).

In the United States and Canada, prevalence as high as 4.6% and 4.7% have been reported, respectively (Feldman 2015). It is estimated that approximately 7.5 million people in the United States have psoriasis. Approximately 80 percent of those affected with psoriasis have mild to moderate disease, while 20 percent have moderate to severe psoriasis affecting more than 5 percent of the body surface area. The most common form of psoriasis is plaque psoriasis, affecting about 80 to 90 percent of patients with psoriasis (Menter et al. 2008).

Psoriasis can first appear at any age, from infancy to the eighth decade of life. Two peaks in age of onset have been reported: one at 20–30 years of age and a second peak at 50–60 years. In approximately 75% of patients, the onset is before the age of 40 years, and in 35–50%, it is before the age of 20 years. The average age of onset is earlier in women than in men (Feldman 2015).

The natural history of psoriasis is chronic with intermittent remissions. Although plaque psoriasis is the most common presentation, other forms of psoriasis include guttate, pustular, erythrodermic, and inverse psoriasis. Psoriasis may affect fingernails and toenails, most frequently in association with psoriatic arthritis. A diagnosis of psoriasis can be made by history and physical examination in most cases. The differential diagnosis of psoriasis may include seborrheic dermatitis, lichen simplex chronicus, atopic dermatitis, and nummular eczema. Occasionally, a skin biopsy is performed to rule out other conditions (Feldman 2015).

The presentation of psoriasis in the pediatric population can be different from that in adults. Psoriasis in infants often presents with involvement of the diaper area. Infants with diaper-area involvement typically develop symmetrical, well-demarcated erythematous patches with little scale. Maceration may be present. Unlike irritant diaper dermatitis, the inguinal folds are usually involved. Affected infants may also have psoriatic plaques in other body areas. These plaques are often smaller and thinner than the psoriatic plaques in adult patients. In children, scalp involvement is a common and often initial presentation of chronic plaque psoriasis. In addition, children with chronic plaque psoriasis are more likely to have facial involvement than adults (Feldman 2015).

A number of comorbid systemic conditions occur more frequently in patients with psoriasis. Examples of these conditions include cardiovascular disease, malignancy, diabetes, hypertension, metabolic syndrome, inflammatory bowel disease, serious infections, and autoimmune disorders. Psychiatric comorbidities associated with psoriasis include depression and suicidal ideation; neurotic, stress-related, or somatoform disorders; and personality and behavioral disorders (Korman 2017).

The impact of psoriasis on the daily lives of patients was among the topics discussed at a Patient-Focused Drug Development meeting for psoriasis held by the Agency on March 17, 2016. Patients who attended the meeting described severe physical, social and emotional impact including depression, anxiety, limitations on activities, embarrassment, stigma, and social discrimination. Patients shared their experiences with currently available therapies, and they described varying degrees of success in managing symptoms with these therapies. Patients stressed need to enlarge the treatment armamentarium, given current challenges with variability in effectiveness, tolerability, access to available treatments, and uncertainty regarding long-term effects of available treatments.

Psoriasis is a chronic, debilitating disease with significant impacts on the lives of affected patients. At the Patient-Focused Drug Development meeting, patients discussed current challenges with variability in effectiveness, tolerability, access to available treatments, and uncertainty regarding long-term effects of available treatments. Therefore, development of additional safe and effective therapies continues to be an important goal. This is especially true for certain subgroups of patients with psoriasis.

2.2. Analysis of Current Treatment Options

Moderate to Severe Plaque Psoriasis

The FDA-approved systemic products for the treatment of moderate to severe plaque psoriasis belong to multiple categories, including Antimetabolite/Immunosuppressant (e.g., methotrexate), Tumor Necrosis Factor Inhibitor (e.g., infliximab, adalimumab, etanercept, certolizumab), interleukin (IL)-12/IL-23 Inhibitor (e.g., ustekinumab), IL-17A Inhibitor (e.g., secukinumab, ixekizumab), IL-17A receptor antagonist (e.g., brodalumab), IL-23 Inhibitor (e.g., guselkumab, tildrakizumab, rizankizumab), T-Cell Inhibitor/ Immunosuppressant (e.g.,

cyclosporine), Retinoid (e.g., acitretin), PDE-4 Inhibitor (e.g., apremilast [approved for mild to severe]), and phototherapy.

Mild to Moderate Plaque Psoriasis

In clinical practice (Armstrong and Read 2020), treatment options for patients with mild to moderate plaque psoriasis include targeted phototherapy (e.g., excimer light therapy with UV-B at a wavelength of 308 nm), off-label use of topical calcineurin inhibitors tacrolimus or pimecrolimus (topical calcineurin inhibitors are not FDA-approved for topical treatment of psoriasis); and FDA-approved topical treatments including multiple classes/strengths/ formulations of topical corticosteroids (TCS) approved for the indication of "treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses (CSRD)," Vitamin D analogues (calcipotriene cream), Vitamin D analogues/TCS combination (calcipotriene and betamethasone dipropionate ointment), Keratolytic/Retinoid (tazarotene cream), Retinoid/TCS combination (halobetasol propionate and tazarotene lotion), Aryl hydrocarbon receptor modulating agonist (tapinarof cream), and topical PDE-4 inhibitor (roflumilast cream).

Plaque Psoriasis of the Scalp

FDA approved products with the indication of the treatment of plaque psoriasis of the scalp or labeling information describing their treatment effect on plaque psoriasis of the scalp include TCS (clobetasol propionate foam/shampoo/scalp application), topical synthetic vitamin-D derivative (calcipotriene aerosol foam), topical synthetic vitamin-D derivative/TCS combination (calcipotriene/betamethasone dipropionate suspension); and systemic treatments (including oral PDE-4 inhibitor [OTEZLA], IL-17A antagonist [Secukinumab], and IL-23 antagonist [Guselkumab]) as summarized in the following table.

Table 1. FDA Approved Products for the Treatment of Plaque Psoriasis of the Scalp

Product (s) Name/Year of Approval	Relevant Indication	Dosing/ Administration	Efficacy Information From Labeling	Important Safety and Tolerability Issues
Corticosteroids (Topical Treatment)				
Olux (clobetasol propionate) foam, 0.05% NDA 021142 2000	Treatment of moderate to severe plaque psoriasis of the scalp and mild to moderate plaque psoriasis of non-scalp regions of the body excluding the face and intertriginous areas in subjects 12 years and older.	Apply a thin layer to the affected skin areas twice daily, up to 2 consecutive weeks	From the Label: 1 R, DB, PC trial: Primary treatment success a composite of an IGA =0,1, plaque thickness score =0, erythema score =0, 1, scaling score =0, 1 at 2 Weeks (severity scale 0-4)	W&P: reversible hypothalamic - pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, hyperglycemia, Ophthalmic Adverse Reactions (glaucoma and posterior subcapsular cataract), Allergic contact dermatitis (failure to heal), flammable
Clobex shampoo (clobetasol propionate, 0.05%) shampoo NDA 021644 2004	Treatment of moderate to severe psoriasis of the scalp in subjects 18 years of age and older.	Apply onto dry (not wet) scalp once a day in a thin film to the affected areas only, and left in place for 15 minutes before lathering and rinsing	From the Label: 2 R, DB, PC trials: Trials 1,2-primary scalp PGSS =0,1 (0-5 scale) at Week 4 1-Clobex 42%/ Placebo 2% 2-Clobex 28%/ Placebo 10%	W&P: Similar to Olux foam. atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, and miliaria
Temovate (clobetasol propionate scalp application), 0.05% NDA 19966 1990	Short-term topical treatment of inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses of the scalp	Apply to the affected scalp areas twice daily (up to 2 consecutive weeks)	Not included in label	Similar to other TCS

Product (s) Name/Year of Approval	Relevant Indication	Dosing/ Administration	Efficacy Information From Labeling	Important Safety and Tolerability Issues
Synthetic Vitamin D_3 Derivative (Topical Treatment)				
Sorilux (calcipotriene, 0.005%) aerosol, foam NDA 22563 2010, 11/2019	Topical treatment of plaque psoriasis of the scalp and body in patients (≥12 years in 2010, ≥4 years in 11/2019).	Apply a thin layer of SORILUX Foam twice daily to the affected areas and rub in gently and completely (up to 8 weeks)	From the Label: 1 R, DB, PC trial for psoriasis of the scalp: primary scalp ISGA =0,1 (0-5 scale) at Week 8 1-Sorilux foam 41%/ placebo 24%	Contra-indication: known hypercalcemia. W&P: Flammability of foam, Transient, rapidly reversible elevation of serum calcium. TEAEs: application site erythema (2%) and application site pain (3%)
Synthetic Vitamin D_3 Derivative/ Corticosteroid Combination (Topical Treatment)				
Taclonex (calcipotriene 0.005% and betamethasone Dipropionate 0.064%) topical suspension, NDA 22185 2008, 2019	Topical treatment of plaque psoriasis of the scalp and body in subjects 12 years of age and older	Apply to affected areas on the scalp once daily for 2 weeks or until cleared, may continue up to 8 weeks	From the Label: 2 R, DB, trials (1- PC/AC, 2-AC): Primary: IGA =0,1 at Week 8 1-Taclonex scalp /Betamethasone /calcipotriene/vehicle: 70%/63%/37%/20% 2-Taclonex scalp/Betamethasone/calcipotriene: 67%/60%/41%	W&P: Hypercalcemia and hypercalciuria and W&P similar to other TCS (e.g. Olux, Clobex)
PDE-4 Inhibitor (Systemic Treatment, Oral)				
OTEZLA (apremilast), 2014	Moderate to severe Plaque Psoriasis Involving the Scalp Area	Adult patients: 30 mg BID after titration on days 1-5 Pediatric patients 6 years and older, weighing ≥20 kg: based on body weight	From the label: 1 R, DB, PC trial: ScPGA: 43.3% v. 13.7% at W 16 Whole body itch NRS response: 45.5% v. 22.5% at W 16 Scalp itch NRS response: 47.1% v. 21.1% at W 16	W&P: Hypersensitivity; Diarrhea, Nausea, and Vomiting; Depression; Weight Decrease; Drug Interaction.
IL-17A Antagonist (Systemic Treatment, Injection)				
Cosentyx (Secukinumab), 2015, 2018	Moderate to severe Psoriasis of the scalp	300 mg SC at Weeks 0, 1, 2, 3 and 4 followed by 300 mg SC every 4 weeks. For some patients, a dose of 150 mg may be acceptable	From the label: 1 R, DB, PC trial. Primary: proportion of subjects with PSSI90 at Week 12: 53%/2% secondary: IGA (scalp only)=0,1 at Week 12: Cosentyx: 57%/vehicle 6%	W&Ps: Infections (serious bacterial, fungal and viral), theoretical risk for serious infections, Crohn's disease, hypersensitivity reactions, pretreatment eval for TB.

Product (s) Name/Year of Approval	Relevant Indication	Dosing/ Administration	Efficacy Information From Labeling	Important Safety and Tolerability Issues
IL-23 antagonist (Systemic Treatment, Injection)				
Guselkumab (Tremfya) NDA 761061 2017	Moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy	100mg by subcutaneous injection at Week 0, Week 4, and every 8 weeks thereafter	Section 14 for psoriasis of the scalp: An improvement was seen in psoriasis involving the scalp in subjects randomized to TREMFYA compared to placebo at Week 16.	W&Ps: Infections (upper respiratory tract infections, gastroenteritis, tinea infections, and herpes simplex infections), pretreatment eval for TB, avoid live vaccines.

Source: adapted from the clinical review of sNDA 205437-008 (OTEZLA) for the treatment of psoriasis of the scalp.
Abbreviations: AC, active-comparator; BID, twice daily; DB, double-blind; IGA, Investigator Global Assessment; IL, interleukin; ISGA, Investigator Static Global Assessment; NRS, Numerical Rating Scale; PC, placebo-controlled; PDE-4, phosphodiesterase-4; PGSS, Psoriasis Global Severity Score; PSSI90, achievement of a 90% reduction in PSSI from baseline in Psoriasis Scalp Severity Index; R, randomized; SC, subcutaneous(ly); ScPGA, Scalp Physician Global Assessment; TCS, topical corticosteroid; TEAE, treatment-emergent adverse event; W&P, Warnings and Precautions; W 16, Week 16

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The FDA has approved the following roflumilast products for marketing in the United States:

- ZORYVE foam, 0.3% QD (once daily) was developed by the Applicant under IND 142047; NDA 217242 was approved on December 15, 2023, for the topical treatment of seborrheic dermatitis in patients 9 years of age and older.
- ZORYVE cream, 0.3% QD was developed by the Applicant under IND 135681; NDA 215985 was approved on July 29, 2022, for the topical treatment of plaque psoriasis, including intertriginous areas, in patients 12 years of age and older. Supplement NDA 215985-002 approved on October 5, 2023, expanded the age group to patients 6 years of age and older with plaque psoriasis.
- ZORYVE cream, 0.15% QD was developed by the Applicant under IND 135681; sNDA 215985-007 was approved on July 9, 2024, for the topical treatment of mild to moderate atopic dermatitis in patients 6 years of age and older.
- Roflumilast oral tablets (DALIRESP, 250 mcg, 500 mcg) were approved in 2011 (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.”

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed roflumilast foam for topical treatment of plaque psoriasis of the scalp and body under IND 142047 and submitted their marketing application for sNDA 217242-005 under 505(b)(1) regulatory pathway. Milestone interactions with the Applicant included the following:

Pre-IND Meeting (Roflumilast Foam, 0.3% QD)

A pre-IND-written response only letter (for seborrheic dermatitis) was conveyed to the Applicant on August 13, 2019. No pre-IND meeting was held for supplement-005 (psoriasis of the scalp and body).

Type C Guidance Meeting-Written Response Only (June 21, 2023)

1. Integrated data analysis and pooling for the integrated summary of safety (ISS) and integrated summary of effectiveness (ISE) discussed
2. The format (Clinical Data Interchange Standards Consortium) and placement of ISS/ISE text (M 2.7.3, 2.7.4), statistical analysis plan (SAP) and data (M. 5.3.5.3), discussed
3. Applicant's plan to submit subject narratives and case report forms with electronic links for all deaths, serious adverse events (SAEs), adverse events leading to discontinuation (AELDs), severe adverse events (AEs), all subject discontinuations for any reason, pregnancies, and hypersensitivity reactions was deemed acceptable

End-of-Phase 2 Meeting (April 28, 2021)

Phase 3 (P3) development plans were discussed, including:

1. Establishing substantial evidence of effectiveness based on 1 adequate and well-controlled trial and supportive (confirmatory) evidence; and powering P3 trial and control of type-1 error
2. Design elements of the P3 trial, ARQ-154-309, Inclusion of subjects ≥12 years of age and related inclusion criteria
3. Co-primary efficacy endpoints of S-IGA success and B-IGA success at week 8 was acceptable
4. Statistical testing method, imputation method, and alpha level discussed
5. Assessment of scalp itch (Scalp Itch Numerical Rating Scale [SI-NRS]) and worst (body) itch (Worst Itch NRS [WI-NRS]) success for efficacy
6. Discussed patient-reported outcomes proposed by the Applicant
7. Size and adequacy of the safety database discussed
8. No long-term safety studies planned
9. Clinical pharmacology: maximal use study (MUsT) for roflumilast foam will be required

Agreed iPSP Agreement (April 27, 2022)

An agreed initial pediatric study plan (iPSP) agreement letter was conveyed to the Sponsor, which included the following:

1. Plan to request a waiver for ages 0 to less than <4 years (because necessary studies are impossible or highly impracticable)
2. Deferred PK/safety study in subjects between 4 to less than 12 years of age
3. Inclusion of subjects between ≥12 years of age in the phase 3 trial

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

4.1. Office of Scientific Investigations

The overall quality of the clinical information contained in this submission was adequate. Trial ARQ-154-309 was conducted at sites in the United States and Canada; and Trial ARQ-154-204 was conducted at sites in North America, Australia, and Europe.

The Division did not request that the Office of Scientific Investigations conduct clinical inspections of any sites for this supplement (sNDA 217242-005) because of the history of recent approval of roflumilast cream, 0.3% QD for the indication of treatment of psoriasis [including inspection of 2 trial sites found acceptable]; roflumilast cream, 0.15% QD for the indication of treatment of atopic dermatitis; roflumilast foam, 0.3% QD for the indication of treatment of seborrheic dermatitis; no deviation from the good clinical practice; and no concerns with any sites identified by the statistical reviewer (Daeyoung Lim, PhD.).

4.2. Product Quality

The provided claim of categorical exclusion to the environmental assessment requirements in compliance with categorical exclusion criteria in 21 CFR 25.31(b) and 21 CFR 25.15 (a) is acceptable from the CMC standpoint.

The proposed new indication of plaque psoriasis of the scalp and body uses the same drug product previously approved for the treatment of seborrheic dermatitis (i.e., ZORYVE® (roflumilast) foam, 0.3%). There are no changes proposed in this submission to the drug substance or drug product.

The provided justification to use “foam” instead of “topical foam” as the dosage form is acceptable based on the clinical team’s evaluation and this drug product reviewer’s assessment. Adding a comma in section 11 is acceptable from the CMC standpoint. Moving a period to the end of the sentence in section 16 is acceptable from the CMC standpoint. There

are no changes to CMC relevant sections 3 of the U.S. prescribing information (USPI) or to the corresponding sections of the Highlights. The updated USPI, Patient Information, and Instructions for Use are acceptable from the CMC standpoint.

4.3. Clinical Microbiology

Not applicable to this review.

4.4. Devices and Companion Diagnostic Issues

Not applicable to this review.

5 Nonclinical Pharmacology/Toxicology

Not applicable to this review.

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant is seeking approval of roflumilast foam 0.3% (ZORYVE) for topical treatment of plaque psoriasis of the scalp and body, in patients 12 years of age and older. Roflumilast and its active metabolite (roflumilast N oxide) are selective inhibitors of PDE-4. In December 2023, roflumilast foam 0.3% was approved in the United States for the treatment of seborrheic dermatitis in patients 9 years of age and older. An oral formulation of roflumilast (DALIRESP; NDA 022522) was approved by the FDA in February 2011 to reduce the risk of COPD exacerbations associated with chronic bronchitis. This Applicant has obtained right of reference for non-clinical data submitted in NDA 022522 and have followed a 505(b)(1) regulatory pathway. Additionally, roflumilast cream 0.3% was approved in July 2022 for the treatment of plaque psoriasis in the United States in patients 12 years of age and older and the indication was extended now to 6 years of age in October 2023. In July 2024, roflumilast cream 0.15% was approved for the indication of atopic dermatitis in subjects 6 years of age and older.

The Clinical Pharmacology program in this submission consists of a MUsT to evaluate pharmacokinetics and safety of QD topical application of roflumilast foam 0.3% for two weeks in subjects 12 years of age and older with at least 10% of scalp involved and body psoriasis affecting ≥10% body surface area (BSA; excluding palms and soles) in adolescents, and with at least 10% of scalp involved and body psoriasis affecting at least 20% BSA involvement in adults, respectively (Trial ARQ-154-122).

The mean roflumilast and roflumilast N-oxide exposure in adolescent subjects was lower, although within 2.6- and 2.2-fold, respectively, of mean adult exposure following daily topical administration and this could be due to lower % BSA treated and hence lower dose in adolescent subjects compared to adults. When dose normalized, the resulting exposures were generally comparable between the adolescent and adult populations.

The dose normalized roflumilast and roflumilast-N-oxide systemic exposures following 0.3% foam application in ARQ-154-122 MUsT study were similar to the dose normalized systemic exposures in MUsT study of roflumilast cream 0.3% (ARQ-151-107) in adults and adolescent subjects with plaque psoriasis. In both of these MUsT studies, the systemic exposures in adolescents were lower compared to adults following topical application; however, the dose normalized systemic exposures were comparable between adults and adolescent subjects in both the MUsT studies.

No formal drug-drug interaction studies were conducted by the Applicant and dosing to manage drug interactions in proposed label were similar to the DALIRESP oral tablets label (NDA 022522) initially approved in United States in 2011. No renal and hepatic impairment studies were conducted by the Applicant, and they are relying on the findings from DALIRESP (NDA 022522) to inform the labeling of their topical product.

A single phase 3 trial (ARQ-154-309) was conducted by the Applicant in both adult and adolescent populations; additionally, pre-dose plasma concentrations of roflumilast and roflumilast N-oxide were collected on week 4 and week 8. Plasma roflumilast was measurable at pre-doses on week 4 and week 8 in most of the subjects following daily topical administration of roflumilast 0.3% foam. No meaningful differences in the pharmacokinetics of roflumilast and roflumilast N oxide were observed based on (i) age, when age group from 18-65 years age compared to age group older than 65 years age, (ii) on sex, when adult male subjects were compared to female subjects, (iii) on race, when White, Black, Asian, and other races were compared or (iv) on ethnicity, when Hispanic subjects were compared to non-Hispanic subjects, in the phase 3 trial (report No. AD-23-169).

Recommendation

The office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology finds sNDA 217242-005 acceptable.

Post-marketing Requirement

Conduct an open-label, maximal-use pharmacokinetics, safety and tolerability study in pediatric subjects aged 4 to <12 years old with plaque psoriasis of the scalp and body targeting at least 16 evaluable subjects in whom pharmacokinetic (PK) assessments will be performed under maximal usage conditions.

See Section 13 for additional details.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacokinetics of Roflumilast Under Maximal Use Conditions

The Applicant conducted a MUsT to characterize the plasma PK profile of roflumilast and its major N-oxide metabolite after administration of roflumilast foam 0.3% QD for 2 weeks to adolescent subjects between 12 -17 years of age with scalp and body plaque psoriasis, with at least 10% of scalp involvement and body psoriasis affecting ≥10% BSA (excluding palms and soles) in adolescents, and with at least 10% of scalp involvement and body psoriasis affecting at least 20% BSA involvement in adults, respectively. PK data was collected from at least 7 adolescent subjects with pre-dose on Day 15, and at least 19 adult subjects with pre-dose on Day 8 and multiple collections on Day 15. The MUsT trial was conducted with the to-be-marketed formulation. It is noted that there were only 7 subjects aged 12 years old in MUsT; however, inclusion of additional adolescent subjects in the Phase 3 trial and acceptable safety would support approval.

The Applicant in their study report compared the exposures following topical 0.3% foam in this MUsT trial with PK information following topical 0.3% cream (ARQ-151-107). The Applicant noted that in adults based on cross-study comparison, both mean peak and mean total exposures of roflumilast following topical application of 0.3% foam was slightly higher than the topical 0.3% cream (4.48 vs 3.72 ng/mL, 90.0 vs 72.7 h*ng/mL, respectively) following 2 weeks of QD administration (Table 3, 2.7.2. Clinical Pharmacology Summary). A similar trend was observed for the metabolite roflumilast N-oxide. Mean peak and mean total systemic exposures following 0.3% foam topical application were similar (29.9 vs 30.6 ng/mL, 567 vs 628 h*ng/mL, respectively); additionally, dose normalized mean C_{max} appeared comparable, with the exception of dose-normalized AUC_{0-24} (area under the concentration-time curve from 0 to 24 hours) where the 0.3% cream appeared to be slightly higher (Table 3, 2.7.2. Clinical Pharmacology Summary).

Following daily administration of roflumilast foam 0.3% under maximum use conditions, the Day 15 pre-dose concentration of roflumilast and roflumilast N-oxide was lower in adolescent subjects when compared to adult subjects (1.48 vs 3.89 ng/mL and 11.3 vs 24.7 ng/mL, respectively) and this could be because of lower % BSA and lower dose in adolescent compared to adults. However, the mean dose normalized Day 15 pre-dose concentrations of roflumilast and roflumilast N-oxide appeared to be generally comparable between adolescents and adult subjects (0.101 vs 0.135 ng/mL and 0.771 vs 0.850 ng/mL, respectively) (Table 17 of clinical study report [CSR] ARQ-154-122).

Summary of Safety in MUsT

Roflumilast foam 0.3% appeared to be well tolerated in this study, with no serious adverse events, no deaths, and few treatment-emergent adverse events (TEAEs) observed. One adolescent subject had a TEAE (headache), and 5 adult subjects had at least 1 TEAE during the study. The only TEAE reported in >1 adult subject was insomnia in 2 subjects (1 mild and 1 moderate). Local tolerability was assessed based on both investigator-rated and subject-rated local tolerability assessments and the topical treatment appeared to be well tolerated. Roflumilast foam 0.3% did not appear to have any influence on clinical laboratory assessments, vital signs, including body weight, physical examination findings, or electrocardiogram (ECG) parameters. No discontinuation of investigational product (IP) due to AEs was reported for any subject. See Section 8 for further information on safety.

Pharmacokinetics of Roflumilast in Phase 3 Trial

A single Phase 3 trial (ARQ-154-309) was conducted by the Applicant to evaluate roflumilast foam 0.3% safety and efficacy in subjects 12 years of age and older with plaque psoriasis involving ≥10% of scalp, ≤25% total BSA.

The was a parallel, randomized, double-blind, vehicle controlled, safety and efficacy trial of roflumilast foam 0.3% and vehicle in subjects ≥12 years of age with chronic plaque psoriasis of scalp and body, (excluding palms, and soles) and an IGA of at least mild at baseline. Subjects were randomized 2:1 to receive roflumilast foam 0.3% or matching foam vehicle QD for 8 weeks. Roflumilast plasma concentrations were measured pre-dose at baseline and Weeks 4 and 8. The mean trough concentration at week 8 were lower than the Week 4 for both roflumilast and roflumilast N-oxide, and the decrease was no more than 36% for both analytes in adults and adolescent subjects. This could be due to the healing of the skin which may have changed drug absorption potential. Additionally, a similar trend was observed in dose-normalized pre-dose concentrations (Table 9, 2.7.2 Summary of Clinical Pharmacology). Mean trough concentrations for roflumilast were 2.07 ng/mL at week 4 and 1.55 ng/mL at week 8, and roflumilast N-oxide mean trough concentrations were 13.1 ng/mL and 9.66 ng/mL at week 4 and week 8, respectively, in adult subjects. No clinically meaningful differences in the pharmacokinetics of roflumilast and roflumilast N oxide were observed based on age groups below 65 years vs. above 65 years old, sex, race, or ethnicity in the phase 3 trial.

Drug Interaction of Roflumilast

No drug interaction studies were conducted with roflumilast foam. However, drug-interaction studies were conducted in support of the oral roflumilast. Based on the results from drug interaction studies conducted in support of oral roflumilast, it is anticipated that coadministration of roflumilast with systemic cytochrome P450 3A4 (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. Also, the co-administration of roflumilast with oral contraceptives containing gestodene and ethinyl estradiol were observed to produce an

increase in roflumilast systemic exposure and this may result in increased side effects. The risk of such concurrent use should also be weighed carefully against benefit for this topical product.

Dosing in Subjects With Renal or Hepatic Impairment

No studies were conducted in subjects with renal and hepatic impairment with roflumilast foam. Oral roflumilast is not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh B or C). No specific dosing is being recommended for subjects with renal impairment. The topical label would carry similar recommendations for dosing.

Although this Applicant has not conducted any new drug-drug interaction study and hepatic and renal impairment studies, the maximal use study did capture the worst case scenario for systemic exposure with the mean % BSA of 29.5% and 14.9% in adults and adolescent subjects, respectively, compared to 6.14% and 4.98% in adults and adolescent subjects, respectively, in the Phase 3 trial. Also, the mean predicted dose, assuming 2 mg per cm^2 rate of application, in the maximal use study was 30 mg and 14 mg respectively in adults and adolescent subjects compared to 6.3 mg and 4.72 mg in adults and adolescents respectively, in the Phase 3 trial. Based on this data, it appears that the systemic exposure on actual clinical use might not be as high as those observed in the MUsT trial. Hence, in the opinion of this reviewer, actual clinical use would most likely not produce any increased risk for this topically applied product.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen is to apply a thin layer of roflumilast 0.3% foam to the affected areas once a day is supported by the results of phase 3 trial. See Section 8 for additional information on safety and efficacy.

Therapeutic Individualization

The Applicant did not conduct studies for therapeutic individualization of the proposed roflumilast cream 0.3% product and such assessment is not warranted.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Maximal Use PK Study

Roflumilast is a PDE-4 inhibitor approved as an oral formulation to reduce the risk of exacerbations in patients with severe COPD associated with chronic bronchitis.

This Applicant has developed roflumilast foam 0.3% to be applied topically once daily for the treatment of plaque psoriasis of the scalp and body, in patients 12 years of age and older. The main objective of this study was to determine the systemic exposure and characterization of the plasma PK profile of roflumilast and its major N-oxide metabolite following administration of to-be-marketed formulation of roflumilast foam 0.3% QD for 2 weeks to adolescent subjects (12 -17 years of age) with chronic plaque psoriasis with at least 10% of scalp affected, and at least mild body psoriasis with at least 10% non-scalp BSA involved in adolescents and 20% non-scalp BSA in adults involved in adults. The study was designed to ensure that a suitable number of subjects with plaque psoriasis within the upper range of disease severity would be evaluated, and pharmacokinetics would be adequately characterized. Summary of demographics is shown in Table 2.

Table 2. Summary of Demographics, Trial ARQ-154-122

Variable Statistic/Category	Adolescents (N=7)	Adults (N=23)	Overall (N=30)
Age (year)			
N	7	23	30
Mean (SD)	13.9 (1.77)	52.0 (16.55)	43.1 (21.84)
Median	13.0	53.0	47.5
Min, max	12, 16	20, 83	12, 83
Sex			
Male, n (%)	5 (71.4)	18 (78.3)	23 (76.7)
Female, n (%)	2 (28.6)	5 (21.7)	7 (23.3)
Childbearing potential [a]			
Yes, n (%)	0	4 (80.0)	4 (57.1)
No, n (%)	2 (100)	1 (20.0)	3 (42.9)
Ethnicity			
Hispanic or Latino, n (%)	2 (28.6)	16 (69.6)	18 (60.0)
Not Hispanic or Latino, n (%)	5 (71.4)	7 (30.4)	12 (40.0)
Race			
Asian	0	2 (8.7)	2 (6.7)
Black or African American	2 (28.6)	0	2 (6.7)
White	5 (71.4)	21 (91.3)	26 (86.7)
Height (cm)			
N	7	23	30
Mean (SD)	162.74 (15.035)	168.52 (9.808)	167.17 (11.222)
Median	157.50	170.20	170.20
Min, max	141.8, 183.0	147.3, 188.0	141.8, 188.0
Weight (kg)			
N	7	23	30
Mean (SD)	59.74 (14.194)	84.85 (17.521)	78.99 (19.779)
Median	55.00	86.70	80.15
Min, max	45.1, 79.4	50.4, 110.0	45.1, 110.0

(Continued)

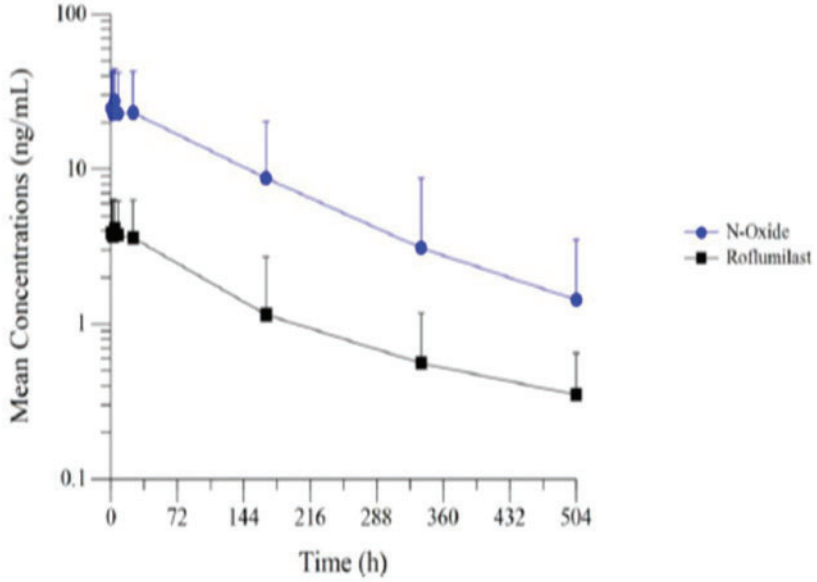
(Table 2, continued)

Variable Statistic/Category	Adolescents (N=7)	Adults (N=23)	Overall (N=30)
Body mass index (kg/m^2)			
N	7	23	30
Mean (SD)	22.53 (4.403)	29.82 (5.772)	28.12 (6.255)
Median	22.30	28.50	27.20
Min, max	18.3, 30.1	21.7, 44.3	18.3, 44.3
Baseline scalp body surface area (%)			
N	7	23	30
Mean (SD)	3.07 (1.484)	2.98 (1.334)	3.00 (1.345)
Median	3.00	3.00	3.00
Min, max	1.0, 5.0	0.8, 5.0	0.8, 5.0
Baseline extent of scalp involvement, % [b]			
N	7	23	30
Mean (SD)	50.0 (35.76)	49.7 (27.24)	49.8 (28.76)
Median	40.0	40.0	40.0
Min, max	10, 100	11, 100	10, 100
Baseline non-scalp body surface area (%)			
N	7	23	30
Mean (SD)	10.57 (0.787)	25.03 (7.942)	21.66 (9.310)
Median	10.00	21.50	21.00
Min, max	10.0, 12.0	20.0, 51.0	10.0, 51.0
Baseline total body surface area (scalp and non-scalp) (%)			
N	7	23	30
Mean (SD)	13.64 (1.651)	28.01 (8.071)	24.66 (9.391)
Median	14.00	25.00	24.00
Min, max	12.0, 16.0	22.0, 56.0	12.0, 56.0

Source: In-text-table Table 13 of ARQ-154-122 CSR.
Note: For additional demographics on the disease classification please refer to Table 13 of CSR ARQ-154-122.
[a] Only captured for female subjects; percentages are based on the number of female subjects in the Safety population.
[b] The extent of scalp involvement measured the extent of scalp affected by psoriasis, expressed as the percentage of total scalp surface area.
Abbreviations: N, number of subjects; SD, standard deviation

Blood samples were taken at Day 8 Predose, Day 15 pre-dose, 1, 2, 4, 8 and 24 h post-dose, and troughs on weeks 3, 4, and 5 in adult subjects and Day 15 troughs in adolescent subjects. Both analyte concentrations appear to decline in mono-exponential way (Figure 1).

Figure 1. Day 15 Mean Concentration vs. Time Plot of Roflumilast and Roflumilast N-Oxide



Source: ARQ-154-122 CSR, Appendix 16.1.13.2, Figure 1

Following daily administration of roflumilast foam 0.3% at maximum use conditions, systemic pharmacokinetic results in ARQ-154-122 are provided in Table 3.

Table 3. Summary of Pharmacokinetic Results on Day 15 After Daily Treatment With Roflumilast 0.3% Foam in Adolescent and Adult Subjects, Trial ARQ-154-122

Analyte Age group	Day	N	Treated BSA Non-scalp (%)[a]	Predicted Dose[b] (mg)	Conc (ng/mL)	Dose-Normalized Conc (ng/mg)	Extrapolated AUC_{0-24} (h*ng/mL)
Roflumilast							
Adolescent	15	7	10.4±0.535	14±0.51	1.48±1.73	0.101±0.115	35.5±41.4
Adult	8	19	25.0±7.88	30±8.1	4.57±3.10	0.148±0.0822	110±74.3
	15	19	25.0±7.88	30±8.1	3.89±2.42	0.135±0.0884	93.3±58.1
N-Oxide							
Adolescent	15	7	10.4±0.535	14±0.51	11.3±12.2	0.771±0.818	270±293
Adult	8	19	25.0±7.88	30±8.1	27.4±20.0	0.882±0.558	657±480
	15	19	25.0±7.88	30±8.1	24.7±18.0	0.850±0.661	593±433

Abbreviations: AUC_{0-24} = area under the plasma concentration by time curve from time 0 to 24 hours post dose administration; BSA = body surface area; Conc = concentration; N = number of subjects; PK = pharmacokinetic
[a] Total BSA treated was "treated BSA non-scalp" plus an additional 4.5% for treatment of the entire scalp.
[b] Includes dose for treated non-scalp BSA plus 4.5 mg of roflumilast for treatment of the entire scalp.
Data presented as mean ± standard deviation.

Source: ARQ-154-122, Appendix 16.1.13.3 Pharmacokinetics report, Table B.

The mean pre-dose exposure in adolescent subjects was lower, although within 2.6- and 2.2-fold of the mean adult roflumilast and N-oxide exposure, respectively, following daily topical administration. When normalizing for the dose applied, the exposures were generally comparable between the adolescent and adult populations (Table 3).

Table 4. Summary of Plasma Pharmacokinetic Parameters Following Daily Topical Administration of Roflumilast Foam 0.3% for 15 days in Adults (PK Population)

Analyte	Treated BSA Non-scalp (%)[a]	Predicted Dose[b] (mg)	C_{max} (ng/mL)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (days)
Roflumilast	25.0±7.88	30±8.1	4.48±2.28	90.0±58.7	4.9±3.3
N-Oxide	25.0±7.88	30±8.1	29.9±17.5	567±436	4.2±1.2

Abbreviations: AUC_{0-24} = area under the plasma concentration by time curve from time 0 to 24 hours post dose administration; BSA = body surface area; C_{max} = maximum concentration; max = maximum; min = minimum; PK = pharmacokinetic; SD = standard deviation; $t_{1/2}$ = half-life.
[a] Total BSA treated was "treated BSA non-scalp" plus an additional 4.5% for treatment of the entire scalp.
[b] Includes dose for treated non-scalp BSA plus 4.5 mg of roflumilast for treatment of the entire scalp.
Note: Values are presented as mean (SD).
Source: ARQ-154-122, Appendix 16.1.13.3 Pharmacokinetics report, Table A.

The Day 15 peak and total exposures (mean ± SD) of roflumilast in adult population following daily administration of 0.3% foam was 4.48 ng/mL and 90 ng/mL, respectively, and the mean apparent half-life of roflumilast in adults was estimated to be 4.9 days (Table 4). Drug half-life was not estimated in the adolescent subjects.

In summary when accounting for dose in adolescent and adult subjects, the mean Day 15 trough values were lower for adolescent subjects as compared to adults. This may be due to the fact that for psoriasis indication in the maximal use study require at least 10% non-scalp BSA affected in adolescents and 20% non-scalp BSA affected in adults and hence, the adolescent dose is expected to be lower than adult dose, thus producing an overall lower exposure. A similar trend was observed in 0.3% cream product.

Mean Dose Used in MUsT and Phase 3 Trials

The mean dose in the maximal use study was 30 mg and 14 mg respectively in adults and adolescent subjects compared to 6.33 mg and 4.72 mg respectively in adults and adolescent subjects in the Phase 3 trial. Based on this data, it appears that the systemic exposure on actual clinical use might not be as high as those observed in MUsT. Hence, in the opinion of this reviewer, actual clinical use would most likely not produce any increased risk for this topically applied product.

Phase 2b Trial

A phase-2b trial, ARQ-154-204, evaluated the safety and efficacy of roflumilast foam 0.3% in a parallel, double-blind, vehicle foam-controlled study in subjects ≥12 years of age with chronic plaque psoriasis of the scalp and body, involving ≥10% of scalp, ≤25% total BSA (excluding palms and soles). Mean treated BSA in Phase 2 trial was approximately 7%.

Either roflumilast foam 0.3% or vehicle foam was applied QD over 8 weeks in 302 subjects between ages 12 to 87 years in this Phase 2b trial. Exposures for roflumilast and roflumilast N-oxide after daily administration of roflumilast foam 0.3% is provided in Table 5.

Phase 3 Trial

A single phase 3 trial, ARQ-154-309, evaluated the safety and efficacy of roflumilast foam 0.3% in a parallel, double-blind, vehicle-controlled study in subjects ≥12 years of age with chronic plaque psoriasis of the scalp and body, involving ≥10% of scalp, ≤25% total BSA (excluding palms and soles). Mean treated BSA in ARQ-154-309 was 6%.

Either roflumilast foam 0.3% or vehicle foam was applied QD over 8 weeks in 432 subjects between ages 12 to 87 years in this phase 3 trial. Roflumilast and roflumilast N-oxide plasma concentrations were measured predose at weeks 4 and 8. Pharmacokinetic parameters for roflumilast and roflumilast N-oxide after daily administration of roflumilast foam 0.3% is provided in Table 5.

Table 5. Summary of Predose Concentrations of Roflumilast and Roflumilast N-Oxide in Adults at Week 4 and Week 8 Following Daily Treatment of Roflumilast 0.3% Foam in Phase 2 (ARQ-154-204) and Phase 3 (ARQ-154-309) Trials

	Treated BSA (%)		Predicted Dose (mg)		Concentration (ng/mL)		Dose-Normalized Concentration[a] (ng/mL/mg)		Extrapolated AUC_{0-24}[b] (ng·h/mL)	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Roflumilast										
ARQ-154-309										
Week 4	249	6.17 (4.27)	249	6.33 (4.38)	249	2.07 (2.21)	249	0.442 (0.491)	240	51.6 (53.2)
Week 8	254	6.14 (4.28)	254	6.30 (4.39)	254	1.55 (1.81)	254	0.345 (0.504)	228	41.6 (43.8)
ARQ-154-204										
Week 4	164	7.38 (5.38)	164	7.57 (5.52)	162	2.35 (2.74)	162	0.402 (0.493)	153	59.7 (66.2)
Week 8	167	7.49 (5.52)	167	7.68 (5.66)	166	2.09 (2.46)	166	0.340 (0.443)	154	54.1 (59.6)
Roflumilast N-oxide										
ARQ-154-309										
Week 4	249	6.17 (4.27)	249	6.33 (4.38)	249	13.1 (14.5)	249	2.81 (3.15)	247	316 (347)
Week 8	254	6.14 (4.28)	254	6.30 (4.39)	254	9.66 (11.2)	254	2.09 (2.77)	248	237 (269)
ARQ-154-204										
Week 4	164	7.38 (5.38)	164	7.57 (5.52)	162	12.1 (13.1)	162	2.11 (2.36)	157	300 (315)
Week 8	167	7.49 (5.52)	167	7.68 (5.66)	166	10.6 (12.2)	166	1.71 (2.07)	158	269 (295)

AUC_{0-24} = area under the plasma concentration-time curve from time zero to 24 hours; BSA = body surface area; SD = standard deviation.
[a] Concentration/dose applied.
[b] Subjects who had no quantifiable concentrations of roflumilast were excluded from the extrapolated AUC analysis. Extrapolated AUC_{0-24} = trough concentration × 24.
All means are arithmetic means.
Source: ARQ-154-309 CSR, Appendix 16.1.13, Table 1; Report ADME.2020.042 for ARQ-154-204, Table 3

In the adult population, arithmetic mean dose-normalized pre-dose concentrations of roflumilast were 0.442 and 0.402 ng/mL/mg in ARQ-154-309 and ARQ-154-204, respectively, at Week 4, and were 0.345 and 0.340 ng/mL/mg respectively, at Week 8. Arithmetic mean dose-normalized concentrations of roflumilast N-oxide were 2.81 and 2.11 ng/mL/mg, respectively, at Day 28, and were 2.09 and 1.71 ng/mL/mg, respectively, at Week 8. The mean pre-dose dose-normalized roflumilast and N-oxide metabolite concentrations appear to be similar in both the trials. The Week 8 concentrations appear to be slightly lower than the Week 4 in both the trials, and this could be due to the healing of the skin which may change the drug permeability potential. Mean extrapolated AUC_{0-24} appeared to be similar in the both the studies for both the analytes.

Trough concentrations on Week 4 and Week 8 were collected from 6 adolescent subjects who participated in the Phase 3 trial (ARQ-154-309). The exposures between adults and the adolescents from age 12 to 17 years are compared in Table 6.

Table 6. Summary of Pharmacokinetic Results on Week 4 and Week 8 After Repeat Dosing, Trial ARQ-154-309

	Treated BSA (%)		Predicted Dose (mg)		Concentration (ng/mL)		Dose-normalized Concentration[a] (ng/mL/mg)		Extrapolated AUC_{0-24}[b] (ng·h/mL)	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Roflumilast										
Adolescents										
Week 4	6	4.98 (2.87)	6	4.72 (2.72)	6	1.90 (1.79)	6	0.384 (0.235)	6	45.7 (43.0)
Week 8	6	4.98 (2.87)	6	4.72 (2.72)	6	1.22 (1.01)	6	0.298 (0.245)	6	29.3 (24.3)
Adults										
Week 4	249	6.17 (4.27)	249	6.33 (4.38)	249	2.07 (2.21)	249	0.442 (0.491)	240	51.6 (53.2)
Week 8	254	6.14 (4.28)	254	6.30 (4.39)	254	1.55 (1.81)	254	0.345 (0.504)	228	41.6 (43.8)
Roflumilast N-oxide										
Adolescents										
Week 4	6	4.98 (2.87)	6	4.72 (2.72)	6	9.62 (5.81)	6	2.77 (2.95)	6	231 (140)
Week 8	6	4.98 (2.87)	6	4.72 (2.72)	6	9.21 (7.29)	6	2.54 (3.07)	6	221 (175)
Adults										
Week 4	249	6.17 (4.27)	249	6.33 (4.38)	249	13.1 (14.5)	249	2.81 (3.15)	247	316 (347)
Week 8	254	6.14 (4.28)	254	6.30 (4.39)	254	9.66 (11.2)	254	2.09 (2.77)	248	248 (232)

AUC_{0-24} = area under the plasma concentration-time curve from time zero to 24 hours; BSA = body surface area; SD = standard deviation.

[a] Concentration/dose applied.

[b] Subjects who had no quantifiable concentrations of roflumilast were excluded from the extrapolated AUC analysis. Extrapolated AUC_{0-24} = trough concentration × 24.

All means are arithmetic means.

Source: ARQ-154-309 CSR, Appendix 16.1.13, Table 1

The mean treated BSA was approximately 5% in adolescents and approximately 6% in adults in this phase 3 trial. Mean trough exposures of both analytes on Week 4 and Week 8 in adolescents were slightly lower than the adults; however, the dose-normalized values were similar between adults and adolescents. These results are consistent with the results of phase 3 pivotal studies of roflumilast cream 0.3%, where exposure was similar in adolescents and adults but was somewhat lower in adolescents (NDA 215985 Module 2.7.2, Section 3.5.1.1).

The dose-normalized exposures in adults and adolescents appear to be similar in MUsT study as well as in phase 3 trial. These results are consistent with studies of roflumilast cream 0.3% in subjects with psoriasis.

Effects of Demographic Characteristics in Adults

Predose plasma concentration values from adults who participated in the pivotal phase 3 trial (ARQ-154-309) were analyzed by age (18 to ≤64 years of age versus ≥65 years of age), sex, race, and ethnicity (Report AD-23-169). In this phase 3 trial, subjects with psoriasis involving ≥10% of the scalp and total plaque psoriasis of the scalp and body involving ≤25% BSA applied roflumilast foam 0.3% QD for 8 weeks. Predose plasma concentration values from Weeks 4 and 8 of treatment with roflumilast foam 0.3% were combined, as steady state was generally achieved by 2 weeks of treatment.

There were no meaningful differences in mean pre-dose concentrations of both analytes between the 70 older subjects (≥65 years of age) and 445 younger (18 to <65 years of age) adult age groups (Table 7).

Table 7. Summary of Roflumilast and N-Oxide Metabolite Predose Concentrations by Adult Age Group, Pivotal Phase 3 Trial ARQ-154-309

Age Group	N	Mean (SD)		
		Treated BSA (%)	Roflumilast (ng/mL)	Roflumilast N-oxide (ng/mL)
≥65 years	70	5.69 (3.78)	2.27 (2.27)	13.2 (11.1)
18 to <65 years	445	6.20 (4.31)	1.73 (1.97)	11.0 (13.1)

BSA = body surface area; SD = standard deviation.
Values from Weeks 4 and 8 of treatment were combined, as steady state has generally been achieved by 2 weeks of treatment. N refers to number of plasma concentrations analyzed rather than number of subjects. All means are arithmetic means.
Source: Report AD-23-169, Table 4

There were no meaningful differences in mean pre-dose concentrations by sex in both the analytes. A summary of the drug concentrations by sex is presented in Table 8.

Table 8. Summary of Roflumilast and N-Oxide Metabolite Predose Concentrations by Sex, Pivotal Phase 3 Trial (ARQ-154-309)

Sex	N	Mean (SD)		
		Treated BSA (%)	Roflumilast (ng/mL)	Roflumilast N-oxide (ng/mL)
Females	270	5.77 (4.06)	1.50 (1.40)	10.2 (10.0)
Males	245	6.52 (4.41)	2.14 (2.49)	12.5 (15.4)

BSA = body surface area; SD = standard deviation.
Values from Weeks 4 and 8 of treatment were combined together, as steady state has generally been achieved by 2 weeks of treatment. N refers to number of plasma concentrations analyzed rather than number of subjects. All means are arithmetic means.
Source: Report AD-23-169, Table 3

Evaluation of predose concentrations across the reported races suggests no meaningful differences between racial subgroups (Table 9). The largest difference between the races for mean roflumilast predose concentrations was 1.8-fold for subjects reporting Black or African (n=24) and Native Hawaiian or other Pacific Islander (n=6).

Table 9. Summary of Roflumilast and N-Oxide Metabolite Predose Concentrations by Race, Pivotal Phase 3 Trial (ARQ-154-309)

Race	N	Mean (SD)		
		Treated BSA (%)	Roflumilast (ng/mL)	Roflumilast N-oxide (ng/mL)
Asian	48	4.40 (2.62)	1.79 (1.48)	14.5 (13.0)
Black or African American	24	8.70 (5.32)	2.16 (2.30)	14.4 (11.3)
Native Hawaiian or other Pacific Islander	6	4.73 (1.97)	1.22 (0.771)	8.91 (6.04)
White	408	6.27 (4.34)	1.80 (2.10)	10.8 (13.2)
Other race	21	5.65 (2.77)	1.94 (1.47)	12.9 (9.29)
More than 1 race	8	3.88 (2.84)	1.22 (1.59)	7.01 (8.52)

BSA = body surface area; SD = standard deviation.
Values from Weeks 4 and 8 of treatment were combined together, as steady state has generally been achieved by 2 weeks of treatment. N refers to number of plasma concentrations analyzed rather than number of subjects. No subjects treated with roflumilast identified as Native Hawaiian or other Pacific Islander. All means are arithmetic means.
Source: Report AD-23-169, Table 1

Comparison of predose concentrations suggests no meaningful differences between ethnicities (Table 10). The difference between ethnicities was less than 1.1-fold for mean roflumilast and mean roflumilast N-oxide predose concentrations. The summary of predose concentrations is presented in Table 10.

Table 10. Summary of Roflumilast and Its N-Oxide Metabolite Predose Concentrations by Ethnicity, Pivotal Phase 3 Trial (ARQ-154-309)

Ethnicity	N	Mean (SD)		
		Treated BSA (%)	Roflumilast (ng/mL)	Roflumilast N-oxide (ng/mL)
Hispanic or Latino	81	7.36 (5.11)	1.73 (2.00)	12.1 (19.5)
Not Hispanic or Latino	417	6.00 (4.06)	1.83 (2.05)	11.1 (11.2)

BSA = body surface area; SD = standard deviation.
Values from Weeks 4 and 8 of treatment were combined, as steady state has generally been achieved by 2 weeks of treatment. N refers to number of plasma concentrations analyzed rather than number of subjects.
Source: Report AD-23-169, Table 2

Drug Metabolism

Drug metabolism of roflumilast was not characterized in the current submission. Applicant is relying on the characterization of drug metabolism of roflumilast during development of oral roflumilast under NDA 22522 for which Applicant has obtained right of reference. Roflumilast is primarily metabolized by CYP1A2, CYP3A4 and CYP3A5, and roflumilast N-oxide was the major metabolite following oral administration with major contribution from CYP3A4. Together, roflumilast and roflumilast N-oxide account for 87.5% of the total dose administered in plasma after oral dosing. In urine, roflumilast was not detectable while roflumilast N-oxide was only a trace metabolite (less than 1%). Other conjugated metabolites such as roflumilast N-oxide glucuronide and 4-amino-3,5-dichloropyridine N-oxide (ADCP N-oxide) were detected in urine.

Following multiple topical applications of roflumilast 0.3% topical foam in the MUsT (ARQ-154-122), the roflumilast N-oxide metabolite appears to circulate at about approximately 6.7-fold higher levels than the parent, which is consistent with the ratio of 7.4-fold observed following a single intravenous administration, while the ratio following oral administration is generally 10 to 12-fold likely due to increased contribution from first pass metabolism.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

No. For topical product, pharmacokinetics assessed under maximal use conditions supports systemic safety rather than efficacy.

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

Yes. The Applicant evaluated the once daily topical application of the product in subjects aged 12 years and older with plaque psoriasis in scalp and body in the phase 3 safety and efficacy trial. See Section 8 for additional information.

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

No specific studies were conducted with topical roflumilast in subjects with hepatic or renal impairment. Roflumilast 250 mcg oral once daily for 14 days was studied in subjects with mild to moderate hepatic impairment classified as Child Pugh A and B (8 subjects in each 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 current labeling recommendation for not using in patients with moderate or severe hepatic impairment is consistent with the approved oral roflumilast labeling.

Oral roflumilast was studied in 12 subjects with severe renal impairment following single administration of oral 500 mcg dose and no clinically significant differences in the pharmacokinetics of roflumilast and roflumilast N-oxide were observed. In an exploratory post-hoc data analysis of subjects with mild and moderate renal insufficiency with topical administration of roflumilast cream 0.3% no meaningful difference in mean roflumilast and mean roflumilast N-oxide metabolite were observed.

Roflumilast is not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh B or C). No specific dosing is being recommended for subjects with renal impairment.

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

Food-drug interactions are not applicable for topical products.

No drug interaction studies were conducted by Applicant with roflumilast foam. No drug interaction studies were conducted with roflumilast cream. However, drug-interaction studies were conducted in support of the oral roflumilast (NDA 022522). In vitro studies suggest that the biotransformation of roflumilast to its N oxide metabolite is mediated by CYP1A2 and 3A4. Based on further in vitro results in human liver microsomes, it was observed that the 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 have demonstrated no induction of the CYP1A2, 2A6, 2C9, 2C19, or 3A4/5 and only a weak induction of CYP2B6 by roflumilast.

Under NDA 022522, in an open-label, three-period, fixed-sequence study in 15 healthy volunteers, coadministration of the strong CYP3A4 inducer rifampicin (600 mg once daily for 11 days) with a single oral dose of 500 µg 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% (AZ-CP-064). Thus, the labeling for oral roflumilast indicates that the concomitant use of strong CYP inducers is not recommended, as a reduction

in systemic exposure could impact the therapeutic effectiveness of oral roflumilast for COPD. However, following topical administration, systemic exposure is not linked to efficacy as the drug is administered directly to the target site (skin) and there would be no negative consequence of a reduction in systemic exposure of roflumilast and its N-oxide metabolite if roflumilast cream were co-administered with a CYP inducer.

The concomitant use of roflumilast and systemic CYP3A4 inhibitors, or dual CYP3A4 and CYP1A2 inhibitors, can increase systemic exposure to roflumilast and may result in adverse reactions. Repeated doses of erythromycin (a moderate CYP3A4 inhibitor) increased the mean systemic exposure of roflumilast by 70% but did not alter that of roflumilast N-oxide; erythromycin increased the mean C_{max} of roflumilast by 40% but decreased that of roflumilast N-oxide by 34%. Repeated doses of ketoconazole (a strong CYP3A4 inhibitor) increased the mean systemic exposure of roflumilast by 99% but did not alter that of roflumilast N-oxide; ketoconazole increased the mean C_{max} of roflumilast by 23% but decreased that of roflumilast N-oxide by 38%. Repeated doses of fluvoxamine (a strong CYP1A2 inhibitor) increased the mean systemic exposure of roflumilast by 156% and that of roflumilast N-oxide by 52%. Fluvoxamine did not alter the mean C_{max} of roflumilast but decreased that of roflumilast N-oxide by 20%. Repeated doses of cimetidine increased the mean systemic exposure of roflumilast by 84% and that of roflumilast N-oxide by 27%; the mean C_{max} of roflumilast was increased by 46% but that of roflumilast N-oxide was unaltered. Thus, the potential risk of adverse events following the concomitant use of roflumilast cream 0.3% with potent systemic CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously should be weighed against the benefit.

Roflumilast and the N-oxide metabolite have been shown to be inhibitors of the CYP3A4 isozyme, with inhibition constant (Ki) values of about 1 and 60µM, respectively, with inhibition at other CYP isozymes being weaker. Under maximal use conditions, the C_{max} of roflumilast and roflumilast N-oxide was generally less than 5 and 50 ng/mL, respectively, equating to about 12 and 120nM, respectively. These total plasma concentrations are almost 100-fold lower for roflumilast and about 500-fold lower for roflumilast N-oxide than the Ki values, which makes the potential for a drug-drug interaction via CYP inhibition unlikely.

A clinical study evaluating the potential for roflumilast following oral administration to impact midazolam (CYP3A4 substrate) pharmacokinetics was investigated. Following a 500-µg oral dose, roflumilast (mean C_{max} of about 8 ng/mL) and roflumilast N-oxide (mean C_{max} of about 25 ng/mL) demonstrated no effect on midazolam exposure, supporting the hypothesis that clinical concentrations of roflumilast have low potential for CYP3A4 inhibition. Since the exposure following topical administration under maximum use conditions is generally within 3-fold of oral administration, the potential of a clinical drug-drug interaction is considered to be low.

Under NDA 022522, in an open-label crossover study in 20 healthy adult volunteers, coadministration of a single oral dose of 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.

Were appropriate bioanalytical assays used for quantification of roflumilast and roflumilast N-oxide in this study?

The bioanalytical method developed and validated for quantification of roflumilast and roflumilast N-oxide is acceptable. Bioanalysis of study PK samples for the studies ARQ-154-122, ARQ-154-204 and ARQ-154-309 meets the acceptability criteria.

The Applicant, Arcutis Biotherapeutics, Inc., and (b) (4) developed and validated liquid chromatography-tandem mass spectrometry bioanalytical methods for determination of roflumilast, roflumilast N-oxide, in human plasma (Revised report# 171410VEMB_ARCMC_R1; original report# 171410VEMB_ARCMC). The lower limit of quantification and calibration range for the analytes are presented in Table 11.

Table 11. Lower Limit of Quantification and Calibration Range for Roflumilast, Roflumilast N-Oxide

Analyte	LLOQ (ng/ml)	Calibration Range (ng/ml)
Roflumilast	0.1	0.1-100
Roflumilast N-oxide	0.1	0.1-100

Source: Method validation report 171410VEMB_ARCMC_R1, 171416VEMB_ARCMC
Abbreviations: LLOQ, lower limit of quantification

The performance characteristics of the developed bioanalytical assay is shown in Table 12.

Table 12. Precision and Accuracy of the Bioanalytical Method

	Roflumilast	Roflumilast N-Oxide
Inter-assay precision (CV)	≤10.3%	≤8.5%
Inter-assay accuracy (RE)	−8.3-0.3%	−6.3-2.0%
Intra-assay precision (CV)	≤12.1%	≤8.7%
Intra-assay accuracy (RE)	−11-3.0%	−7.7-8.0%

Source: Method validation report 171410VEMB_ARCMC_R1, 171416VEMB_ARCMC
Abbreviations: CV, coefficient of variation; RE, relative error

Stability of the analytes under various conditions were analyzed are reported in Table 13.

Table 13. Sample Stability Under Listed Conditions

Analyte	Freeze-Thaw Cycle (−20 to −70 °C)	Benchtop Stability in Human Plasma at Room Temp	Processed Sample (Autosampler)	Long Term Stability		Stock Solution Stability	
			Room Temp	−20 °C	−70 °C	Room Temp	4 °C
Roflumilast	5 cycles	167 hours	73 hours	259 days	671 days	22 hours	820 days
Roflumilast N-Oxide	5 cycles	167 hours	73 hours	259 days	671 days	22 hours	266 days

Source: Method validation report 171410VEMB_ARCMC_R1, 171416VEMB_ARCMC

Bioanalytical Results for the PK MUSE Trial ARQ-154-122

Samples were stored at −70°C and analyzed in 255 days which was within the freezer long-term stability limit of 671 days for roflumilast and roflumilast N-oxide and the long-term storage stability was deemed adequate (Report# 211673AEA_ARCMC for the Trial ARQ-154-122).

Incurred sample reanalysis: The Applicant notes that 97.6% of the repeated sample results for incurred sample reanalysis (ISR) were within 20% of the original results for both roflumilast and roflumilast N-oxide in plasma, confirming the reproducibility of the methods (Report# 211673AEA_ARCMC for the Trial ARQ-154-122).

Bioanalytical Results for the Phase 2 Trial ARQ-154-204

Samples were stored at −70°C and analyzed in 358 days which was within the established freezer stability limit of 671 days at −70°C for roflumilast and roflumilast N-oxide. The long-term storage stability was deemed adequate (Report# 191708AEA_ARCMC for the Trial ARQ-154-204).

Incurred sample reanalysis: The Applicant notes that 88.9% of the repeated sample results for ISR were within 20% of the original results for both roflumilast and roflumilast N-oxide in plasma, confirming the reproducibility of the methods (Report# 191708AEA_ARCMC for the Trial ARQ-154-204).

Bioanalytical Results for the Phase 3 Trial ARQ-154-309

Samples were stored at −70°C and analyzed in 335 days which was within the established freezer stability limit of 671 days at −70°C for roflumilast and roflumilast N-oxide. The long-term storage stability was deemed adequate (Report# 212183AEA_ARCMC for the Trial ARQ-154-309).

Incurred sample reanalysis: The Applicant notes that 100% of the repeated sample results for ISR were within 20% of the original results for both roflumilast and roflumilast N-oxide in plasma, confirming the reproducibility of the methods (Report# 212183AEA_ARCMC for the Trial ARQ-154-309).

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The development program for roflumilast foam, 0.3% QD for topical treatment of plaque psoriasis of the scalp and body (for subjects ≥12 years of age) included the following studies:

- ARQ-154-309 (N=432) — A phase 3, R (2:1), double-blind (DB), placebo-controlled (PC), PK/safety/efficacy trial
- ARQ-154-204 (N=304) — A phase 2b, R (2:1), DB, PC, PK/safety/efficacy trial
- ARQ-154-122 (N=30) — A phase 1, maximal use, open-label, PK/safety study (MuST)

The ISS includes pooled safety data from the phase 2b (-204) and phase 3 (-309) trials which shared a similar population, study design, dose/dosing regimen, treatment duration, and randomization ratios (2:1).

Long-Term Safety

The Applicant did not conduct a long-term safety study for roflumilast foam, 0.3% QD for the indication of treatment of psoriasis of the scalp and body. The Applicant provided the following rationale: "Given the virtually identical compositions of roflumilast foam 0.3% and roflumilast cream 0.3%, the same dosing regimen (QD), the similar PK profiles in subjects treated with roflumilast foam or cream, the similar patient populations treated in the 2 development programs, and the similar safety profiles in randomized, vehicle-controlled studies, the long-term safety data generated in the roflumilast cream development program in plaque psoriasis can be used to support the long-term safety of roflumilast foam in this patient population."

Table 14. Listing of Clinical Trials Relevant to sNDA 217242-005

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	y Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Controlled Studies To Support Efficacy and Safety								
ARQ-154-309 (ARRECTOR)	05028582	Randomized, double-blind, vehicle-controlled, parallel-group safety and efficacy in adolescents and adults	Roflumilast foam 0.3% QD or Vehicle foam QD applied topically to scalp and body lesions	Co-primary endpoints: Scalp (S-IGA) success* at W8 Body (B-IGA) success at W8 Secondary endpoint: SI-NRS success at W8, W4, W1, D3, D1, WI-NRS success at W 8 PASI-75 at W8 Other (PROs)	8 weeks	432	Subjects ≥12 years of age with plaque psoriasis involving ≥10% of scalp, S-IGA ≥3 (Moderate), B-IGA ≥2 (Mild), and total (scalp and non-scalp) psoriasis ≤25% total BSA (excluding palms and soles)	53 centers in the United States (US) and Canada
ARQ-154-204	04128007	Same as in Trial -309	Same as in Trial -309	Primary endpoint: Scalp (S-IGA) success at W8 Secondary endpoint: Body (B-IGA) success at W8 SI-NRS success at W8, W4, W2 Other (PROs)	8 weeks	302	Same as in Trial -309. S-IGA ≥2 (Mild) (original protocol and Amendment 1) or S-IGA ≥3 (Moderate) (Amendment 2).	46 sites in North America, Australia, and Europe

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	y Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Other Studies Pertinent to the Review of Efficacy or Safety (e.g., Clinical Pharmacological Studies)								
ARQ-154-122		Single-arm, open-label, MUSE, PK, and safety in adolescents and adults	Applied QD for 2 weeks, 1.5 g to the entire scalp and 2 mg/cm^2 to affected non-scalp areas: Optional additional 6-week QD treatment for adolescents, applied to active lesions only: **Stud**	Primary endpoints: PK, safety, and tolerability.	2 weeks	30	Subjects ≥12 years of age with plaque psoriasis involving ≥10% of scalp, S-IGA ≥3 (Moderate), B-IGA ≥2 (Mild), and Body psoriasis (non-scalp) involving at least 10% BSA in adolescents and at least 20% in adults at baseline.	9 centers in the United States and the Dominican Republic

*S-IGA treatment success and B-IGA treatment success were defined as a score of "Clear" (0) or "Almost Clear" (1), plus a 2-grade score improvement from baseline at Week 8. SI-NRS success and WI-NRS success were defined as a reduction of at least 4 points from baseline with a baseline score of at least 4.
Abbreviations: BSA, body surface area; B-IGA, Body–Investigator Global Assessment; D(X), Day X (X=1 or 3); MUSE, maximal useage systemic exposure; NCT, National Clinical Trial; PASI-75, ≥75% reduction in Psoriasis Area and Severity Index score from baseline; PK, pharmacokinetics; PRO, patient-reported outcome; QD, once daily; SI-NRS, Scalp Itch Numerical Rating Scale; S-IGA, Scalp–Investigator Global Assessment; W(X), Week X (X=1, 2, 4, or 8); WI-NRS, Worst Itch Numerical Rating Scale

7.2. Review Strategy

Data Sources

The Applicant provided CSR and datasets by electronic submission at the following network path: \\CDSESUB1\evsprod\NDA217242\0032\m5\datasets

A consultation for review of data fitness was requested on July 24, 2024, from the CDER Office of Computational Sciences (OCS) SpAS team. OCS team performed exploratory safety analysis and data fitness analysis for Trial ARQ-154-122, Trials ARQ-154-204 and ARQ-154-309, and ISS for this sNDA and found the data quality acceptable.

Data and Analysis Quality

In collaboration with the OCS and as follow up to the July 24, 2024, data fitness consult request, the statistical and clinical reviewers held the following meetings with the OCS team:

1. August 2, 2024 Drug-induced liver injury (DILI): Specialized Analysis Support Request Deliverables
2. August 2, 2024 Adverse Event Bundle
3. August 2, 2024 Individual CSR Analysis Data Model (ADaM) to ISS ADaM traceability assessment
4. August 5, 2024 Annotated Individual Study ADaM to ISS ADaM Traceability Assessment
5. August 6, 2024 Laboratory Analysis Bundle
6. August 7, 2024 ISS overview assessment
7. August 14, 2024 Exploratory safety assessment

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

- 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 ZORYVE 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-154-309

Trial Design

Trial ARQ-154-309 (Trial 309) is a randomized, multicenter, double-blind, vehicle-controlled, parallel-group phase 3 trial in subjects 12 years of age and older with plaque psoriasis of the scalp and body. Subjects were to have a total overall psoriasis involvement on scalp and non-scalp areas of up to 25% BSA at baseline. Subjects were also to have the extent of scalp psoriasis involvement of at least 10% of the total scalp at baseline. The trial was designed to enroll approximately 420 subjects, randomized in a 2:1 ratio to roflumilast foam or vehicle foam. Subjects were to apply treatment QD for 8 weeks. Randomization was stratified by study site, baseline S-IGA [3 vs. 4], and baseline B-IGA [2 vs. ≥3].

Study Endpoints

The co-primary efficacy endpoints were S-IGA Success, defined as achievement of S-IGA score of 'Clear' or 'Almost Clear' plus a 2-grade improvement from baseline, and B-IGA Success, defined as achievement of B-IGA score of 'Clear' or 'Almost Clear' plus a 2-grade improvement from baseline.

Table 15. Scalp–Investigator Global Assessment of Disease

Scale	Grade	Description
0	Clear	Plaque thickening = no elevation or thickening over normal skin Scaling = no evidence of scaling Erythema = none (no residual red coloration but post-inflammatory hyperpigmentation may be present)
1	Almost clear	Plaque thickening = none or possible thickening but difficult to ascertain if there is a slight elevation above normal skin level Scaling = none or residual surface drying and scaling Erythema = light pink coloration
2	Mild	Plaque thickening = slight but definite elevation Scaling = fine scales partially or mostly covering the lesions Erythema = light red coloration
3	Moderate	Plaque thickening = moderate elevation with rounded or sloped edges Scaling = most lesions at least partially covered Erythema = definite red coloration
4	Severe	Plaque thickening = marked or very marked elevation typically with hard or sharp edges Scaling = non-tenacious or thick tenacious scale, covering most or all of lesions Erythema = very bright red coloration; extreme red coloration; deep red coloration

Source: Page 44 of the protocol

Table 16. Body–Investigator Global Assessment of Disease (i.e., Non-Scalp)

Scale	Grade	Description
0	Clear	Plaque thickening = no elevation or thickening over normal skin Scaling = no evidence of scaling Erythema = none (no residual red coloration but post-inflammatory hyperpigmentation may be present)
1	Almost clear	Plaque thickening = none or possible thickening but difficult to ascertain if there is a slight elevation above normal skin level Scaling = none or residual surface drying and scaling Erythema = light pink coloration
2	Mild	Plaque thickening = slight but definite elevation Scaling = fine scales partially or mostly covering the lesions Erythema = light red coloration
3	Moderate	Plaque thickening = moderate elevation with rounded or sloped edges Scaling = most lesions at least partially covered Erythema = definite red coloration
4	Severe	Plaque thickening = marked or very marked elevation typically with hard or sharp edges Scaling = non-tenacious or thick tenacious scale, covering most or all of lesions Erythema = very bright red coloration; extreme red coloration; deep red coloration

Source: Page 45 of the protocol

The multiplicity-controlled secondary endpoints were:

- For subjects with baseline SI-NRS ≥4, achievement of ≥4-point improvement from baseline in SI-NRS at Week 8 ("SI-NRS Success at Week 8)
- SI-NRS Success at Week 4
- SI-NRS Success at Week 2
- SI-NRS Change from baseline (CFB) at Week 1
- SI-NRS CFB at 72 hours
- SI-NRS CFB at Day 1
- For subjects with baseline WI-NRS score ≥4, achievement of ≥4-point improvement from baseline in WI-NRS at Week 8 ("WI-NRS Success at Week 8")
- ≥75% reduction from baseline in Psoriasis Area and Severity Index (PASI) [PASI-75] at Week 8
- CFB in Psoriasis Symptoms Diary (PSD) Items related to Itching, Pain, and Scaling (Questions 1, 9, and 11) aggregate score at Week 8
- PSD Item related to Scaling (Question 11) =0 at Week 8
- PSD Item related to Itching (Question 1) =0 at Week 8
- PSD Item related to Pain (Question 9) =0 at Week 8
- ≥75% reduction from baseline in Psoriasis Scalp Severity Index (PSSI) [PSSI-75] at Week 8
- S-IGA score of 'Clear' at Week 8

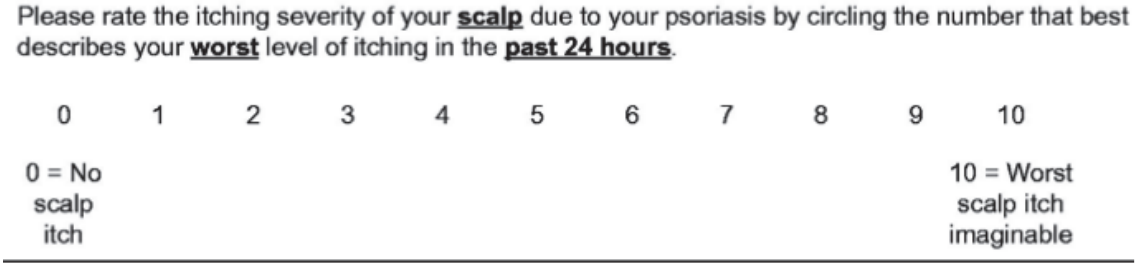
- S-IGA Success at Week 4
- CFB in PASI at Week 2
- S-IGA Success at Week 2
- PSD Total Score =0 at Week 8

Scalp Itch-NRS

The Scalp Itch-NRS is a single-item scale to assess the patient-reported severity of their symptom at the highest intensity of scalp itching over the past 24 hours. Scalp Itch-NRS will be determined by asking the subject's assessment of worst itching of the scalp over the past 24 hours. The scale is from '0' to '10' ('no scalp itch' to 'worst scalp itch imaginable'). Subjects will complete the Scalp Itch-NRS assessment.

SI-NRS Assessment will be performed by subjects daily at home according to the Schedule of Visits and Assessments starting 7 days prior to the scheduled Baseline/Day 1 visit up to the Week 8/Day 57 visit. The SI-NRS should be completed first and then WI-NRS.

Figure 2. Scalp Itch Numerical Rating Scale



Source: Protocol Amendment 3, p. 47

Worst Itch-Numerical Rating Scale

The WI-NRS is a single-item scale to assess the patient-reported severity of this symptom at its highest intensity during the previous 24-hour period. The WI-NRS will be determined by asking the subject's assessment of worst itch over the past 24 hours. The scale is from '0' to '10' ("no itch" to "worst imaginable itch"). Subjects will be asked on a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable," how would you rate your itch at the worst moment during the previous 24 hours?

WI-NRS Assessment will be performed by subjects daily at home according to the Schedule of Visits and Assessments starting 7 days prior to the scheduled Baseline/Day 1 visit up to the Week 8/Day 57 visit.

Figure 3. Worst Itch Numerical Rating Scale

Source: Protocol Amendment 3, p. 47

The SAP stated that for SI-NRS and WI-NRS endpoints assessed at or before Week 1, baseline is defined as the last non-missing assessment prior to the first study treatment. For average weekly SI-NRS and WI-NRS (i.e., those assessed at Week 2 or later), baseline is defined as the average of all non-missing scores reported during the last 7 days prior to treatment if at least 4 of 7 evaluable daily questionnaires scores are available.

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 S-IGA and B-IGA assessment due to coronavirus disease 2019 (COVID-19) disruption. In Trial 309, there was one subject disrupted by COVID-19, and the ITT population and mITT population were different by one subject. The Pruritus ITT (PRU4-ITT) population was defined as all randomized subjects with a baseline WI-NRS ≥4, and the Scalp Pruritus ITT (SPRU4-ITT) population was defined as all randomized subjects with a baseline SI-NRS ≥4. The co-primary endpoints were analyzed with the Cochran-Mantel-Haenszel test stratified by pooled study site, baseline S-IGA, and baseline B-IGA. The intercurrent events of discontinuation due to lack of efficacy or adverse events were handled using a composite strategy (i.e., such subjects were treated as non-responders). Missing data were handled with multiple imputation (MI). The overall Type I error was prespecified to be controlled at a 2-sided 0.025 level. Therefore, the Applicant presented both 97.5% and 95% confidence intervals (CIs) for the efficacy results.

Analysis Populations

The SAP specified the following analysis populations:

- Safety Population: All randomized subjects who received at least 1 confirmed dose of IP.
- ITT Population: All randomized subjects.
- Per Protocol Population: All subjects in the ITT population who were at least 80% compliant with the study drug application, have an S-IGA and B-IGA assessment at Week 8, and showed no important deviations from the study protocol that would affect the interpretation of efficacy.
- mITT Population: All randomized subjects with the exception of subjects who missed the Week 8 S-IGA or B-IGA assessment specifically due to COVID-19 disruption.

- SPRU4-ITT Population: All subjects in the ITT population with an average weekly SI-NRS score ≥4 at baseline.
- PRU4-ITT Population: All subjects in the ITT population with an average weekly WI-NRS score ≥4 at baseline.
- PK Population: All subjects who received at least one confirmed dose of IP and provided at least one PK sample.

Estimands

The SAP specified the following as the main estimand for the co-primary endpoints:

- Treatments: Roflumilast foam 0.3% and vehicle
- Population: Subjects with scalp and body psoriasis
- Endpoints: S-IGA Success and B-IGA Success
- Intercurrent Events (ICEs) and Handling Strategy: The SAP specified treatment discontinuation due to a specific adverse effect or a lack of effect as an ICE. The SAP specified using a composite variable strategy where subjects who discontinue treatment due to lack of efficacy or adverse event are considered non-responders.
- Population-level Summary Measure: The ratio of the odds of achieving S-IGA/B-IGA success at Week 8 using roflumilast foam 0.3% relative to the odds of S-IGA/B-IGA success at Week 8 using the matching vehicle foam. The SAP also specified calculating the difference in proportions and associated 95% CI.

For the binary secondary efficacy endpoints, the SAP specified that the estimands for the SI-NRS Success endpoints and the WI-NRS Success endpoint would be identical to the main estimand for the co-primary endpoints, except that the analysis populations are SPRU4-ITT and PRU4-ITT populations, respectively. The SAP stated that all other SI-NRS related endpoints will be analyzed based on the ITT population.

For the continuous secondary efficacy endpoints, the SAP specified that the corresponding estimand is identical to that of the co-primary endpoints except for the population-level summary being change from baseline. While change from baseline is not a valid population-level summary of the treatment effect, as it describes only the within-treatment summary and not the between-treatment summary statistic, the Applicant reported the difference in mean changes from baseline between roflumilast and vehicle and the 95% CI for each continuous secondary efficacy endpoint in the clinical study report.

Analysis Methods

The SAP specified analyzing the co-primary and binary secondary efficacy endpoints using the Cochran-Mantel-Haenszel test stratified by pooled study site, baseline S-IGA, and baseline B-IGA. The odds ratio and its 97.5% and 95% CIs were specified to be calculated from the Cochran-Mantel-Haenszel (CMH) test. In addition to calculating the odds ratio, associated CIs,

and p-values for the pairwise comparisons of roflumilast and vehicle, the SAP specified calculating the risk difference (using Mantel-Haenszel stratum weights and the Sato variance estimator) and its 97.5% and 95% CIs. This review presents the risk difference estimates (or equivalently difference in proportions) instead of the odds ratios as the difference is easier to interpret and is the population-level summary measure of greater interest.

The SAP specified analyzing the continuous secondary efficacy endpoints using analysis of covariance (ANCOVA). The model was specified to include pooled site group, baseline S-IGA category, baseline B-IGA category, and baseline score of the variable of interest as covariates. The least-squares mean for each treatment group was calculated based on the ANCOVA model. In addition, for the comparison between roflumilast and vehicle, the difference between the least-squares means and its 97.5% and 95% CIs were calculated.

The primary method for handling missing data specified in the SAP was the MI approach. For each treatment group separately, intermittent missing data was specified to be first imputed using the Markov chain Monte Carlo method to achieve a monotone missing data pattern, followed by the predictive mean matching method for monotone missing data. This generated a total of 150 complete MI analysis datasets, each of which was analyzed using the prespecified analysis method for the corresponding endpoint (i.e., CMH test or ANCOVA).

Multiplicity Adjustment Plan

The SAP specified testing the co-primary endpoints first and proceeding to test the secondary endpoints only if both co-primary endpoints are statistically significant. Multiplicity was controlled across the secondary endpoints by organizing the secondary endpoints into three families and using the fallback method between families and the sequential method within families. Family 1 included the SI-NRS endpoints (i.e., SI-NRS Success at Week 8, SI-NRS Success at Week 4, SI-NRS Success at Week 2, and SI-NRS CFB at Week 1, 72 hours, and Day 1), and these endpoints were analyzed sequentially in that order. Initially α=0.01 was allocated to Family 1. If all 6 SI-NRS endpoints were statistically significant, then the α=0.01 was passed to Family 2, and the Family 2 endpoints were analyzed at α=0.015; otherwise, the endpoints in Family 2 were analyzed using α=0.005. Family 2 contained the symptomatic endpoints (i.e., WI-NRS Success at Week 8, PASI-75 at Week 8, CFB in total PSD score at Weeks 8, 4, and 2, and PSSI-75 at Week 8), analyzed in that order. If all 6 symptomatic endpoints were statistically significant, then the α=0.015 or α=0.005 was passed to Family 3, and the Family 3 endpoints were analyzed at α=0.025 or α=0.015; otherwise, the endpoints in Family 3 were analyzed using α=0.01. Family 3 contained S-IGA score of 'clear' at Week 8, S-IGA Success at Week 4, CFB in PASI at Week 2, and S-IGA Success at Week 2.

Sensitivity and Supplementary Analyses

For the co-primary efficacy endpoints, the SAP specified the following sensitivity analyses for the handling of missing data:

- Non-Responder Imputation: missing data imputed as non-responders.
- Observed Case: missing data is not imputed. Subjects with missing data or who had prematurely discontinued IP were excluded.
- Tipping Point Analysis: The stated objective of the tipping point analyses is to determine the inflection point at which the inference under the missing-not-at-random assumption changes substantially and to check the robustness of the imputation. The SAP specified a sequence of shift parameters from 0 to 2 by 0.5 for roflumilast and −2 to 0 by 0.5 for vehicle. If a likely tipping point is identified, the SAP specified that the analysis may be re-run using a more focused range of shift parameters around the suspected tipping point, to zero in on the value at which the p-value "tips" from significant to non-significant (e.g., greater than 0.025).

The SAP specified conducting a supplementary analysis where the identified ICE (i.e., discontinuation of study treatment due to an AE or lack of efficacy prior to Week 8) is handled using a treatment policy strategy (i.e., assessments after the ICE are used as is).

Protocol Amendments

Protocol 309 was amended twice after enrollment began. In Protocol Amendment 2 dated May 12, 2022, the multiplicity control strategy related to the secondary endpoints was updated to include use of the fallback method, allowing unused α to pass from one family to another.

8.1.2. Trial ARQ-154-204

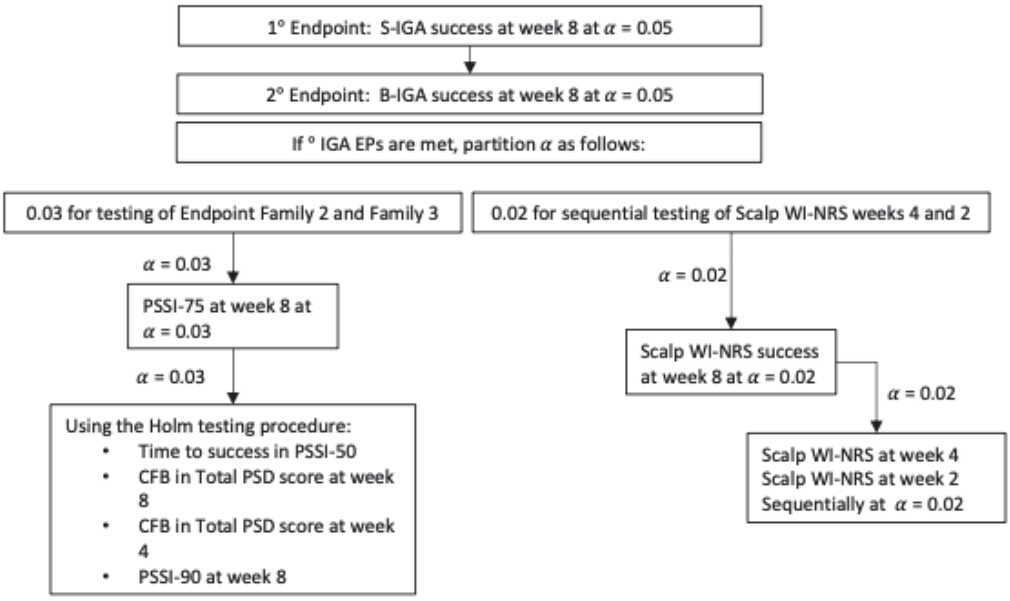
Trial Design

Trial ARQ-154-204 (Trial 204) is a randomized, multicenter, double-blind, vehicle-controlled, parallel-group phase 2 trial in subjects 12 years of age and older with plaque psoriasis of the scalp and body. Subjects were to have a total overall psoriasis involvement on scalp and non-scalp areas of up to 25% BSA at baseline, not including palms or soles. Subjects were also to have the extent of scalp psoriasis involvement of at least 10% of the total scalp at baseline. The trial was designed to enroll approximately 300 subjects, randomized in a 2:1 ratio to roflumilast foam or vehicle foam. Subjects were to apply treatment QD for 8 weeks. Randomization was stratified by country, baseline S-IGA [3 vs. 4], and baseline B-IGA [2 vs. ≥3].

The statistical methods for Trial 204 were the same as for Trial 309; however, because it was designed as a phase 2 trial, Trial 204 had the following design limitations: (a) no missing data handling methods were prespecified, (b) assessments for SI-NRS were conducted only at study visits rather than via daily diary; thus, the SI-NRS and WI-NRS endpoints in this trial were based on a single assessment per visit, rather than a weekly average, and (c) an endpoint based on the WI-NRS was not multiplicity-controlled. Because of the challenges with interpreting the trial results based only on observed data, results for Trial 204 were re-analyzed using the specifications for Trial 309, including using MI as prespecified for Trial 309 to handle missing data. In addition, the statistical methods were aligned so that (a) the Cochran-Mantel-Haenszel test for binary endpoints was stratified by pooled study sites in lieu of country, baseline S-IGA, and baseline B-IGA; and (b) ANCOVA for continuous endpoints was stratified by pooled study sites in lieu of country, baseline S-IGA, and baseline B-IGA.

Trial 204's prespecified multiplicity control procedure differed from that of Trial 309 described above. Figure 4 describes Trial 204's multiplicity control procedure:

Figure 4. Multiplicity Control Scheme, Trial ARQ-154-204



Achievement of IGA success is a score of 'clear' or 'almost clear' plus a 2 grade improvement from baseline.
Scalp WI-NRS success is a 4 point reduction in WI-NRS among subjects with WI-NRS ≥ 4 at baseline.
CFB – Change from baseline

Source: page 60 of the amended protocol for Trial ARQ-154-204
Note: The endpoint of "Scalp WI-NRS" in the figure is identical to SI-NRS per Applicant's clarification.
Abbreviations: B-IGA, Body-Investigator Global Assessment; CFB, change from baseline; IGA, Investigator Global Assessment; PSD, Psoriasis Symptoms Diary; PSSI, Psoriasis Scalp Severity Index; PSSI-50, Achievement of a 50% reduction in PSSI from baseline in Psoriasis Scalp Severity Index; PSSI-75, Achievement of a 75% reduction in PSSI from baseline in Psoriasis Scalp Severity Index; S-IGA, Scalp–Investigator Global Assessment; WI-NRS, Worst Itch-Numerical Rating Scale

Of note, in Trial 204, the endpoints of CFB in SI-NRS at Week 1 and CFB SI-NRS at 72 hours were not assessed as part of the protocol, and WI-NRS was assessed but not included in the multiplicity control procedure. Note that the overall significance level for Trial 309 was prespecified to be 0.025, because Trial 204 was intended to be supportive for determining substantial evidence of effectiveness.

Study Endpoints

The key efficacy endpoints were the same as those of Trial 309: the primary efficacy endpoint was S-IGA Success, defined as achievement of S-IGA score of 'Clear' or 'Almost Clear' plus a 2-grade improvement from baseline, and the first key secondary efficacy endpoint was B-IGA Success, defined as achievement of B-IGA score of 'Clear' or 'Almost Clear' plus a 2-grade improvement from baseline.

The remaining multiplicity-controlled secondary efficacy endpoints were:

- B-IGA Success at Week 8, defined as achievement of Body IGA score of 'Clear' or 'Almost Clear' plus a 2-grade improvement from baseline.
- PSSI-75 at Week 8
- For subjects with baseline SI-NRS score ≥4, achievement of ≥4-point improvement from baseline in SI-NRS at Week 8
- For subjects with baseline SI-NRS score ≥4, achievement of ≥4-point improvement from baseline in SI-NRS at Week 4
- For subjects with baseline SI-NRS score ≥4, achievement of ≥4-point improvement from baseline in SI-NRS at Week 2
- Time to PSSI-50
- CFB in total PSD score at Week 8
- CFB in total PSD score at Week 4
- PSSI-90 at Week 8

Trial 204 and Trial 309 used the same instruments to define the endpoints (e.g., S-IGA, B-IGA, SI-NRS score, WI-NRS score, PASI score, PSSI, and PSD items). However, in Trial 204, the SI-NRS and WI-NRS were assessed only at study visits, rather than via a daily diary.

8.1.3. Study Results

Compliance With Good Clinical Practices

The Applicant states that Trial 309 was conducted in accordance with the principles of the Tri-Council Policy Statement, the ethical principles set forth in the Declaration of Helsinki, and the International Council for Harmonisation Tripartite Guideline *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018). The Applicant states that Trial 204 was performed in compliance with Good Clinical Practices and applicable regulatory requirements, including the archiving of essential documents.

Financial Disclosure

See Section 19.2.

Patient Disposition

Trial 309 enrolled and randomized a total of 432 subjects from 51 investigational sites, with 281 randomized to roflumilast and 151 randomized to vehicle. Table 17 presents the subject disposition for the treatment period (Weeks 0 to 8). All subjects received their randomized treatment. Thirteen percent of subjects withdrew from the study. The most common reasons for study discontinuation were lost to follow-up and withdrawal of consent. Approximately 4% of roflumilast and 6% of vehicle subjects discontinued the trial due to lost to follow-up, and approximately 3% of roflumilast and 7% of vehicle subjects discontinued the trial by withdrawal of consent. Overall, the trial discontinuation rate was higher in the vehicle group than in the roflumilast group (11% vs. 17%).

Table 17. Subject Disposition, Trial ARQ-154-309

Disposition	Roflumilast Foam 0.3%	Vehicle	Overall
Randomized	281	151	432
ITT population	281	151	432
mITT population	280	151	431
Completed study, n (%)	250 (89)	126 (83)	376 (87)
Prematurely withdrawn from study, n (%)[1]	31 (11)	25 (17)	56 (13)
Lost to follow-up	11 (3.9)	9 (6)	20 (5)
Withdrawal of consent	9 (3)	10 (7)	19 (4)
Adverse event	5 (2)	2 (1)	7 (2)
Other	3 (1)	2 (1)	5 (1)
Lack of efficacy	3 (1)	1 (<1)	4 (<1)
Physician decision	0	1 (<1)	1 (<1)
Reason for withdrawal, COVID, n (%)[1]			
Subject decision	1 (<1)	0	1 (<1)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt
[1] The percentages were calculated based on the number of randomized subjects.
Abbreviations: COVID, coronavirus disease; ITT, intent-to-treat; mITT, modified intent-to-treat; n, number of subjects with disposition

Protocol Violations/Deviations

In Trial 309, the two treatment arms had similar rates of protocol deviations (63% in the roflumilast group and 62% in the vehicle group). The most common protocol violations were with investigational product administration (7% for roflumilast and 4% for vehicle), inclusion criteria (4% for both roflumilast and vehicle), and visits held outside of protocol-defined windows (4% for roflumilast and 3% for vehicle).

Table of Demographic Characteristics and Other Baseline Characteristics

The demographic characteristics were generally balanced across the two treatment arms, though more subjects 65 years of age or older were randomized to roflumilast (14%) than to vehicle (9%). Approximately 13% of subjects were 65 years of age or older. Approximately 82% of subjects were white, 7% were Asian, and 4% were Black or African American. The trial enrolled more female subjects (56%) than male subjects (44%). Approximately 18% of subjects were Hispanic or Latino.

The majority of subjects (72%) had moderate or severe B-IGA at baseline, and another majority (86%) had moderate S-IGA at baseline.

Table 18. Demographic Characteristics and Baseline Disease Characteristics, Trial ARQ-154-309 (ITT[1])

Characteristics	Roflumilast Foam 0.3% (N=281)	Vehicle (N=151)	Total (N=432)
Age group, n (%)			
12–17 years	7 (3)	3 (2)	10 (2)
18–64 years	234 (83)	134 (89)	368 (85)
≥65 years	40 (14)	14 (9)	54 (13)
Sex, n (%)			
Female	152 (54)	91 (60)	243 (56)
Male	129 (46)	60 (40)	189 (44)
Race, n (%)			
American Indian or Alaska Native	0	3 (2)	3 (<1)
Asian	26 (9)	4 (3)	30 (7)
Black or African American	12 (4)	6 (4)	18 (4)
Multiple	4 (1)	1 (<1)	5 (1)
Native Hawaiian or other Pacific Islander	3 (1)	1 (<1)	4 (<1)
Other	11 (4)	7 (5)	18 (4)
White	225 (80)	129 (85)	354 (82)
Ethnicity, n (%)			
Hispanic or Latino	48 (17)	28 (19)	76 (18)
Not Hispanic or Latino	224 (80)	121 (80)	345 (80)
Not reported	9 (3)	2 (1)	11 (3)
Country, n (%)			
Canada	97 (35)	51 (34)	148 (34)
United States	184 (66)	100 (66)	284 (66)
Baseline weight (kg)			
Mean (SD)	85.2 (20.0)	90.0 (21.4)	86.9 (20.6)
Median	82.0	89.4	84.3
Range	32.0, 145.4	49.5, 150.1	32.0, 150.1

Characteristics	Roflumilast Foam 0.3% (N=281)	Vehicle (N=151)	Total (N=432)
Baseline BMI (kg/m^2), n (%)			
Normal: 18.5≤BMI ≤24.9	59 (21)	28 (19)	87 (20)
Obese: BMI ≥30.0	120 (43)	83 (55)	203 (47)
Overweight: 25.0≤BMI ≤29.9	100 (36)	39 (26)	139 (32)
Underweight: BMI <18.5	2 (<1)	1 (<1)	3 (<1)
Baseline S-IGA (N)			
Categories, n (%)			
3	238 (85)	132 (87)	370 (86)
4	43 (15)	19 (13)	62 (14)
Baseline B-IGA			
Categories, n (%)			
2	75 (27)	44 (29)	119 (28)
≥3	206 (73)	107 (71)	313 (72)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects.
Abbreviations: BMI, body mass index; B-IGA, Body-Investigator Global Assessment; N, number of subjects in treatment arm; n, number of subjects with given characteristic; SD, standard deviation; S-IGA, Scalp–Investigator Global Assessment

Efficacy Results – Primary Endpoint

Table 19 presents the results for the co-primary efficacy endpoints at Week 8 for Trials 309 and 204. The endpoints were analyzed with the CMH test stratified by pooled sites, baseline S-IGA, and baseline B-IGA. Note that the results for Trial 204 were reanalyzed using the specifications of Trial 309. That is, Trial 204 was re-analyzed using MI as the primary method of handling missing data and the same stratification factors for the CMH test that were used in Trial 309. In both trials, roflumilast was statistically superior to vehicle (p-values <0.0001).

Table 19. Results for the Co-Primary Efficacy Endpoints at Week 8 (ITT[1])

	ARQ-154-309		ARQ-154-204 (Reanalysis)	
Endpoint	Roflumilast Foam 0.3% (N=281)	Vehicle (N=151)	Roflumilast Foam 0.3% (N=200)	Vehicle (N=104)
B-IGA success at Week 8	46%	20%	39%	7%
Difference from vehicle (97.5% CI)[2]	24.82% (13.65%, 36.00%)		32.43% (21.94%, 42.91%)	
Difference from vehicle (95% CI)[2]	24.82% (15.05%, 34.59%)		32.43% (23.26%, 41.59%)	
p-value[2]	<0.0001		<0.0001	
S-IGA success at Week 8	66%	28%	57%	11%
Difference from vehicle (97.5% CI)[2]	37.13% (25.69%, 48.58%)		47.7% (36.53%, 58.88%)	
Difference from vehicle (95% CI)[2]	37.13% (27.13%, 47.14%)		47.7% (37.93%, 57.47%)	
p-value[2]	<0.0001		<0.0001	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt, admibiga.xpt, admisiga.xpt
[1] Intent-to-treat population: all randomized subjects. Subjects with an ICE (i.e., discontinuation of study treatment due to an AE or lack of efficacy prior to Week 8) were treated as non-responders. Missing data was imputed using multiple imputation (MI).
[2] Difference, 97.5% and 95% CIs, and p-value were based on the Cochran-Mantel-Haenszel test stratified by pooled sites, baseline S-IGA, and baseline B-IGA.
Abbreviation: AE, adverse event; B-IGA, Body–Investigator Global Assessment; CI, confidence interval; ICE, intercurrent event; ITT, intent-to-treat; N, number of subjects in treatment arm; S-IGA, Scalp–Investigator Global Assessment

Table 20 presents the results for the B-IGA and S-IGA success endpoints at Week 8 for Trial 204 using the analysis methods prespecified in the protocol. That is, the analysis was based on observed cases (instead of multiple imputation to handle missing data) and stratified by country (instead of pooled site). The results based on the methods as originally specified in Protocol 204 are similar to the re-analyzed results using the methods as specified in Protocol 309.

Table 20. Results for the Co-Primary Endpoints at Week 8 (ITT, OC[1])

	ARQ-154-204 (Original)	
Endpoint	**Roflumilast Foam 0.3% (N=181)**	**Vehicle (N=88)**
B-IGA success at Week 8	40%	7%
Difference from vehicle (97.5% CI)[2]	33% (22.68%, 43.32%)	
Difference from vehicle (95% CI)[2]	33% (23.98%, 42.03%)	
p-value[2]	<0.0001	
S-IGA success at Week 8	59%	11%
Difference from vehicle (97.5% CI)[2]	48.38% (37.62%, 59.15%)	
Difference from vehicle (95% CI)[2]	48.38% (38.97%, 57.79%)	
p-value[2]	<0.0001	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt, adeff.xpt
[1] Intent-to-treat population: all randomized subjects. Subjects with an ICE (i.e., discontinuation of study treatment due to an AE or lack of efficacy prior to Week 8) were treated as non-responders. The results were based on observed cases (i.e., missing data was deleted from analysis).
[2] Difference, 97.5% and 95% CIs, and p-value were based on the Cochran-Mantel-Haenszel test stratified by country, baseline S-IGA, and baseline B-IGA.
Abbreviation: AE, adverse event; B-IGA, Body–Investigator Global Assessment; CI, confidence interval; ICE, intercurrent event; ITT, intent-to-treat; N, number of subjects in treatment arm; OC, observed cases; S-IGA, Scalp–Investigator Global Assessment

Table 21 presents the number and percentage of subjects with missing data for the co-primary efficacy endpoints at Week 8. Approximately 13% and 12% of the subjects had missing data in Trials 309 and 204, respectively.

Table 21. Missing Data for the Co-Primary Efficacy Endpoints at Week 8 (ITT[1])

	ARQ-154-309		ARQ-154-204 (Reanalysis)	
Subjects With Missing Data at Week 8, n (%)	**Roflumilast Foam 0.3% (N=281)**	**Vehicle (N=151)**	**Roflumilast Foam 0.3% (N=200)**	**Vehicle (N=104)**
All subjects	30 (11%)	25 (17%)	19 (10%)	16 (15%)
Excluding subjects with a preceding ICE[2]	22 (8%)	22 (15%)	-	-

Source: Statistical Reviewer's Analysis (similar to Applicant's Analysis); adeff.xpt
[1] ITT population: all randomized subjects.
[2] Subjects missing data at Week 8 without a preceding ICE are unreported for Trial ARQ-154-204.
Abbreviations: ICE, intercurrent event; ITT, intent-to-treat; N, number of subjects in treatment arm; n, number of subjects with missing data

The Applicant conducted a tipping point analysis for the co-primary endpoints. For Trial 204, the results for the co-primary endpoints of B-IGA success and S-IGA success remained statistically significant (i.e., p-value<0.025) even under the worst-case scenario (i.e., the mean score of subjects on the roflumilast arm was shifted upward by two units and that of subjects on the vehicle arm was shifted downward by two units).

For Trial 309, the primary endpoint of S-IGA success remained statistically significant (i.e., p-value<0.025) even under the worst-case scenario; however, the results for the primary endpoint of B-IGA success tip from significant to non-significant (i.e., p-value>0.025) over part of the evaluated region. In particular, the Applicant identified two points along the tipping boundary, including when the mean of the B-IGA scores of subjects on the vehicle arm with missing data is adjusted downward by 2 units and the mean score of subjects on the roflumilast arm was shifted upward by approximately 0.42 units, and where the mean of the B-IGA scores of subjects on the vehicle arm with missing data is adjusted downward by 1.5 units and the mean score of subjects on the roflumilast arm was shifted upward by approximately 0.85 units. The worst-case scenario produced a p-value of 0.0668 (i.e., the mean score of subjects on the roflumilast arm was shifted upward by 2 units and that of subjects on the vehicle arm was shifted downward by 2 units). Because the analysis did not tip for the S-IGA success endpoint in either trial, and only tipped for the B-IGA success endpoint in Trial 309 under relatively extreme assumptions, the results for the S-IGA and B-IGA success endpoints are robust to the handling of missing data.

Data Quality and Integrity

No issues related to data quality or integrity were identified in either Trial 204 or Trial 309.

Efficacy Results – Secondary and other relevant endpoints

Table 22, Table 23, and Table 24 present the results for the secondary efficacy endpoints in both trials. The secondary endpoint results were supportive of the primary efficacy endpoints. The results for all secondary efficacy endpoints for which the data were collected were statistically significant under the prespecified multiplicity control scheme. Unlike Trial 309, Trial 204 did not define any endpoints at timepoints prior to Week 2 or include endpoints based on the WI-NRS in the multiplicity control scheme. In Trial 309, the SI-NRS and WI-NRS were assessed in a daily diary, and endpoints based on these two instruments represent a weekly average. In Trial 204, the SI-NRS and WI-NRS were assessed only at study visits. All but one secondary efficacy endpoint (i.e., SI-NRS CFB at Day 1) had p-values smaller than 0.001. While the p-value of SI-NRS CFB at Day 1 in Trial 309 was slightly greater than 0.01, it was still statistically significant under the prespecified multiplicity control scheme.

Table 22. Results for Key Secondary Efficacy Endpoints in Family 1

	ARQ-154-309		ARQ-154-204 (Reanalysis)	
Endpoint	**Roflumilast, 0.3%**	**Vehicle**	**Roflumilast, 0.3%**	**Vehicle**
Randomized	281	151	200	104
ITT[1]	281	151	200	104
SPRU4-ITT[2]	203	123	176	96
SI-NRS success[2] (Week 8)	65%	30%	67%	21%
Risk difference (97.5%)	35.44% (22.26%, 48.62%)		43.56% (29.43%, 57.69%)	
Risk difference (95%)	35.44 (23.91%, 46.97%)		43.56% (31.21%, 55.92%)	
p-value	<0.0001		<0.0001	
SI-NRS success[2] (Week 4)	46%	17%	58%	25%
Risk difference (97.5%)	28.41% (16.12%, 40.7%)		30.24% (15.24%, 45.25%)	
Risk difference (95%)	28.41% (17.67%, 39.16%)		30.24% (17.12%, 43.37%)	
p-value	<0.0001		<0.0001	
SI-NRS success[2] (Week 2)	25%	8%	42%	18%
Risk difference (97.5%)	17.28% (7.72%, 26.84%)		20.66% (6.72%, 34.6%)	
Risk difference (95%)	17.28% (8.92%, 25.64%)		20.66% (8.47%, 32.85%)	
p-value	<0.0001		0.0009	
SI-NRS CFB (Week 1)				
LS means	−1.078	−0.531		
Difference (97.5%)	−0.55	−0.87, −0.22)	Endpoint not defined	
Difference (95%)	−0.55	−0.83, −0.26)		
p-value	0.0002			
SI-NRS CFB (72 hours)				
LS means	−1.113	−0.356		
Difference (97.5%)	−0.76	−1.12, −0.39)	Endpoint not defined	
Difference (95%)	−0.76	−1.07, −0.44)		
p-value	<0.0001			

Source: Statistical Reviewer's Analysis; adsl.xpt
[1] ITT population: all randomized subjects.
[2] SI-NRS success is defined as achievement of a ≥4-point reduction in average SI-NRS weekly score from baseline. SI-NRS Success endpoints were analyzed using the Scalp Pruritus ITT population, defined as all randomized subjects whose weekly average SI-NRS score is at least 4 at baseline. All other key secondary efficacy endpoints in Family 1 were analyzed using the ITT population.
Abbreviations: CFB, change from baseline; ITT, intent-to-treat; LS, least-squares; NRS, numerical rating scale; SI-NRS, Scalp Itch Numerical Rating Scale; SPRU4-ITT, Scalp Pruritus ITT

Table 23. Results for the Key Secondary Efficacy Endpoints in Family 2 (ITT[1])

	ARQ-154-309		ARQ-154-204 (Reanalysis)	
Endpoint	**Roflumilast, 0.3%**	**Vehicle**	**Roflumilast, 0.3%**	**Vehicle**
Randomized	281	151	200	104
ITT[1]	281	151	200	104
PRU4-ITT[2]	203	110	170	93
WI-NRS success[2] (Week 8)	63%	30%	65%	25%
Risk difference (97.5%)	32.75% (18.56%, 46.94%)		38.88% (23.61%, 54.14%)	
Risk difference (95%)	32.75% (20.34%, 45.16%)		38.88% (25.53%, 52.23%)	
p-value	<0.0001		<0.0001	
PASI-75 (Week 8)	50%	17%	42%	8%
Risk difference (97.5%)	32.33% (21.9%, 42.75%)		37.14% (26.15%, 48.13%)	
Risk difference (95%)	32.33% (23.21%, 41.44%)		37.14% (27.53%, 46.75%)	
p-value	<0.0001		<0.0001	

	ARQ-154-309		ARQ-154-204 (Reanalysis)	
Endpoint	**Roflumilast, 0.3%**	**Vehicle**	**Roflumilast, 0.3%**	**Vehicle**
CFB in PSD (Week 8)				
LS means	-10.869	-5.748	-10.779	-5.133
Difference (97.5%)	-5.12	−6.64, −3.60)	-5.65	−7.52, −3.77)
Difference (95%)	-5.12	−6.45, −3.79)	-5.65	−7.29, −4.01)
p-value		<0.0001		<0.0001
PSD-S=0 (Week 8)	42%	14%	33%	7%
Risk difference (97.5%)	27.39% (17.12%, 37.66%)		24.12% (13.62%, 34.61%)	
Risk difference (95%)	27.39% (18.41%, 36.37%)		24.12% (14.94%, 33.3%)	
p-value		<0.0001		<0.0001
PSD-I=0 (Week 8)	32%	10%	28%	5%
Risk difference (97.5%)	22.56% (13.24%, 31.88%)		19.85% (9.72%, 29.97%)	
Risk difference (95%)	22.56% (14.41%, 30.71%)		19.85% (11%, 28.7%)	
p-value		<0.0001		<0.0001
PSD-P=0 (Week 8)	65%	40%	53%	32%
Risk difference (97.5%)	26.35% (14.65%, 38.06%)		25.18% (11.2%, 39.17%)	
Risk difference (95%)	26.35% (16.12%, 36.59%)		25.18% (12.96%, 37.41%)	
p-value		<0.0001		<0.0001
PSSI-75 (Week 8)	71%	31%	65%	22%
Risk difference (97.5%)	37.62% (26.19%, 49.05%)		43.32% (30.65%, 56%)	
Risk difference (95%)	37.62% (27.62%, 47.62%)		43.32% (32.24%, 54.41%)	
p-value		<0.0001		<0.0001

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt
[1] ITT population: all randomized subjects.
[2] WI-NRS success is defined as achievement of ≥4-point reduction in average WI-NRS weekly score from baseline. The WI-NRS Success endpoint was analyzed using the Pruritus ITT population, defined as all randomized subjects whose weekly average WI-NRS score is at least 4 at baseline. All other key secondary efficacy endpoints in Family 2 were analyzed using the ITT population.
Abbreviations: CFB, change from baseline; ITT, intent-to-treat; PASI-75, ≥75% reduction in Psoriasis Area and Severity Index score from baseline; PRU4-ITT, Pruritus ITT; PSD, Pain Symptom Diary; PSD-I, PSD Item related to Itching; PSD-P, PSD Item related to Pain; PSD-S, PSD Item related to Scaling; PSSI, Psoriasis Scalp Severity Index; WI-NRS, Worst Itch Numerical Rating Scale

Table 24. Results for the Key Secondary Efficacy Endpoints in Family 3 (ITT[1])

	ARQ-154-309		ARQ-154-204 (Reanalysis)	
Endpoint	**Roflumilast, 0.3%**	**Vehicle**	**Roflumilast, 0.3%**	**Vehicle**
S-IGA 0[2] (Week 8)	40%	9%	33%	3%
Risk difference (97.5%)	31.9% (22.41%, 41.4%)		30.48% (21.02%, 39.94%)	
Risk difference (95%)	31.9% (23.6%, 40.2%)		30.48% (22.2%, 38.75%)	
p-value		<0.0001		<0.0001
S-IGA success[3] (Week 4)	54%	19%	40%	5%
Risk difference (97.5%)	32.98% (22.17%, 43.8%)		34.83% (24.5%, 45.16%)	
Risk difference (95%)	32.98% (23.53%, 42.44%)		34.83% (25.8%, 43.86%)	
p-value		<0.0001		<0.0001
CFB in PASI (Week 2)				
LS means	−2.306	−1.027	−1.962	−1.004
Difference (97.5%)	−1.28	−1.71, −0.85)	−0.96	−1.57, −0.35)
Difference (95%)	−1.28	−1.65, −0.91)	−0.96	−1.49, −0.42)
p-value		<0.0001		0.0004
S-IGA success (Week 2)	30%	12%	18%	3%
Risk difference (97.5%)	18.48% (9.81%, 27.15%)		14.46% (6.96%, 21.95%)	
Risk difference (95%)	18.48% (10.9%, 26.06%)		14.46% (7.91%, 21.01%)	
p-value		<0.0001		<0.0001

	ARQ-154-309		ARQ-154-204 (Reanalysis)	
Endpoint	**Roflumilast, 0.3%**	**Vehicle**	**Roflumilast, 0.3%**	**Vehicle**
PSD total score=0 (Week 8)	20%	7%	17%	2%
Risk difference (97.5%)	13.63% (5.35%, 21.9%)		12.63% (4.58%, 20.68%)	
Risk difference (95%)	13.63% (6.39%, 20.86%)		12.63% (5.6%, 19.67%)	
p-value	0.0002		0.0004	
SI-NRS CFB (Day 1)				
LS means	−0.440	−0.090		
Difference (97.5%)	−0.35	−0.68, −0.02)	Endpoint not defined	
Difference (95%)	−0.35	−0.64, 0.06)		
p-value	0.0164			

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt
[1] ITT population: all randomized subjects.
[2] S-IGA 0 is defined as S-IGA score of Clear.
[3] S-IGA Success is defined as an IGA score of Clear (0) or Almost Clear (1) plus a ≥2-grade improvement from baseline.
Abbreviations: CFB, change from baseline; ITT, intent-to-treat; LS, least-squares; PASI, Psoriasis Area and Severity Index; PSD, Psoriasis Symptom Diary; S-IGA, Scalp–Investigator Global Assessment; SI-NRS, Scalp Itch Numerical Rating Scale

8.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

Efficacy on the co-primary efficacy endpoints of B-IGA success and S-IGA success at Week 8 was demonstrated in both Trials 309 and 204. The risk difference estimate for B-IGA success was 25% in Trial 309 and 32% in Trial 204, while that for S-IGA success was 37% in Trial 309 and 48% in Trial 204, respectively. The response rates of both treatment arms were higher in Trial 309 than in Trial 204; however, Trial 309's smaller treatment effects stemmed from Trial 309's higher vehicle response rate relative to Trial 204's.

Subpopulations

Table 25, Table 26, Table 27, and Table 28 present the results of the co-primary endpoints – S-IGA Success and B-IGA Success – at Week 8 by age, sex, race, ethnicity, baseline B-IGA category, and baseline S-IGA category. There were generally no substantial differences in treatment effect across these subgroups. However, the sample size for some of the subgroups (e.g., age ≥65 years) was relatively small; therefore, it would be difficult to detect any difference in efficacy between these subgroups and their complements.

Table 25. Results of the Primary Efficacy Endpoint of B-IGA Success at Week 8 by Subgroup, Trial ARQ-154-309 (ITT[1])

Subgroup (n_{rofl}, $n_{vehicle}$)	**Roflumilast, 0.3%**	**Vehicle**	**Difference From Vehicle (95% CI)**
Age (years)			
12–17 (7, 3)	71%	33%	-
18–64 (234, 134)	47%	17%	32% (22%, 42%)
≥65 40, 14	30%	52%	-34% −71%, 3%)
Sex			
Female (152, 91)	51%	27%	24% (9%, 38%)
Male (129, 60)	39%	9%	29% (15%, 43%)

Subgroup (n_{rofl}, $n_{vehicle}$)	Roflumilast, 0.3%	Vehicle	Difference From Vehicle (95% CI)
Race			
White (225, 129)	47%	19%	28% (18%, 39%)
Black or African American (12, 6)	17%	35%	-
Other (44, 16)	45%	25%	5% −37%, 47%)
Ethnicity			
Hispanic or Latino (48, 28)	50%	30%	11% −15%, 37%)
Not Hispanic or Latino (224, 121)	45%	18%	25% (14%, 37%)
Baseline B-IGA category			
B-IGA =2 (75, 44)	46%	19%	26% (7%, 45%)
B-IGA ≥3 (206, 107)	45%	20%	24% (13%, 36%)
Baseline S-IGA category			
S-IGA =3 (239, 131)	48%	21%	26% (16%, 36%)
S-IGA =4 (42, 20)	32%	12%	11% −20%, 43%)

Source: Statistical Reviewer's Analysis (similar to Applicant's Analysis); adsl.xpt, admibiga.xpt
[1] ITT population: all randomized subjects. Subjects with an ICE (i.e., discontinuation of study treatment due to an AE or lack of efficacy prior to Week 8) were treated as non-responders. Missing data was imputed using multiple imputation (MI).
Abbreviations: AE, adverse event; B-IGA, Body-Investigator Global Assessment; CI, confidence interval; ICE, intercurrent event; ITT, intent-to-treat; S-IGA, Scalp–Investigator Global Assessment

Table 26. Results of the Primary Efficacy Endpoint of S-IGA Success at Week 8 by Subgroup, Trial ARQ-154-309 (ITT[1])

Subgroup (n_{rofl}, $n_{vehicle}$)	Roflumilast, 0.3%	Vehicle	Difference From Vehicle (95% CI)
Age (years)			
12–17 (7, 3)	71%	33%	-
18–64 (234, 134)	70%	25%	44% (34%, 54%)
≥65 40, 14	46%	56%	-19% −60%, 23%)
Sex			
Female (152, 91)	64%	29%	33% (18%, 48%)
Male (129, 60)	69%	26%	42% (26%, 58%)
Race			
White (225, 129)	66%	24%	43% (32%, 53%)
Black or African American (12, 6)	50%	57%	-
Other (44, 16)	70%	50%	31% −3%, 66%)
Ethnicity			
Hispanic or Latino (48, 28)	65%	18%	44% (20%, 68s%)
Not Hispanic or Latino (224, 121)	68%	30%	35% (24%, 47%)
Baseline B-IGA category			
B-IGA =2 (75, 44)	66%	30%	32% (12%, 52%)
B-IGA ≥3 (206, 107)	67%	27%	39% (27%, 50%)
Baseline S-IGA category			
S-IGA =3 (239, 131)	70%	31%	38% (27%, 49%)
S-IGA =4 (42, 20)	4%	6%	33% (8%, 57%)

Source: Statistical Reviewer's Analysis (similar to Applicant's Analysis); adsl.xpt, admisiga.xpt
[1] ITT population: all randomized subjects. Subjects with an ICE (i.e., discontinuation of study treatment due to an AE or lack of efficacy prior to Week 8) were treated as non-responders. Missing data was imputed using multiple imputation (MI).
Abbreviations: AE, adverse event; B-IGA, Body–Investigator Global Assessment; CI, confidence interval; ICE, intercurrent event; ITT, intent-to-treat; S-IGA, Scalp–Investigator Global Assessment

Table 27. Results of the Primary Efficacy Endpoint of B-IGA Success at Week 8 by Subgroup, Trial ARQ-154-204 (ITT[1])

Subgroup (n_{rofl}, $n_{vehicle}$)	Roflumilast, 0.3%	Vehicle	Difference From Vehicle (95% CI)
Age (years)			
12–17 (1, 1)	100%	100%	-
18–64 (183, 91)	39%	5%	31% (22%, 41%)
≥65 16, 12	40%	17%	-
Sex			
Female (104, 57)	49%	11%	40% (25%, 54%)
Male (96, 47)	28%	4%	31% (18%, 43%)
Race			
White (180, 91)	39%	7%	33% (23%, 43%)
Black or African American (9, 6)	37%	0%	-
Other (9, 6)	44%	18%	-
Ethnicity			
Hispanic or Latino (38, 25)	32%	10%	19% −1%, 39%)
Not Hispanic or Latino (161, 79)	41%	7%	34% (24%, 45%)
Baseline B-IGA category			
B-IGA =2 (75, 40)	44%	12%	31% (14%, 47%)
B-IGA ≥3 (125, 64)	36%	4%	33% (23%, 44%)
Baseline S-IGA category			
S-IGA =2 (25, 15)	30%	14%	35% (8%, 62%)
S-IGA ≥3 (175, 89)	40%	6%	32% (22%, 42%)

Source: Statistical Reviewer's Analysis (similar to Applicant's Analysis); adsl.xpt, admibiga.xpt
[1] ITT population: all randomized subjects. Subjects with an ICE (i.e., discontinuation of study treatment due to an AE or lack of efficacy prior to Week 8) were treated as non-responders. Missing data was imputed using multiple imputation (MI).
Abbreviations: AE, adverse event; B-IGA, Body–Investigator Global Assessment; CI, confidence interval; ICE, intercurrent event; ITT, intent-to-treat; S-IGA, Scalp–Investigator Global Assessment

Table 28. Results of the Primary Efficacy Endpoint of S-IGA Success at Week 8 by Subgroup, Trial ARQ-154-204 (ITT[1])

Subgroup (n_{rofl}, $n_{vehicle}$)	Roflumilast, 0.3%	Vehicle	Difference From Vehicle (95% CI)
Age (years)			
12–17 (1, 1)	100%	100%	-
18–64 (183, 91)	57%	8%	49% (38%, 59%)
≥65 16, 12	44%	25%	-
Sex			
Female (104, 57)	54%	13%	41% (25%, 57%)
Male (96, 47)	59%	9%	57% (43%, 71%)
Race			
White (180, 91)	56%	11%	49% (38%, 59%)
Black or African American (9, 6)	61%	0%	-
Other (9, 6)	67%	18%	-
Ethnicity			
Hispanic or Latino (38, 25)	54%	17%	32% (8%, 57%)
Not Hispanic or Latino (161, 79)	58%	9%	52% (41%, 63%)
Baseline B-IGA category			
B-IGA =2 (75, 40)	68%	16%	58% (41%, 75%)
B-IGA ≥3 (125, 64)	50%	8%	43% (31%, 54%)

Subgroup (n_{rofl}, $n_{vehicle}$)	Roflumilast, 0.3%	Vehicle	Difference From Vehicle (95% CI)
Baseline S-IGA category			
S-IGA =2 (25, 15)	54%	14%	64% (36%, 91%)
S-IGA ≥3 (175, 89)	57%	10%	46% (36%, 57%)

Source: Statistical Reviewer's Analysis (similar to Applicant's Analysis); adsl.xpt, admisiga.xpt
[1] ITT population: all randomized subjects. Subjects with an ICE (i.e., discontinuation of study treatment due to an AE or lack of efficacy prior to Week 8) were treated as non-responders. Missing data was imputed using multiple imputation (MI).
Abbreviations: AE, adverse event; B-IGA, Body–Investigator Global Assessment; CI, confidence interval; ICE, intercurrent event; ITT, intent-to-treat; S-IGA, Scalp–Investigator Global Assessment

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 psoriasis of the scalp and body relied on pooled safety data from one phase 2 (ARQ-154-204) and one phase 3 (ARQ-154-309) randomized, DB, PC trial which shared similar inclusion/exclusion criteria, study designs, dosing regimen, treatment durations (8 weeks), and primary and secondary efficacy endpoints. Trials -204/-309 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 30 days after last study drug application. In addition, the Applicant submitted safety data from a phase 1, MUsT (ARQ-154-122) conducted with roflumilast foam, 0.3% for psoriasis.

During the roflumilast foam development program for psoriasis, 509 subjects (including 479 subjects in the VC trials and 30 subjects in the MUsT) were exposed to roflumilast foam, 0.3% at least once. For the pooled VC studies, the mean number of drug applications were 52.1 for roflumilast group and 48.7 for the vehicle group.

To determine the safety profile of roflumilast foam, 0.3% QD for the treatment of psoriasis, the review team analyzed the data for exposure, demographics, baseline characteristics, TEAEs (including severe TEAEs, SAEs, AELDs), directed physical examinations [including height and weight], vital signs (systolic and diastolic blood pressures, heart rate, temperature), local tolerability assessments by investigator [Berger and Bowman scoring scale] and by subject [0-3 scale], clinical laboratory parameters (hematology, chemistry, urinalysis), pregnancy tests [urine or serum] for female subjects of child-bearing potential, and psychiatric assessments for depression and suicidality (eight-item Patient Health Questionnaire [PHQ-8]/modified PHQ-9 for adolescents [PHQ-A], Columbia-Suicide Severity Rating Scale [C-SSRS]). No adverse events of special interest 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, 427/479 (89%) subjects in the roflumilast group and 213/255 (84%) subjects in the vehicle group completed treatment with the study drug at Week 8.

AELDs were reported for 10/479 (2.1%) subjects in the roflumilast group and 4/255 (1.6%) 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 plaque psoriasis of the scalp and body. Safety assessments were reasonable and consistent with known adverse events for roflumilast in the target population:

- The size of safety database is adequate. In the VC pool, a total of 479 subjects received at least one dose of roflumilast foam, 0.3%.; of which 427 subjects were treated for 8 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 53.5 (13.1) in the roflumilast group and 50.1 (16.7) in the vehicle group for the VC pool.
- The demographics of the study population are sufficiently representative of the target population as presented in Table 29.

Table 29. Demographic and Baseline Disease Characteristics: Roflumilast Foam, 0.3% QD for Plaque Psoriasis of the Scalp and Body (Safety Population)

	VC Pool: ARQ-154-204 and ARQ-154-309	
Demographic Characteristics	**Roflumilast Foam, 0.3% (N=479)**	**Vehicle Foam (N=255)**
Age (years)		
Mean (SD)	47.1 (14.8)	45.0 (14.9)
Median (min to max)	48.0 (12, 87)	46.0 (15, 87)
Age group (years), n (%)		
≥12 and ≤17	8 (1.7)	4 (1.6)
≥18 and ≤64	415 (86.6)	225 (88.2)
≥65	56 (11.7)	26 (10.2)
Sex, n (%)		
Male	225 (47.0)	107 (42.0)
Female	254 (53.0)	148 (58.0)

	VC Pool: ARQ-154-204 and ARQ-154-309	
Demographic Characteristics	**Roflumilast Foam, 0.3% (N=479)**	**Vehicle Foam (N=255)**
Race, n (%)		
American Indian or Alaska native	0 (0)	3 (1.2)
Asian	33 (6.9)	8 (3.1)
Black or African American	21 (4.4)	12 (4.7)
Native Hawaiian or other Pacific Islander	3 (0.6)	2 (0.8)
White	403 (84.1)	220 (86.3)
Other	12 (2.5)	7 (2.7)
Multiple	5 (1.0)	2 (0.8)
Missing	2 (0.4)	1 (0.4)
Ethnicity, n (%)		
Hispanic or Latino	86 (18.0)	53 (20.8)
Not Hispanic or Latino	383 (80.0)	200 (78.4)
Unknown/unreported	10 (2.1)	2 (0.8)
Baseline Characteristics		
Weight (kg)		
Mean (SD)	87.2 (22.6)	90.1 (23.5)
Median (min to max)	83.6 (32.0, 199.2)	85.9 (46.3, 226.8)
BMI (kg/m^2)		
Mean (SD)	30.4 (7.1)	31.5 (7.4)
Median (min to max)	29.2 (16.1, 61.3)	30.5 (18.1, 64.2)
Total affected BSA (%)		
Mean (SD)	6.9 (5.0)	6.7 (4.9)
Median (min to max)	5.1 (0.6, 24.0)	5.0 (1.0, 25.0)
S-IGA, n (%)		
Mild (2)	18 (3.8)	14 (5.5)
Moderate (3)	390 (81.4)	211 (82.7)
Severe (4)	71 (14.8)	30 (11.8)
B-IGA, n (%)		
Mild (2)	145 (30.3)	82 (32.2)
Moderate (3)	310 (64.7)	159 (62.4)
Severe (4)	24 (5.0)	14 (5.5)

Source: adapted from sNDA 217242-005, M 2.7.4 (SCS) Section 1.3.1, Tables 8, 9. Consistent with Clinical Reviewer's Analysis Studio and JMP Clinical 8.1 analysis.
Abbreviations: B-IGA, Body–Investigator Global Assessment; BMI, body mass index; BSA, body surface area; N, number of subjects in treatment arm; n, number of subjects with given characteristic; QD, once daily; S-IGA, Scalp–Investigator Global Assessment; SD, standard deviation; VC, vehicle-controlled

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 plaque psoriasis of the scalp and body. 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 electronic case report form (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 25.0. 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 (version 4) 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).

The Applicant's assessment of adverse events conducted for the VC studies 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), local tolerability assessment by investigator and by subject according to the schedules of activities during the VC trials. No ECGs were conducted during phase 2 or phase 3 trials.

8.2.4. Safety Results

Deaths

No deaths were reported in clinical studies of roflumilast foam for plaque psoriasis of the scalp and body.

Serious Adverse Events

In the VC pool, SAEs were reported for 1/225 (0.4%) subject in the vehicle group [a 32-year-old female subject hospitalized for severe SAEs/AELDs of radius fracture, joint dislocation, and peripheral artery occlusion (Days 50-62); deemed as unrelated to study drug by the investigator and led to subject's withdrawal from the trial] and the following 3/479 (0.6%) subject in the roflumilast group as summarized in Table 30.

Table 30. Summary of Serious Adverse Events by SOC and PT in the VC Pool (Safety Population)

System Organ Class Preferred Term	Roflumilast Foam 0.3% N=479		Vehicle N=255	
	n	(%)	n	(%)
Any SAE	3	(0.6)	1	(0.4)
Gastrointestinal disorders	1	(0.2)	0	(0.0)
Gastritis	1	(0.2)	0	(0.0)
Injury, poisoning and procedural complications	0	(0.0)	1	(0.4)
Joint dislocation	0	(0.0)	1	(0.4)
Radius fracture	0	(0.0)	1	(0.4)
Psychiatric disorders	1	(0.2)	0	(0.0)
Bipolar disorder	1	(0.2)	0	(0.0)
Reproductive system and breast disorders	1	(0.2)	0	(0.0)
Testicular torsion	1	(0.2)	0	(0.0)

System Organ Class Preferred Term	Roflumilast Foam 0.3% N=479		Vehicle N=255	
	n	(%)	n	(%)
Vascular disorders	0	(0.0)	1	(0.4)
Peripheral artery occlusion	0	(0.0)	1	(0.4)

Source: Clinical Reviewer's analysis by OCS Analysis Studio, Safety Explorer. Consistent with sNDA 217242-005, M 2.7.4, Table 13.
Filters: TRT01A = "Roflumilast Foam 0.3%" and STUDYID = "ARQ-154-204" or "ARQ-154-309" and SAFFL = "Y" (Roflumilast Foam 0.3%); TRT01A = "Vehicle" and STUDYID = "ARQ-154-204" or "ARQ-154-309" and SAFFL = "Y" (Vehicle); TRTEMFL = "Y" and AESER = "Y" (Adverse Events).
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SAE, serious adverse event; SOC, system organ class; VC, vehicle-controlled

Table 31. Narratives of Serious Adverse Events in Subjects Treated With Roflumilast Foam, 0.3% in the VC Pool (Safety Population)

Study ID/ Subject ID/ Age (Years) / Sex	PT(s)	Start Day/ End Day	Severity (CTCAE Toxicity Grade	Relationship to Roflumilast/ Outcome	Action Taken
ARQ-154-309 (b) (6) 21/F	Bipolar disorder	Days 28 to 36	3 (severe)	Unrelated/ Unknown (lost to follow-up on D 58)	Study drug interrupted
ARQ-154-309 (b) (6) 74/F	Gastritis	Days 7 to 12	3 (severe)	Possibly related/ Recovered/resolved	Hospitalized, study drug interrupted (history of Barrett's esophagus)
ARQ-154-204 (b) (6) 19/M	Testicular torsion	Day 38 to 39	3 (severe)	Unrelated Recovered/resolved	None. Hospitalized for surgical repair. History of connective tissue disorder and orchiopexy for undescended testicle

Source: Adapted from sNDA 217242-005, M. 2.7.4, Table 13 and CSRs for Trials -204/-309. Consistent with Clinical Reviewer's JMP Clinical 8.1 analysis.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Event; D 58, Day 58; F, female; M, male; PT, preferred term; VC, vehicle-controlled

Dropouts and/or Discontinuations Due to Adverse Effects

In the VC pool, AELDs were reported for 12/479 (2.5%) subjects in the roflumilast group compared to 4/255 (1.6%) subjects in the vehicle group. AELDs for subjects in the vehicle group included application site dermatitis (1), application site erythema (1), diarrhea (1), headache (1), joint dislocation (1), radius fracture (1), psoriasis (1), and peripheral artery occlusion (1).

AELDs by preferred terms reported in >1 subject in the roflumilast group, compared to the vehicle group included diarrhoea (3 [0.6%] v. 1 [0.4%]), application site irritation (2 [0.4%] v. 0 [0%]), and COVID-19 (2 [0.4%] v. 0 [0%]). AELDs reported for the roflumilast group were all non-serious and are summarized in the following table.

Table 32. Summary of TEAEs Leading to Discontinuation by SOC and PT in the VC Pool (Safety Population)

System Organ Class Preferred Term	Roflumilast Foam 0.3% N=479		Vehicle N=255	
	n	(%)	n	(%)
Any AE	12	(2.5)	4	(1.6)
Congenital, familial and genetic disorders	1	(0.2)	0	(0.0)
Gilbert's syndrome	1	(0.2)	0	(0.0)
Gastrointestinal disorders	3	(0.6)	1	(0.4)
Abdominal discomfort	1	(0.2)	0	(0.0)
Diarrhoea	3	(0.6)	1	(0.4)
Nausea	1	(0.2)	0	(0.0)
General disorders and administration site conditions	5	(1.0)	2	(0.8)
Application site dermatitis	1	(0.2)	1	(0.4)
Application site discolouration	1	(0.2)	0	(0.0)
Application site erythema	0	(0.0)	1	(0.4)
Application site irritation	2	(0.4)	0	(0.0)
Application site pain	1	(0.2)	0	(0.0)
Application site paraesthesia	1	(0.2)	0	(0.0)
Application site pruritus	1	(0.2)	0	(0.0)
Application site warmth	1	(0.2)	0	(0.0)
Infections and infestations	2	(0.4)	0	(0.0)
Covid-19	2	(0.4)	0	(0.0)
Injury, poisoning and procedural complications	0	(0.0)	1	(0.4)
Joint dislocation	0	(0.0)	1	(0.4)
Radius fracture	0	(0.0)	1	(0.4)
Investigations	1	(0.2)	0	(0.0)
Bilirubin conjugated increased	1	(0.2)	0	(0.0)
Blood bilirubin increased	1	(0.2)	0	(0.0)
Nervous system disorders	2	(0.4)	1	(0.4)
Headache	1	(0.2)	1	(0.4)
Lethargy	1	(0.2)	0	(0.0)
Skin and subcutaneous tissue disorders	0	(0.0)	1	(0.4)
Psoriasis	0	(0.0)	1	(0.4)
Vascular disorders	0	(0.0)	1	(0.4)
Peripheral artery occlusion	0	(0.0)	1	(0.4)

Source: Clinical Reviewer's analysis by OCS Analysis Studio, Safety Explorer. Consistent with sNDA 217242-005, M 2.7.4, Table 14.
Filters: TRT01A = "Roflumilast Foam 0.3%" and STUDYID = "ARQ-154-204" or "ARQ-154-309" and SAFFL = "Y" (Roflumilast Foam 0.3%); TRT01A = "Vehicle" and STUDYID = "ARQ-154-204" or "ARQ-154-309" and SAFFL = "Y" (Vehicle); TRTEMFL = "Y" and AEACN = "DRUG WITHDRAWN" (Adverse Events).
Abbreviations: AE, adverse event; Covid-19, coronavirus disease 2019; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event; VC, vehicle-controlled

Table 33. Narratives of Adverse Events Leading to Study Drug Discontinuation in Subjects Treated With Roflumilast Foam, 0.3% in the VC Pool (Safety Population)

Study ID/ Subject ID/ Age (Years) /Sex	PT(s)	Start Day/ End Day	Severity (CTCAE Toxicity Grade	Relationship to Roflumilast	Outcome/ Withdrew From Study?
ARQ-154-309 (b) (6) 42/F	Bilirubin conjugated increased	27/56	1	Possibly related	Recovered/ No
	Blood bilirubin increased	27/56			
	Gilbert's syndrome	49/ongoing		Not related	Not recovered/ No
ARQ-154-309 (b) (6) 23/M	COVID-19	54/68	1	Not related	Recovered/ No
ARQ-154-309 (b) (6) 74/F	Diarrhoea	23/28	1	Possibly related	Recovered/ Yes
	Nausea	23/24			
ARQ-154-309 (b) (6) 79/F	Diarrhoea	20/36	2	Probably related	Recovered/ Yes
ARQ-154-309 (b) (6) 30/F	COVID-19	16/30	2	Not related	Recovered/ Yes
ARQ-154-309 (b) (6) 69/F	Application site dermatitis	9/16	2	Possibly related	Recovered/ Yes
ARQ-154-309 (b) (6) 36/M	Application site paraesthesia	26/28	2	Possibly related	Recovered/ Yes
	Application site warmth				
ARQ-154-204 (b) (6) 65/F	Application site pruritus	18/ ongoing	2	Possibly related	Not recovered /Yes
ARQ-154-204 (b) (6) 35/M	Abdominal discomfort	2/20	2	Possibly related	Recovered/ Yes
	Diarrhoea		1		
	Headache		2		
ARQ-154-204 (b) (6) M/25	Application site irritation	12/27	2	Likely related	Recovered/ Yes
	Application site pain	13/27	2		
	Application site discolouration	18/27	2		
ARQ-154-204 (b) (6) 31/F	Application site irritation	7/12	1	Likely related	Recovered/ Yes
ARQ-154-204 (b) (6) 48/M	Lethargy	27/33	2	Likely related	Recovered/ Yes

Source: Adapted from sNDA 217242-005, M. 2.7.4; Tables 14, 74, and CSRs for Trials -204/-309. Consistent with Clinical Reviewer's JMP Clinical 8.1 analysis.
Abbreviations: COVID-19, coronavirus disease 2019; CTCAE, Common Terminology Criteria for Adverse Event; F, female; M, male; PT, preferred term; VC, vehicle-controlled

Pregnancy

No pregnancies were reported in clinical studies of roflumilast foam for plaque psoriasis of the scalp and body.

Significant Adverse Events

Severe (Grade 3) AEs

In the VC pool, severe AEs were reported in 7/479 (1.5%) subjects in the roflumilast group compared to 3/255 (1.2%) subjects in the vehicle group. No AEs were reported as severity Grades of 4 or 5.

Contact Dermatitis

For the VC pool, contact dermatitis was reported at a frequency of 1/479 (0.2%) in the roflumilast group compared to 0/225 (0%) in the vehicle group.

A 69-year-old female subject (ARQ-154-309-(b) (6)) who received treatment with roflumilast foam was reported with a non-serious AELD of (irritant) contact dermatitis on Days 9-16 which was deemed as probably related to the study drug and led to subject's withdrawal from the trial. The AE outcome was reported as recovered.

Adverse Events Potentially Related to PDE-4 Inhibition

The Applicant proactively assessed the frequency of weight decrease, psychiatric AEs (insomnia, anxiety, and depression), and gastrointestinal AEs in clinical trials of roflumilast foam for plaque psoriasis because oral PDE-4 inhibitors (roflumilast and apremilast) have been associated with increased frequency of these AEs. Similarly, the Applicant had assessed the frequency of these AEs in clinical trials of roflumilast cream (for plaque psoriasis and atopic dermatitis) and roflumilast foam (for seborrheic dermatitis) and concluded that roflumilast cream or foam were not associated with depression or weight decrease, while diarrhea and nausea were reported at significantly lower frequency for roflumilast cream or foam than for oral PDE-4 inhibitors. TEAEs potentially related to PDE-4 Inhibition (reported in ≥2 subjects) in the VC pool are summarized in the following table.

Table 34. Summary of TEAEs [Potentially Related to PDE-4 Inhibition] (Reported for ≥2 Subjects) by SOC and PT in the VC Pool (Safety Population)

System Organ Class Preferred Term	Roflumilast Foam 0.3% N=479		Vehicle N=255	
	n	(%)	n	(%)
Any AE	121	(25.3)	45	(17.6)
Gastrointestinal disorders	22	(4.6)	5	(2.0)
Abdominal discomfort	2	(0.4)	1	(0.4)
Diarrhoea	12	(2.5)	4	(1.6)
Gastritis	2	(0.4)	1	(0.4)
Nausea	8	(1.7)	0	(0.0)
Paraesthesia oral	2	(0.4)	0	(0.0)
Investigations	9	(1.9)	3	(1.2)
Weight decreased	2	(0.4)	0	(0.0)
Psychiatric disorders	5	(1.0)	0	(0.0)
Insomnia	3	(0.6)	0	(0.0)

Source: Clinical Reviewer's analysis by OCS Analysis Studio, Safety Explorer. Consistent with sNDA 217242-005, M 2.7.4, Table 18, 19.
Filters: TRT01A = "Roflumilast Foam 0.3%" and STUDYID = "ARQ-154-204" or "ARQ-154-309" and SAFFL = "Y" (Roflumilast Foam 0.3%); TRT01A = "Vehicle" and STUDYID = "ARQ-154-204" or "ARQ-154-309" and SAFFL = "Y" (Vehicle); TRTEMFL = "Y" (Adverse Events).
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; PDE-4, phosphodiesterase-4; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event; VC, vehicle-controlled

The Applicant proposes the following as Adverse Drug Reactions of the roflumilast foam for inclusion in Sec. 6.1 of the label under subheading of Plaque Psoriasis:

- Headache (3.1%)
- Diarrhea (2.5%)
- Nausea (1.7%)
- Nasopharyngitis (1.3%)
- Insomnia (0.3%) [not included in the AE table in Sec. 6.1 of the label]

Psychiatric AEs

Prespecified assessments of depression and suicidality (PHQ-8, modified PHQ-A, and C-SSRS) did not raise any safety concerns for any subjects in the clinical trials of roflumilast foam. In the VC pool, TEAEs in the SOC of Psychiatric disorders were reported for 5/479 (1.0%) subjects in the roflumilast group compared to 0/255 (0%) subject in the vehicle group. AEs in the SOC of Psychiatric Disorders in the roflumilast group included Insomnia for 3 (0.6%) subjects, middle insomnia for 1 (0.2%) subject, and bipolar disorder for 1 (0.2%) subject. No subject was reported with AEs of depression or anxiety. Insomnia is the only AE in the SOC of Psychiatric disorders proposed by the Applicant for inclusion in Sec. 6.1 of the label for roflumilast foam.

Gastrointestinal AEs

In the VC pool, TEAEs in the SOC of Gastrointestinal Disorders were reported for 22 (4.6%) subjects in the roflumilast group compared to 5 (1.9%) subject in the vehicle group; and included the following AEs (reported for ≥2 subjects) in the roflumilast group, compared to the

vehicle group, respectively: diarrhea 12 (2.5%) versus 4 (1.6%), nausea 8 (1.7%) versus 0, abdominal discomfort 2 (0.4%) versus 1 (0.4%), gastritis 2 (0.4%) versus 1 (0.4%), and paresthesia oral 2 (0.4%) versus 0. Diarrhea and nausea are the only AEs in the SOC of Gastrointestinal Disorders proposed by the Applicant for inclusion in Sec. 6.1 of the label for roflumilast foam.

Weight Decrease

The Applicant considered a change of ≥5% of body weight from baseline as clinically significant.

In the VC pool, the mean (SD) change from baseline in weight at Week 8 was -0.87 (2.01) kg in the roflumilast group compared with +0.23 (2.36) kg in the vehicle group. In general, the mean changes from baseline in subjects' weights were not considered clinically significant.

In the VC pool, AEs for the PT of "weight decreased" was reported for 2 (0.4%) subjects in the roflumilast group (from Trial -309) compared to 0 subject in the vehicle group, as listed below.

1. Subject (b) (6): a 62-year-old obese female subject was reported with an AE of weight decreased of 5.7% from baseline to Week 8; reported as mild and possibly related to roflumilast. A moderate AE of diarrhea and concomitant use of semaglutide for intentional weight loss was also reported.
2. Subject (b) (6): a 42-year-old obese male subject, was reported with an AE of weight decreased of 2.4% from baseline to Weeks 2 and 4; reported as mild and not related to roflumilast. The subject's weight returned to the baseline weight at Week 8.

For the roflumilast group compared to the vehicle group, respectively, a weight loss (≥5% from baseline) was reported at week 4 for 11 (2.4%) subjects compared to 2 (0.9%) subjects; and at week 8 for 23 (5.3%) subjects compared to 5 (2.3%) subjects [weight decrease for most subjects were intentional and related to diet and lifestyle modifications; other reasons included COVID-19 (1), illness/ dehydration/procedural preparation (1), concomitant medication (1), unexplained (1), or unintentional (1)].

An obese 61-year-old female subject ((b) (6), Trial -309) was reported with a weight loss ≥10% of baseline body weight at Week 8 as a result of intentional diet or lifestyle modifications (not reported as an AE). No subject in the vehicle group was reported with a weight decrease of ≥10% at Week 8.

In the VC pool, the mean (SD) change from baseline in body-mass index (BMI) at Week 8 was −0.37 (0.88) in the roflumilast group compared with +0.13 (0.898) in the vehicle group. In general, the mean changes from baseline in subjects' BMIs were not considered clinically significant.

In the VC pool, a shift in the BMI from normal (19.0) to underweight (18.1) was reported at week 4 for a 74-year-old female subject ((b) (6), trial-309) with history of Barrett's esophagus in the roflumilast group. This subject was reported with a severe AE of nausea and a severe SAE

of Gastritis within the first 2 weeks of treatment, which led to discontinuation from treatment on D 23 and from the trial on D 28.

Treatment Emergent Adverse Events and Adverse Reactions

For the VC pool, the incidence of TEAEs were 121/479 (25.3%) in the roflumilast group, compared to 45/255 (17.7%) in the vehicle group. The PTs reported as TEAEs at a frequency of ≥1% in the roflumilast group (and a greater frequency than the vehicle group), compared to the vehicle group, respectively, included the following:

- Headache 15 (3.1%) v. 3 (1.2%)
- Diarrhea 12 (2.5%) v. 4 (1.6%)
- Nausea 8 (1.7%) v. 0 (0%)
- Hypertension 6 (1.3%) v. 3 (1.2%)
- Nasopharyngitis 6 (1.3%) v. 2 (0.8%)

Insomnia was reported for 3 (0.6%) v. 0 (0%). The most frequent TEAEs reported for subjects in the VC pool are summarized in the following table.

Table 35. 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)

	Roflumilast Foam 0.3% N=479		Vehicle N=255	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Any AE	121	(25.3)	45	(17.6)
Headache	15	(3.1)	3	(1.2)
Diarrhoea	12	(2.5)	4	(1.6)
Nausea	8	(1.7)	0	(0.0)
Hypertension	6	(1.3)	3	(1.2)
Nasopharyngitis	6	(1.3)	2	(0.8)

Source: Clinical Reviewer's by OCS Analysis Studio, Safety Explorer. Consistent with sNDA 217242-005, M 2.7.4, Tables 10, 12.
Filters: TRT01A = "Roflumilast Foam 0.3%" and STUDYID = "ARQ-154-204" or "ARQ-154-309" and SAFFL = "Y" (Roflumilast Foam 0.3%); TRT01A = "Vehicle" and STUDYID = "ARQ-154-204" or "ARQ-154-309" and SAFFL = "Y" (Vehicle); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Roflumilast Foam 0.3% ≥1%.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with AE; PT, preferred term; TEAE, treatment-emergent adverse event; VC, vehicle-controlled

Adverse Drug Reactions

For the VC pool, adverse drug reactions (ADRs; defined as possibly, probably, or likely related to the study drug) occurred in 24/479 (5.0%) subjects in the roflumilast group, compared to 12/255 (4.7%) subjects in the vehicle group.

The Applicant proposed Adverse Reactions of headache, diarrhea, nausea, and nasopharyngitis as ADRs for inclusion in Sec. 6.1 of the prescribing information.

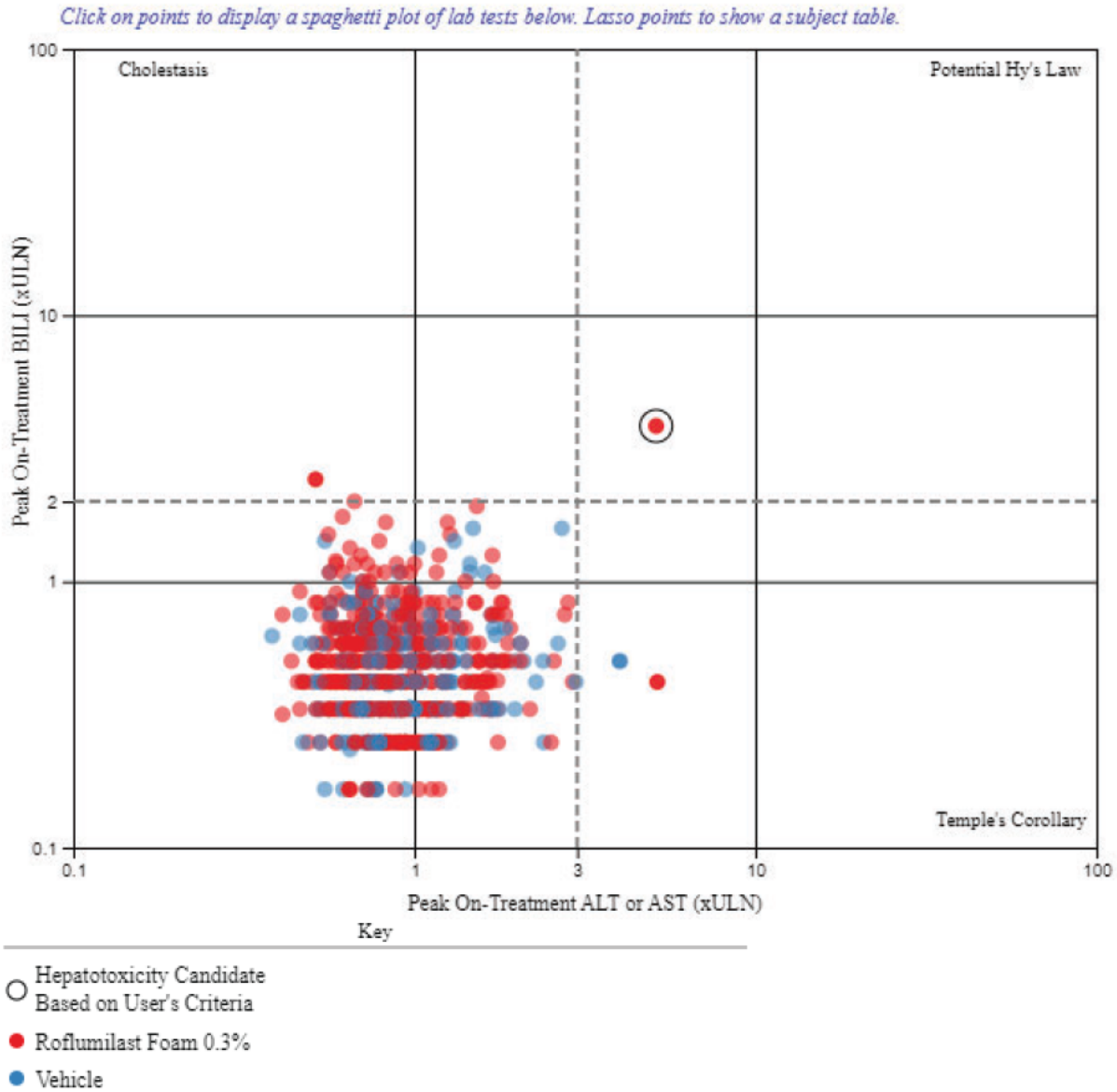
Laboratory Findings

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.

The proportion of subjects with shifts from normal to high was similar between roflumilast and vehicle treatment groups for alanine aminotransferase (ALT; roflumilast [8.7%] v. vehicle [8.0%]) and for aspartate aminotransferase (AST; roflumilast [3.8%] v. vehicle [4.7%]). TEAEs reported for the roflumilast group compared to the vehicle group, respectively, for PTs of “ALT increased” (roflumilast 4 [0.8%] v. vehicle 1 [0.4%]), “AST increased” (roflumilast 2 [0.4%] v. vehicle 0 [0%]), and “Blood bilirubin increased” (roflumilast 2 [0.4%] v. vehicle 0 [0%]) were similar between treatment groups.

Figure 5. Hepatocellular DILI Screening Plot of the VC Pool (Safety Population)



Source: Clinical Reviewer's analysis by OCS Analysis Studio, Hepatic Explorer.
Filters: STUDYID = "ARQ-154-204" or "ARQ-154-309."
*Hepatotoxicity Candidates: ALT or AST ≥3*ULN; BILI ≥2*ULN (0-30 days forward); ALP <2*ULN (0-999 days backward). *Results missing ULN values were imputed using the weighted mean of the lab code.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; DILI, drug-induced liver injury; ULN, upper limit of normal; VC, vehicle-controlled

Table 36. Subjects in Each Quadrant for Hepatocellular DILI Screening Plot

Quadrant	Roflumilast Foam 0.3% N=456 n (%)	Vehicle N=232 n (%)
Potential Hy's Law (right upper)	1 (0.2%)	0 (0%)
Cholestasis (left upper)	2 (0.4%)	0 (0%)
Temple's Corollary (right lower)	1 (0.2%)	1 (0.4%)
Total	**4 (0.9%)**	**1 (0.4%)**

Source: OCS Specialized Analysis Support and Clinical Reviewer's analysis by OCS Analysis Studio, Hepatic Explorer.
Abbreviations: DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria

Hy's Law Quadrant

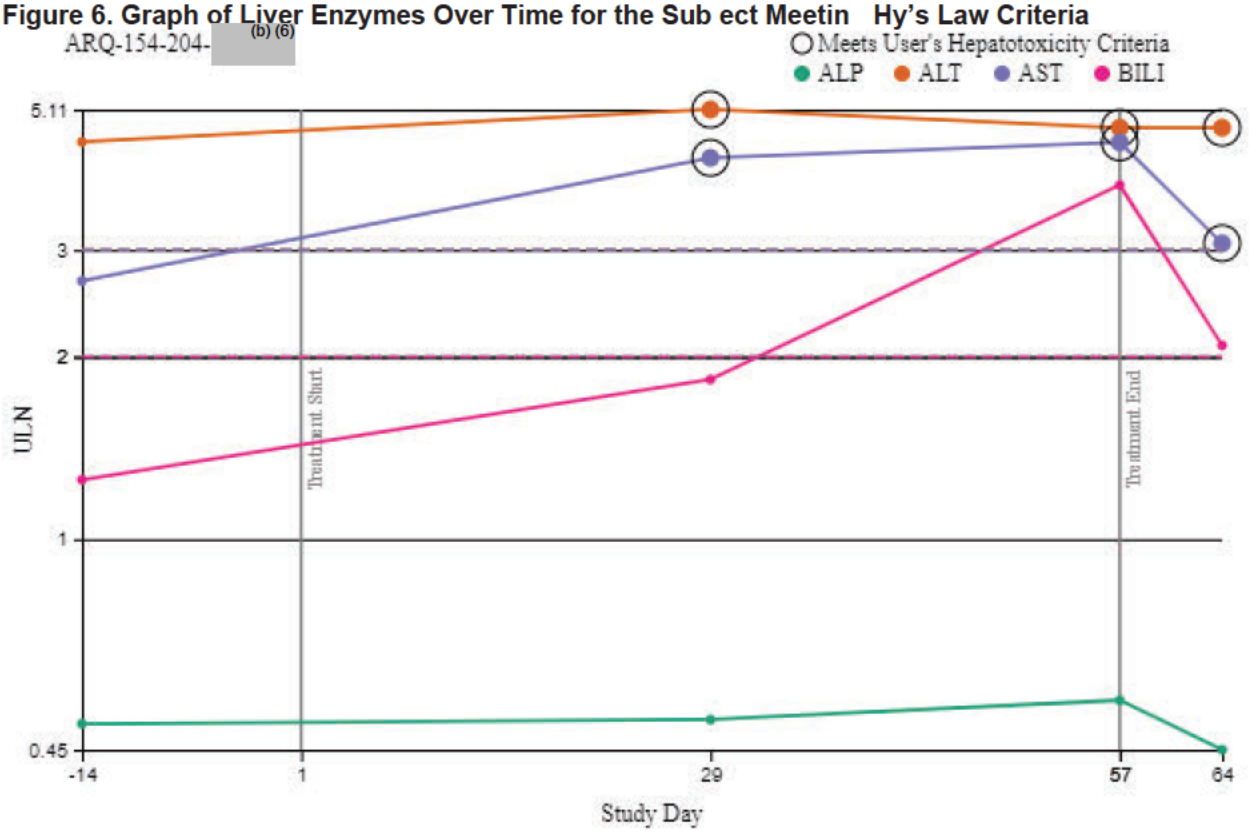
Subject (ARQ-154-204-(b) (6)), an obese 32-year-old male with history of alcohol use (no history of liver disease) was reported with normal alkaline phosphatase (ALP) and elevated AST, ALT, and total bilirubin measurements at screening and baseline.

At week 8, subject was reported with concomitantly elevated AST, ALT ≥3x ULN (upper limit of normal) and Bilirubin ≥2x ULN; which met the biochemical criteria for Hy's law. Additionally, TEAEs for ALT increased/AST increased (Grade 2) and bilirubin increased (Grade 3) were reported. The ALT, AST, and bilirubin values remained stable or improved at Week 9 (not considered clinically significant by the investigator).

According to the Applicant, "While this event met the biochemical criteria for Hy's law, an external hepatologist assessed that this was not a case of drug-induced liver injury based on international consensus criteria, as there was little change in ALT, AST, and ALP. The expert assessed this event to be the result of alteration of bilirubin homeostasis in a patient with pre-existing liver disease and possibly Gilbert's syndrome; the case did not suggest a significant liver safety concern."

The following figure (Figure 6) depicts the pattern of liver enzymes for this subject.

Figure 6. Graph of Liver Enzymes Over Time for the Sub ect Meetin Hy's Law Criteria



Source: OCS Specialized Analysis Support and Clinical Reviewer's analysis by the OCS Analysis Studio, Hepatic Explorer.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; ULN, upper limit of normal

DILI Consultation

The clinical review team requested a consultation from the FDA DILI team for subject ARQ-154-204- (b) (6) who met Hy's law criteria. The DILI team agreed with the Applicant's "external hepatologist" assessment that this was not a case of Hy's law (email dated (b) (6), by Paul "Skip" Hayashi, MD, MPH, FAASLD).

Cholestasis Quadrant

The following 2 subjects were reported in the cholestatic quadrant (see Table 37).

Table 37. Subjects Reported in the Cholestasis Quadrant of Hepatocellular DILI Screening Plot

Subject	TRT01A	Peak ALT or AST	Peak BILI
ARQ-154-204- (b) (6)	Roflumilast foam	0.5128	2.4195
ARQ-154-309- (b) (6)	Roflumilast foam	0.6667	2

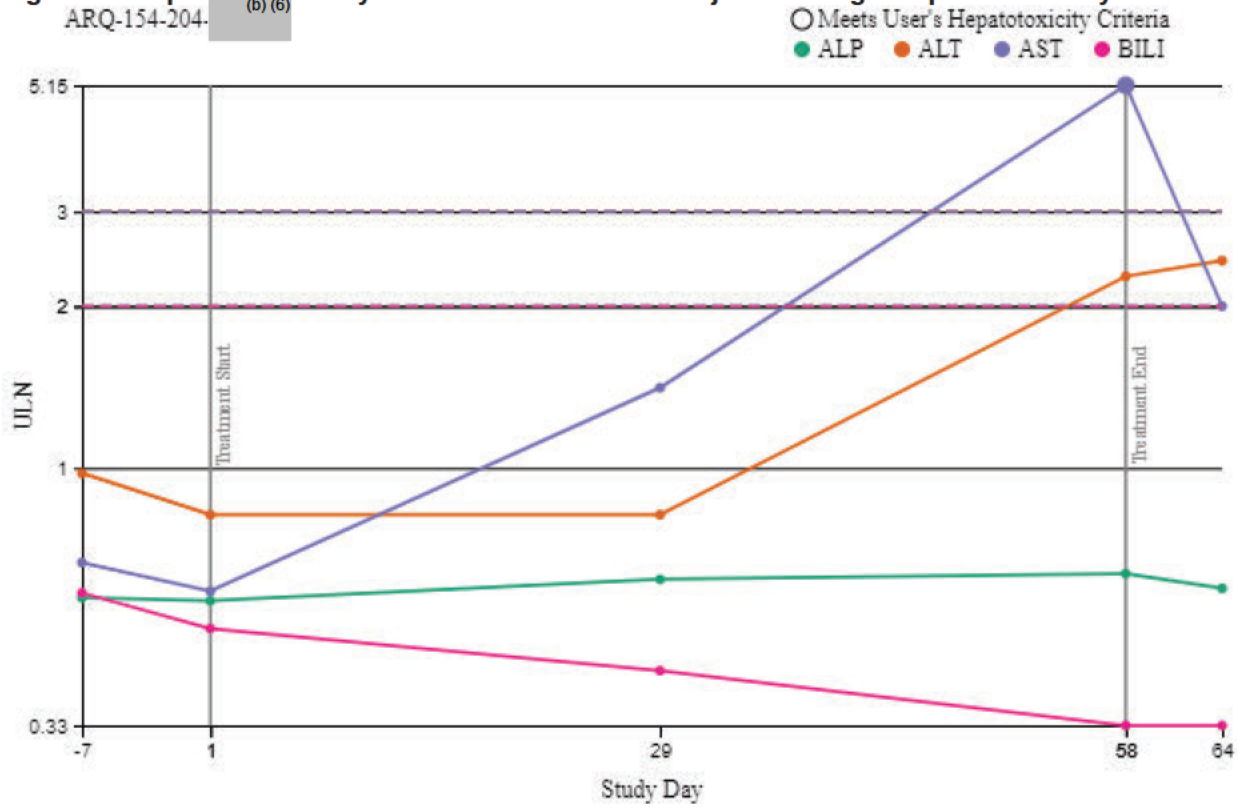
Source: OCS Specialized Analysis Support and Clinical Reviewer's analysis by OCS Analysis Studio, Hepatic Explorer.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin

1. Subject ARQ-154-204-(b) (6) was reported with normal ALT, AST, ALP throughout the trial. The peak bilirubin value of 2.4x ULN was measured on Day 1 and continuously decreased over time.
2. Subject ARQ-154-309-(b) (6) was reported with normal ALT, AST throughout the trial. ALP was slightly elevated at baseline and returned to normal range at weeks 4 and 8. The peak bilirubin measurement was between ULN to <2x ULN during weeks 0-8. The peak bilirubin of 2x ULN was measured at Week 9.

Temple's Corollary Quadrant

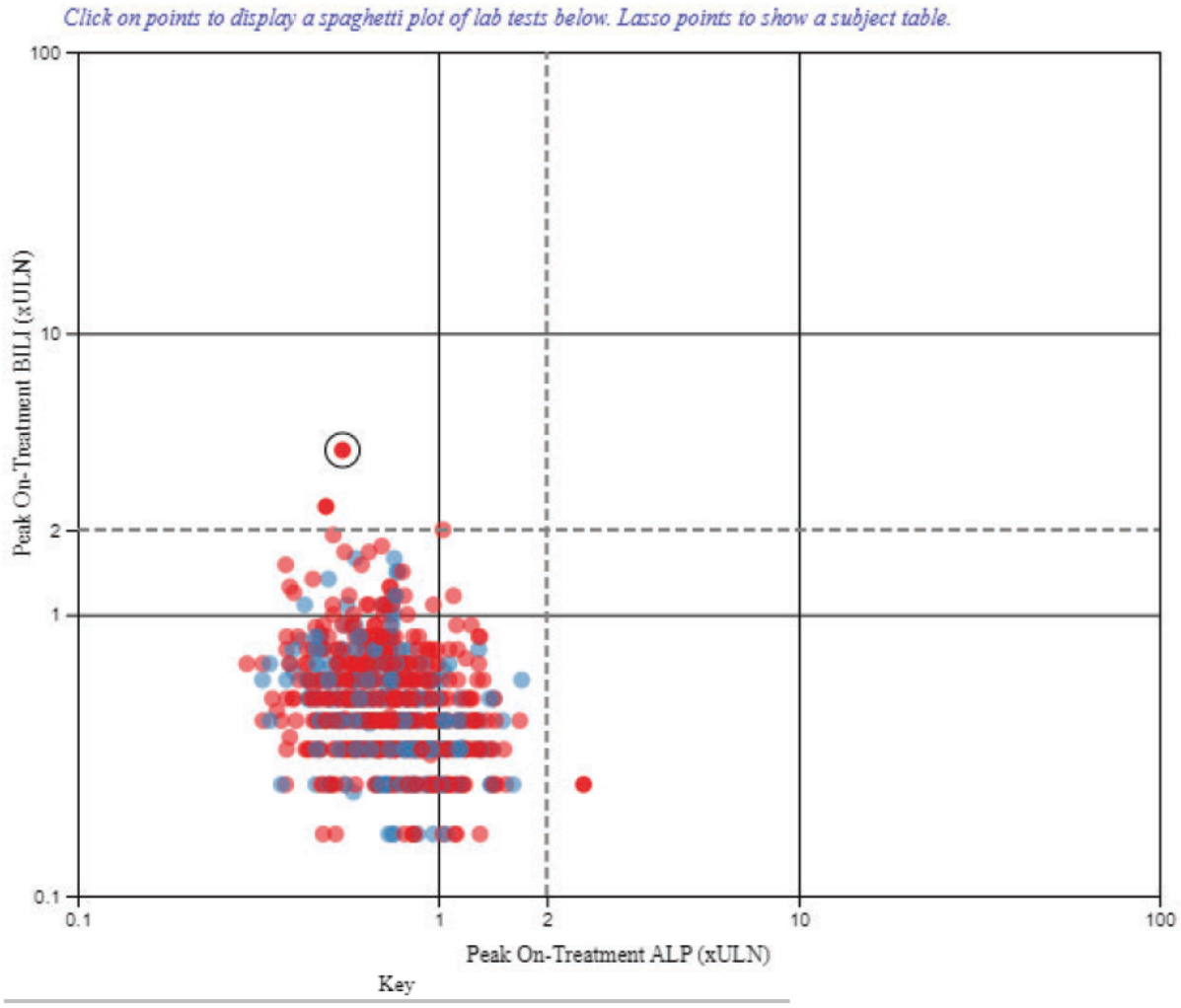
Subject ARQ-154-204-(b) (6) was reported with normal ALP and bilirubin measurements throughout the trial. ALT and AST values were <ULN at baseline, with increase over time to Week 8; as depicted in the following graph.

Figure 7. Graph of Liver Enzymes Over Time for the Subject Meeting Temple's Corollary Criteria



Source: OCS Specialized Analysis Support and Clinical Reviewer's analysis by OCS Analysis Studio, Hepatic Explorer
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; ULN, upper limit of normal

Figure 8. Cholestatic DILI Screening Plot of the VC Pool (Safety Population)



Source: OCS Specialized Analysis Support and Clinical Reviewer's analysis by the OCS Analysis Studio, Hepatic Explorer.
Filters: STUDYID = "ARQ-154-204" or "ARQ-154-309."
*Hepatotoxicity Candidates: ALT or AST ≥3*ULN; BILI ≥2*ULN (0-30 days forward); ALP <2*ULN (0-999 days backward).
*Results missing ULN values were imputed using the weighted mean of the lab code.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; DILI, drug-induced liver injury; ULN, upper limit of normal; VC, vehicle-controlled

Table 38. Subjects in Each Quadrant for Cholestatic DILI Screening Plot

Quadrant	Roflumilast Foam 0.3% N=456 n (%)	Vehicle N=232 n (%)
Bilirubin ≥2x ULN and ALP ≥2x ULN (right upper)	0 (0%)	0 (0%)
Bilirubin ≥2x ULN and ALP <2x ULN (left upper)	3 (0.7%)	0 (0%)
Bilirubin <2x ULN and ALP ≥2x ULN (right lower)	1 (0.2%)	0 (0%)
Total	**4 (0.9%)**	**0 (0%)**

Source: OCS Specialized Analysis Support and Clinical Reviewer's analysis by OCS Analysis Studio, Hepatic Explorer.
Abbreviations: ALP, alkaline phosphatase; DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; ULN, upper limit of normal

The three subjects in the left upper quadrant of the cholestatic DILI screening plot are the same subjects discussed under the hepatocellular DILI screening plots (Hy's law quadrant and cholestasis quadrant).

A subject *ARQ-154-204-* (b) (6) in the right lower quadrant of the cholestatic DILI plot was reported with elevated ALP and normal ALT, AST, and bilirubin measurements throughout the trial.

Vital Signs

For the VC pool, the mean and median changes from the baseline for all vital signs were small and similar between the roflumilast and vehicle groups, and not clinically significant.

The mean (SD) changes from baseline to Week 8 for roflumilast group compared to vehicle group were −1.3 (12.1) versus 0.2 (11.7) mm Hg in systolic blood pressure, -0.6 (8.2) versus −0.4 (8.1) mm Hg in diastolic blood pressure, 1.4 (10.0) versus −0.6 (9.2) beats per minute in heart rate, and −0.02 (0.4) versus 0.02 (0.34) (°C) in Temperature, respectively.

Electrocardiograms

ECG data were collected only for the phase 1 MUsT (ARQ-154-122) during roflumilast foam Psoriasis clinical development program; with no clinically significant changes in ECG parameters reported. Of note, at the end-of-phase 2 meeting for roflumilast cream, 0.3% for the treatment of psoriasis (November 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 January 12, 2023, based on the thorough QT 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 Analyses Informing Safety/Tolerability

Local safety and tolerability assessments (by investigator [Berger and Bowman Scoring Scale] and by subject (stinging and burning) [0 (none), 1 (mild), 2 (moderate), 3 (severe)] were conducted for subjects in the VC pool at baseline, weeks 4, and week 8 visits according to the following instruments.

Table 39. Investigator's (Berger and Bowman) Scoring Scale

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

Source: sNDA 217242-005 Submission, Module 2.7.4 (Table 70).

Table 40. 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: sNDA 217242-005 Submission. Module 2.7.4 (Table 71).

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.

Local Safety Assessment by Investigators

For subjects in the VC pool, all subjects had a score of 0 at baseline. For the roflumilast group, a score =1 was reported for 3 (0.8%) subjects at Week 4 and for 1 (0.3%) subject at Week 8. No subject was reported with a score ≥2 at any time.

Local Tolerability Assessment by Subjects

For subjects in the VC pool, the proportion of subjects with a score =0 increased over time from baseline (62%) to Week 8 (72%). 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.

Dermal Safety Studies

Provocative dermal safety studies were not conducted for roflumilast foam, 0.3% in the Psoriasis of the scalp and body clinical development program.

At the end-of-phase 2 meeting (on December 16, 2020) for roflumilast foam, 0.3% [for the indication of treatment of seborrheic dermatitis], the FDA agreed that the results of dermal safety studies (ARQ-151-108/-109/-110/-111) conducted with roflumilast cream, 0.3% in healthy subjects for the psoriasis development program may be used to support dermal safety of roflumilast foam, 0.3%; and that distinct dermal safety studies in healthy subjects were not necessary for roflumilast 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 affected at baseline [<5%, 5% to <10%, ≥10%], S-IGA at baseline) subgroups; and reported no clinically significant differences in the AE profiles by subgroups in the VC pool.

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 (or between subgroups within the same treatment 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 is 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 12 to <18 years: 4/8 (50.0%) v. 0/4 (0%)
- Age 18 to <65 years: 106/415 (25.5%) v. 37/225 (16.4%)
- Age ≥65 years: 11/56 (19.6%) v. 8/26 (30.8%)

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: 59/225 (26.2%) v. 18/107 (16.8%)
- Female: 62/254 (24.4%) v. 27/148 (18.2%)

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: 3/21 (14.3%) v. 0/12 (0%)
- White: 99/403 (24.6%) v. 37/220 (16.8%)
- All other races: 19/53 (35.8%) v. 8/22 (36.4%)

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: 15/86 (17.4%) v. 11/53 (20.8%)
- Not Hispanic or Latino: 103/383 (26.9%) v. 34/200 (17.0%)

TEAEs by Baseline S-IGA

For the VC pool, 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:

- Mild (S-IGA =2): 3/18 (16.7%) v. 1/14 (7.1%)
- Moderate (S-IGA =3): 95/390 (24.4%) v. 40/211 (19.0%)
- Severe (S-IGA =4): 23/71 (32.4%) v. 4/30 (13.3%)

TEAEs by Baseline BSA

For the VC pool, the following proportion of subjects in each group of BSA <5%, BSA 5% to <10%, and BSA ≥10% [affected by psoriasis] at baseline were reported with a TEAE for the roflumilast group compared to the vehicle group, respectively:

- BSA <5%: 43/198 (21.7%) v. 29/113 (25.7%)
- 5% ≤ BSA <10%: 56/183 (30.6%) v. 13/91 (14.3%)
- BSA ≥10%: 22/98 (22.4%) v. 3/51 (5.9%)

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% was approved by the FDA for marketing in the United States on December 15, 2023, for the indication of treatment of seborrheic dermatitis in patients 9 years of age and older.

The development safety update report (#4) for roflumilast cream and roflumilast foam submitted on January 26, 2024 (IND 142047/SDN 111) covered the reporting period of November 28, 2022, to November 27, 2023, and did not include postmarketing safety data for roflumilast foam.

Postmarketing safety data submitted under Periodic Adverse Drug Experience Report for roflumilast foam, 0.3% (data lock date of March 14, 2024) and for roflumilast cream 0.3% (data lock date of April 28, 2024) did not identify new safety concerns.

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 benefit/risk 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 plaque psoriasis of the scalp and body relied on the evaluation of pooled safety data from 734 subjects enrolled in two VC trials comprising the VC safety pool (one phase 2 trial [ARQ-154-204] and one phase 3 trial [ARQ-154-309]) which were similar in design, trial population, dosing regimen, and key primary and secondary endpoints. Eligible subjects were randomized in a 2:1 ratio to receive roflumilast foam (n=479) or vehicle foam (n=255) once daily for 8 weeks. The following safety results were reported for the VC safety pool:

- No deaths were reported during any clinical trials of roflumilast foam, 0.3%.
- SAEs were reported at a similar frequency for 3/479 (0.6%) subjects treated with roflumilast foam compared to 1/255 (0.4%) subject treated with the vehicle foam. One SAE (Gastritis) was deemed by the investigator as possibly related to roflumilast foam, led to interruption of study drug, and was reported as resolved.
- AELDs were reported at a higher frequency for 12/479 (2.5%) subjects treated with roflumilast foam compared to 4/255 (1.6%) subjects treated with the vehicle foam.
- TEAEs were reported at a higher frequency for 121/479 (25.3%) subjects treated with roflumilast foam compared to 45/255 (17.6%) 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 reported in subjects treated with the vehicle foam) included headache (3.1% versus 1.2%), diarrhea (2.5% versus 1.6%), nausea (1.7% versus 0%), and nasopharyngitis (1.3% versus 0.8%) for subjects treated with roflumilast foam compared to the vehicle foam, respectively. Although insomnia (0.6% versus 0%) was reported at a frequency of <1%, it will be included in Sec. 6.1 of the label; hypertension was reported at a frequency of (1.3% versus 1.2%) was deemed as not related to study drug by the review team and will not be included in the label.
- Severe (Grade 3) AEs were reported at a similar frequency for 7/479 (1.5%) subjects treated with roflumilast foam compared to 3/255 (1.2%) subjects treated with the vehicle foam.

- ADRs: Adverse drug reactions (possibly, probably, or likely related to the study drug) were reported at a similar frequency for 24/479 (5.0%) subjects treated with roflumilast foam compared to 12/255 (4.7%) subjects treated with the vehicle foam.
- AEs potentially related to PDE-4 inhibition: In general, 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 and behavior were not reported, and 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 generally similar in subjects treated with roflumilast foam or the vehicle foam.

The available data from the VC trials demonstrated that roflumilast foam, 0.3% was safe for the treatment of subjects ≥12 years of age with plaque psoriasis of the scalp and body. Postmarketing risk management will include professional labeling and routine pharmacovigilance. One Pediatric Research Equity Act (PREA) post marketing requirement (PMR) will be issued for roflumilast foam, 0.3% for the Applicant to conduct a PK/MUsT in subjects between 4 to <12 years of age.

120-Day Safety Update

Because Studies ARQ-154-122/ARQ-154-204/ARQ-154-309 submitted under NDA 217242/S-005 had already been completed prior to the submission of S-005 on July 22, 2024, the Applicant did not submit a 120-Day Safety Update Report per 21 CFR 314.50(d)(5)(vi)(b).

The annual report for ZORYVE topical foam, 0.3% for the reporting period (December 15, 2023, to December 14, 2024) was submitted on February 14, 2025 (SDN 42). The review team identified no new safety signals in the annual report.

8.3. Statistical Issues

No significant statistical issues were identified with Trial 309. The primary and key secondary endpoints were statistically significant at the two-sided 0.025 level and were robust to the handling of missing data.

Because Trial 204 was designed to be a phase 2 trial, the trial had certain design limitations. Trial 204 did not prespecify a missing data handling method, and the analyses were based on observed data. In addition, the assessment frequency for the SI-NRS and WI-NRS, and the set of endpoints included under the multiplicity control hierarchy differed from that of Trial 309. To evaluate whether the results remain robust using the ITT population with missing data imputation, Trial 204 (especially the primary endpoint of S-IGA success and the first key secondary endpoint of B-IGA success) was re-analyzed using Trial 309's specifications, including using multiple imputation to handle missing data. The endpoints remained statistically significant under the re-analysis conditions, supporting the robustness of Trial 204, despite the

initial deficiencies in analysis method specification. However, the response rates and treatment effect estimates were consistently higher in Trial 204 than in Trial 309 (see Table 19 and Table 20). Re-analysis results based on Trial 309's specifications are recommended for use in labeling as they rely on more defensible assumptions regarding missing data.

In Trial 204, the WI-NRS endpoint was not included in the multiplicity control hierarchy. Therefore, WI-NRS results for Trial 204 are not recommended for inclusion in labeling. For the SI-NRS endpoints in Trial 204, assessments were conducted only at study visits rather than by study subjects using daily diary. Thus, the SI-NRS endpoints in this trial were based on a single assessment per visit, rather than a weekly average. The Applicant did not submit information to support that the endpoints based on a single assessment at study visits were fit for purpose or comparable to use of a weekly average based on a daily diary. Therefore, the SI-NRS endpoint results from Trial 204 may not be comparable to those from Trial 309 and therefore are not recommended for inclusion in labeling. However, the results for SI-NRS success at Week 8 in Trial 204 are consistent with the results from Trial 309. The SI-NRS and WI-NRS results in Trials 204 are also consistent with the corresponding S-IGA and B-IGA success endpoints in the trial. Thus, it is reasonable to include the Week 8 S-IGA and B-IGA success endpoints from Trial 309 in labeling.

8.4. Conclusions and Recommendations

To establish the safety and efficacy of roflumilast foam, 0.3% for the treatment of plaque Psoriasis of the scalp and body, the Applicant submitted data from two adequate and well-controlled, randomized (2:1), double-blind, vehicle-controlled, parallel-group, similarly designed trials (ARQ-154-204 and ARQ-154-309) [-204/-309, respectively]. Subjects applied roflumilast foam, 0.3% once daily to affected areas for 8 weeks. Trials -204/-309 enrolled a total of 734 subjects ≥12 years of age with plaque psoriasis (total BSA involvement of <25% [excluding palms, and soles]; non-scalp BSA <20%); a scalp psoriasis S-IGA score of ≥3 (moderate), body psoriasis B-IGA score of ≥2 (mild); a PASI score of ≥2 and a PSSI score of ≥6] at baseline. Trials -204/-309 evaluated the primary and secondary efficacy endpoints, respectively [in Trial -204]; or the co-primary efficacy endpoint [in Trial -304], of S-IGA success and B-IGA success defined as an IGA score of 0 ("clear") or 1 ("almost clear") and a ≥2-point improvement from baseline for S-IGA or B-IGA at Week 8.

Secondary efficacy endpoints (intended for labeling) included "S-IGA success" (defined as a score of (0) "Clear" or (1) "Almost Clear" and a ≥2-grade improvement from baseline at multiple earlier timepoints, and scalp itch "SI-NRS" success (defined as a ≥4-point improvement in SI-NRS score from baseline [in subjects with a baseline SI-NRS ≥4 score]) at Weeks 8, and multiple earlier time points.

In both Trials -204 and -309, respectively; roflumilast foam was superior to the vehicle foam for the primary efficacy endpoint of S-IGA success at Week 8 (56.7% versus 11.0% [treatment effect of 47.7%; 95% CI: (37.9%, 57.5%)]) and 66.4% versus 27.8% [treatment effect of 37.1%; 95% CI: (27.1%, 47.1%)]). Roflumilast foam was also superior to the vehicle foam for the efficacy

endpoint of B-IGA success at Week 8 (39.0% versus 7.4% [a treatment effect of 32.4%; 95% CI: (23.3%, 41.6%)] and 45.5% versus 20.1% [a treatment effect of 24.8%; 95% CI: (15.0%, 34.6%)] In Trials -204 and -309, respectively. The results for the secondary efficacy endpoints of SI-NRS success at multiple timepoints were in alignment with the results for the (co-) primary efficacy endpoint (s) for the S-IGA success and the B-IGA success. 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 deaths and 1 possible drug-related SAE (Gastritis). The size of the safety database, subject exposure, and safety assessments were adequate to characterize the safety profile of roflumilast foam, 0.3%.

In the VC safety data pool of 734 subjects, the most frequently reported adverse events were headache (3.1%), diarrhea (2.5%), nausea (1.7%), and nasopharyngitis (1.3%)

The Applicant provided adequate efficacy and safety data to support the conclusion that the benefit-risk analysis is favorable for approval of this sNDA. This reviewer recommends approval of roflumilast foam, 0.3%, applied topically once a day, for the treatment of plaque psoriasis of the scalp and body in patients ≥12 years of age.

9 Advisory Committee Meeting and Other External Consultations

The Agency did not hold an advisory committee meeting for this supplemental application, because there were no efficacy, safety, or novel/complex regulatory issues that required input from an advisory committee.

Additionally, 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 psoriasis of the scalp and body in pediatric patients unless this requirement is waived, deferred, or inapplicable.

In an Agreed iPSP letter of April 27, 2022, the Agency agreed with the Applicant's plan to request a waiver for pediatric subjects between ages of 0 to <4 years of age (because necessary studies are impossible or highly impracticable), a request for deferral of pediatric studies for subjects between 4 to <12 years of age, and inclusion of pediatric subjects between ages of 12 to <18 years of age in the Phase 3 clinical trial, ARQ-154-309.

An Amended Agreed iPSP Agreement letter (IND 142047) issued on November 7, 2024, agreed with the Applicant's Amendment to iPSP (dated October 2, 2024), including the Applicant's proposed timeline for completion of the Deferred PK/MUSE (maximal usage systemic exposure) Study in Subjects 4 years to <12 Years of Age as follows:

- Estimated Protocol Submission Date No later than July 2025
- Estimated Study Initiation Date No later than October 2025
- Estimated Study Completion Date No later than April 2027
- Estimated Final Report Submission Date No later than October 2027

The Applicant's PREA Waiver/Pediatric Plan and Assessment request was presented and discussed at the Pediatric Review Committee (PeRC) meeting on April 1, 2025. The PeRC agreed with the Division's recommendation to grant a partial waiver to subjects under 4 years of age, and pediatric assessment for subjects ≥12 years of age. The PeRC also agreed with the Division's recommendation for issuing a PREA PMR to conduct a PK/MUsT study in subjects between 4 to <12 years of age 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), Instructions for use (IFU), 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.

The Division of Medical Policy Programs and the Office of Prescription Drug Promotion reviewed the PPI and IFU and found them acceptable (with comments to convey to the Applicant) on March 16, 2025.

The Office of Prescription Drug Promotion reviewed the proposed PI/PPI/IFU and provided comments on March 20, 2025.

Other Prescription Drug Labeling

The labeling discussions are ongoing at the time this review is written. 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

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 following PREA PMR to conduct the following study will be issued to the Applicant:

Conduct an open-label, maximal-use PK, safety and tolerability study in pediatric subjects aged 4 to <12 years old with plaque psoriasis of the scalp and body targeting at least 16 evaluable subjects in whom PK assessments will be performed under maximal usage conditions.

- Estimated Protocol Submission Date — No later than July 2025
- Estimated Study Initiation Date — No later than October 2025
- Estimated Study Completion Date — No later than April 2027
- Estimated Final Report Submission Date — No later than October 2027

14 Division Director (DHOT) Comments

None.

15 Division Director (OCP) Comments

None.

16 Division Director (OB) Comments

None.

17 Division Director (Clinical) Comments

None.

18 Office Director (or Designated Signatory Authority) Comments

None.

19 Appendices

19.1. References

Journal Articles

Armstrong, AW and C Read, 2020, Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review, JAMA, 323(19):1945-1960.

Menter, A, A Gottlieb, SR Feldman, AS Van Voorhees, CL Leonardi, KB Gordon, M Lebwohl, JYM Koo, CA Elmets, NJ Korman, KR Beutner, and R Bhushan, 2008, Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis: Section 1. Overview of Psoriasis and Guidelines of Care for the Treatment of Psoriasis With Biologics, J Am Acad Dermatol, 58(5):826-850.

Guidances

Guidance for Industry *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018).

Others

Blauvelt, A and B Ehst, 2015, Pathophysiology of Psoriasis. In: Connor, R, editors, UpToDate: Wolters Kluwer.

Feldman, S, 2015, Epidemiology, Clinical Manifestations, and Diagnosis of Psoriasis. In: Connor, R, editors, UpToDate: Wolters Kluwer.

Korman, N, 2017, Comorbid Disease in Psoriasis. In: Connor, R, editors, UpToDate: Wolters Kluwer.

19.2. 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-154-204/-309, which provided the primary data to establish effectiveness and safety of this product. Refer to Section 8 of this review for the trial designs. According to the Applicant, there were no investigators of the covered studies that disclosed participation in financial arrangements with the Applicant or the holding of financial interests [21 CFR 54.4(a)(3) (ii), 54.2 (f)].

Covered Clinical Study: ARQ-154-204

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 46		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 46		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study: ARQ-154-309

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 53		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 53		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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/s/

HAMID N TABATABAI
05/22/2025 08:35:55 AM

TATIANA OUSSOVA
05/22/2025 10:05:26 AM