NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA, 505(b)(1)
Application Number(s)	NDA 215985/IND 135681
Priority or Standard	Standard
Submit Date(s)	September 29, 2021
Received Date(s)	September 29, 2021
PDUFA Goal Date	July 29, 2022
Division/Office	DDD/OII
Review Completion Date	
Established/Proper Name	roflumilast cream, 0.3%
(Proposed) Trade Name	Zoryve
Pharmacologic Class	Psoriasis Agents (4029050)
Code name	ARQ-151
Applicant	Arcutis Biotherapeutics, Inc.
Dosage form	Cream
Applicant proposed Dosing Regimen	Apply (b) (4) to affected area(s) once daily
Applicant Proposed Indication(s)/Population(s)	Topical treatment of plaque psoriasis, including intertriginous areas, 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)	Indicated for the topical treatment of plaque psoriasis in patients 12 years and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Plaque psoriasis (disorder)
Recommended Dosing Regimen	Apply (b) (4) to affected area(s) once daily

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Qianyiren Song
Nonclinical Reviewer	Jianyong Wang
Nonclinical Supervisor	Barbara Hill
Office of Clinical Pharmacology Reviewer(s)	Satish Sharan
Office of Clinical Pharmacology Team Leader(s)	Chinmay Shukla
Clinical Reviewer	Hamid Tabatabai
Clinical Team Leader	David Kettl
Statistical Reviewer	Marilena Flouri
Statistical Team Leader	Mohamed Alosh
Cross-Disciplinary Team Leader	David Kettl
Division Director (or designated signatory authority)	Shari Targum

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

Additional Reviewers of Application

DBVI	Hepei Chen, Karl Lin
DDD	Tatiana Oussova
OPDP	Laurie Buonaccorsi, James Dvorsky
OPQ	Friedrich Burnett, Jane Chang, Raeann Wu, Koushik Paul, Assad Noory, Lawrence Perez, Nina Ni, Ying Zhang, Jesse Wells, Tapash Ghosh, Grafton Adams
DMPP	Ruth Mayrosh, LaShawn Griffiths
OSI	Elena Boley, Phillip Kronstein, Yolanda Patague, Kassa Ayalew, Loreto Corazon Lim
OSE/DMEPA	Madhuri Patel, Mishale Mistry

Abbreviations: DBVI: Division of Biometrics VI; DMEPA, Division of Medication Error Prevention and Analysis; OPDP, Office of Prescription Drug Promotion; DMPP, Division of Medical Policy Programs; 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
Nonclinical Reviewer	Jianyong Wang, PhD	OII/DPT-II	Sections: 5, 19.3	Select one: _X_ Authored ___ Approved
	Signature: *{See appended electronic signature page}*			
Nonclinical Supervisor	Barbara Hill, PhD	OII/DPT-II	Sections: 5, 19.3	Select one: ___ Authored _X_ Approved
	Signature: *{See appended electronic signature page}*			
Senior Product Quality Assessment Lead	Nina Ni, PhD	OPQ/ONDP/DNDP II	Sections: 4.2	Select one: ___ Authored __x_ Approved
	Signature: *{See appended electronic signature page}*			
Clinical Pharmacology Reviewer	Satish Sharan, PhD	OCP/DIIP	Section: 6 and 19.4	Select one: _X_ Authored ___ Approved
	Signature: *{See appended electronic signature page}*			
Clinical Pharmacology Team Leader	Chinmay Shukla, PhD	OCP/DIIP	Section: 6 and 19.4	Select one: ___ Authored _X_ Approved
	Signature: *{See appended electronic signature page}*			
Clinical Pharmacology Division Director	Suresh Doddapaneni, PhD	OCP/DIIP	Section: 6 and 19.4	Select one: ___ Authored _X_ Approved
	Signature: *{See appended electronic signature page}*			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Hamid Tabatabai, MD	OII/DDD	Sections: 1, 2, 3, 4.1, 7, 8.2, 8.4, 9, 10, 11, 12, 13, 19.1-2	Select one: __X_ Authored ___ Approved
	Signature: *{See appended electronic signature page}*			
Clinical Team Leader	David Kettl, MD	OII/DDD	Sections: 1, 2, 3, 4.1, 7, 8.2, 8.4, 9, 10, 11, 12, 13, 19.1-2	Select one: ___ Authored __X_ Approved
	Signature: *{See appended electronic signature page}*			
Statistical Reviewer	Marilena Flouri, PhD	OB/DBIII	Sections: 8.1, 8.3, 19.5	Select one: _ X __ Authored ___ Approved
	Signature: *{See appended electronic signature page}*			
Statistical Team Leader	Mohamed Alosh, PhD	OB/DBIII	Sections: 8.1, 8.3, 19.5	Select one: ___ Authored _ X __ Approved
	Signature: *{See appended electronic signature page}*			
Deputy Division Director (Clinical)	Shari Targum, MD	OII/DDD	Sections: ALL	Select one: ___ Authored __ X _ Approved
	Signature: *{See appended electronic signature page}*			

Glossary

ADCP	4-amino-3,5-dichloropyridine
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AELD	adverse event leading to discontinuation
AMP	3,5-adenosine monophosphate
AUC	area under the concentration-time curve
BLA	biologics license application
BSA	body surface area
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
COPD	chronic obstructive pulmonary disease
COVID19	coronavirus disease 2019
CSR	clinical study report
CSRD	corticosteroid-responsive dermatoses
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DHOT	Division of Hematology Oncology Toxicology
DNA	deoxyribonucleic acid
EAIR	exposure-adjusted incidence rate
ECAC	Executive Carcinogenicity Assessment Committee
ECG	electrocardiogram
eCRF	electronic case report form
EOP	end of phase
ET	end of trial
FDA	Food and Drug Administration
HPRT	hypoxanthine phosphorybosyl transferase
I-IGA	Intertriginous Investigator's Global Assessment
IGA	Investigator's Global Assessment
IL	interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
ISS	integrated summary of safety
ITT	intent-to-treat
IVRS	interactive voice response system
LT	long-term
LTS	long-term safety
MCMC	Markov-Chain Monte-Carlo
MI	multiple imputation
mITT	modified intent-to-treat

MRHD	maximum recommended human dose
MTP	multiplicity testing procedure
MUsT	maximal use study
NDA	new drug application
NOAEL	no-observed adverse effect level
OCP	Office of Combination Products
OCS	Office of Computational Science
PASI	Psoriasis Area and Severity Index
PDE-4	phosphodiesterase 4
PHQ-8	Patient Health Questionnaire depression scale
PI	prescribing information
PK	pharmacokinetics
PMR	postmarketing requirement
PO	orally
PPI	patient package insert
PREA	Pediatric Research Equity Act
PSD	Psoriasis Symptoms Diary
PT	preferred term
PYE	patient-years of exposure
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TCS	topical corticosteroids
TEAE	treatment emergent adverse event
TK	toxicokinetic
VC	vehicle-controlled
WI-NRS	worst itch numerical rating scale

Executive Summary

Product Introduction

Zoryve (roflumilast cream, 0.3%) is a phosphodiesterase-4 (PDE-4) inhibitor developed by the Applicant under IND 135681 for the indication of topical treatment of plaque psoriasis.

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

The Applicant has acquired right of reference to relevant clinical, nonclinical, and chemistry, manufacturing, and controls (CMC) information in NDA 022522, and submitted NDA 215985 under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for marketing Zoryve for the indication of topical treatment of plaque psoriasis in patients ≥12 years of age.

Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from two adequate and well-controlled trials ARQ-151-301 and ARQ-151-302 (Trials -301 and -302) which provided evidence of the effectiveness of roflumilast cream, 0.3% for the topical treatment of plaque psoriasis in the target population. Both trials assessed Investigator's Global Assessment (IGA) success compared to vehicle at Week 8, defined as the proportion of subjects who achieved an IGA Score of clear(0) or almost clear(1) and ≥2 grade improvement from baseline.

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

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 Sections 0 and 0 of this review for a discussion of plaque psoriasis and available treatment options, respectively). The Applicant proposes Zoryve (roflumilast) cream, 0.3% applied daily for the topical treatment of subjects (≥12 years of age) with mild to severe 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-151-201) and two Phase 3 (ARQ-151-301/-302) randomized, double-blind, vehicle-controlled Trials. Additionally, the Applicant submitted safety data from two open-label, long-term safety Studies (ARQ-151-202/-306) and Dermal Safety Studies (ARQ-151-108/-109/-110/-111).

Efficacy:

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

1. For the primary efficacy endpoint of Investigator's Global Assessment (IGA) response (IGA score =0 or 1 with ≥2-grade improvement from baseline) at week 8, the roflumilast group, compared to the vehicle group, achieved a response of 41.5% vs. 5.8% (p-value<0.001) [a treatment effect of 39.7%], and 36.7% vs. 7.1% (p-value<0.001) [a treatment effect of 29.5%] in Trials ARQ-151-301 and ARQ-151-302, respectively.
2. For the secondary efficacy endpoint of whole-body itch (≥4-points improvement from baseline) at week 8, the roflumilast group, compared to the vehicle group, achieved a response of 66.7% vs. 25.7% (p<0.001), [a treatment effect of 41.1%], and 68.6% vs. 33.3% (p-value<0.001) [a treatment effect of 30.3%] in Trials ARQ-151-301 and ARQ-151-302, respectively.
3. For the secondary efficacy endpoint of Intertriginous-IGA (I-IGA) response (I-IGA score of 0 (clear) or 1 (almost clear) with ≥2-grade improvement from baseline) at Week 8, the roflumilast group, compared to the vehicle group, achieved a response of 71.5% vs. 13.8% (p<0.001) [a treatment effect of approximately 63.6%], and 67.5% vs. 17.4% (p-value<0.001) [a treatment effect of 52.7%] in Trials ARQ-151-301 and ARQ-151-302, respectively.

Safety:

Analysis of the Phase 3 pool safety database for Trials ARQ-151-301/-302 did not identify any significant safety signals and was adequate to characterize the safety profile of roflumilast cream, 0.3% for the treatment of mild to severe plaque psoriasis. Adverse events reported through

Week 8 in ≥1% of subjects treated with roflumilast (and more frequently than subjects receiving vehicle) included diarrhea (3.1%), headache (2.4%), insomnia (1.4%), nausea (1.2%), application site pain (1.0%), upper respiratory tract infection (1.0%), and urinary tract infection (1.0%).

Roflumilast cream, 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. 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 U.S. 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)	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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	– Combination topical therapies [TCS/vitamin D analogue, TCS/retinoid] – Aryl hydrocarbon receptor (AhR) modulating agonist (e.g., tapinarof) • Approved products for the systemic treatment of (moderate to severe) plaque psoriasis include anti-metabolites (methotrexate), tumor necrosis factor inhibitors (etanercept, adalimumab and infliximab), 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.	more serious adverse reactions, including malignancy, serious infections, teratogenicity, depression, nephrotoxicity, hepatotoxicity, and bone marrow suppression (Menter et al. 2008). Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is a need for additional therapeutic options.
Benefit	• For Phase 3 trials (ARQ-151-301 and ARQ-151-302), the primary efficacy endpoint (IGA success, defined as IGA =0 or 1 and ≥2-point improvement from baseline at Week 8) results showed that in the ITT population, roflumilast cream, 0.3% was statistically superior to vehicle cream: – Trial ARQ-151-301: 41.5% versus 5.8% (p-value<0.001) – Trial ARQ-151-302: 36.7% versus 7.1% (p-value<0.001)	The data submitted by the Applicant met the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The secondary efficacy endpoints in the Phase 3 Trials included: – The proportion of subjects achieving WI-NRS response (≥4-point improvement from baseline) at Week 8 – The proportion of subjects (with baseline I-IGA score ≥2 (mild)) achieving I-IGA success (I-IGA score of 0 (clear) or 1 (almost clear) with ≥2-grade reduction from baseline) at Week 8. For all secondary efficacy endpoints intended for labeling, roflumilast cream, 0.3% was statistically superior to placebo for the ITT population at Week 8.	Trials ARQ-151-301/-302 were adequate and well-controlled; and the results are persuasive.
Risk and Risk Management	• The primary safety database consisted of 881 subjects from the Phase 3 Trials (ARQ-151-301/-302), treated once daily for 8 weeks. • In addition, two long-term, open-label safety Studies (ARQ-151-202 [52 weeks], and ARQ-151-306 [24 weeks]) resulted in exposures to roflumilast cream of ≥24 weeks in 486 subjects, ≥52 weeks in 195 subjects, and ≥66 weeks in 41 subjects. • The safety database is adequate to characterize the safety profile of Zoryve cream, 0.3%. • During the Phase 3 trials (ARQ-151-301/-302), SAEs occurred in 2/576 (0.3%) subjects in the Zoryve group (all unrelated to Zoryve), and 2/305(0.7%) subjects in the vehicle group. Adverse drug reactions (possibly, probably, or likely related to study drug) occurred in 23/576 (4.0%) of subjects in the Zoryve group, compared to 11/305 (3.6%) subjects in the vehicle group. • The most common (in ≥1% of subjects) adverse events reported in Zoryve group, and more frequent than placebo group, were diarrhea (3.1%), headache (2.4%), insomnia (1.4%), nausea (1.2%), application site pain	The safety profile of Zoryve cream, 0.3% has been adequately characterized by the pre-market safety data for psoriasis. Prescription labeling, patient labeling and routine pharmacovigilance are adequate to manage the potential risks of the product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(1.0%), upper respiratory tract infection (1.0%), and urinary tract infection (1.0%). • The effects of Zoryve cream on pregnant or lactating women are unknown.	

Abbreviations: IGA, Investigator's Global Assessment; I-IGA, Intertriginous-Investigator's Global Assessment; ITT, intent-to-treat; SAE, serious adverse event; WI-NRS, worst itch numerical rating scale

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		
		□	Patient reported outcome (PRO)	WI-NRS, PSD Score, local tolerability score, C-SSRS, PHQ-8/PHQ-A, CDI-2, DLQI/CDLQI
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	IGA, I-IGA, PASI
		□	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: CDI-2, Children's Depression Inventory 2; 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's Global Assessment; I-IGA, Intertriginous-Investigator's 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; WI-NRS, Worst Itch-Numeric Rating Scale

Therapeutic Context

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 U.S. 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, such as women during pregnancy and pediatric patients.

Analysis of Current Treatment Options

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.

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.

The proposed indication for Zoryve cream, 0.3% is the topical treatment of plaque psoriasis, including treatment of psoriasis in the intertriginous areas, in patients 12 years of age and

older. Other FDA-approved topical treatment options for this target population include 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, Keratolytic/Retinoid (tazarotene), and Combination topical therapies [TCS/Vitamin D analogue, and TCS/Retinoid], and Aryl hydrocarbon receptor (AhR) modulating agonist as summarized in Table 1.

Table 1. Summary of Topical Treatments for Plaque Psoriasis

Product Class	Example Product/ Year Approved	Relevant Indication[1]	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Cortico-steroid	Olux E (clobetasol propionate) Foam/ 2007	CSRD (one trial was done in mild-to moderate Plaque-type psoriasis)	Apply a thin layer twice daily. Treatment should be limited to 2 consecutive weeks and patients should not use greater than 50 g per week	In a randomized study of subjects 12 years of age and older with mild-to-moderate plaque psoriasis, 253 subjects were treated with Olux-E Foam and 123 subjects were treated with vehicle foam. 41 of 253 subjects (16%) treated with Olux-E Foam compared with 5 of 123 (4%) treated with vehicle foam achieved treatment success. Treatment success was defined by an Investigator's Static Global Assessment (ISGA) score of clear (0) or almost clear (1) with at least 2-grade improvement from baseline, scores of none or faint/minimal (0 or 1) for erythema and scaling, and a score of none (0) for plaque thickness.	Use in pediatric patients under 12 years of age is not recommended because of numerically high rates of hypothalamic pituitary-adrenal (HPA) axis suppression.

[1] Some corticosteroids are indicated for the "treatment (or relief) of inflammatory and pruritic manifestations of moderate-to-severe corticosteroid responsive dermatoses (CSRD)," which is inclusive of the psoriasis indication.

Product Class	Example Product/ Year Approved	Relevant Indication[1]	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Synthetic vitamin D3 derivative	Dovonex (calcipotriene cream)/1996	Plaque psoriasis	Apply a thin layer twice daily	Adequate and well-controlled trials have demonstrated improvement usually beginning after 2 weeks of therapy. This improvement continued with approximately 50% of patients showing at least marked improvement in the signs and symptoms of psoriasis after 8 weeks of therapy, but only approximately 4% showed complete clearing.	Reversible elevation of serum calcium has occurred.
Synthetic vitamin D3 derivative/ corticosteroid combination product	Taclonex (calcipotriene and betamethasone dipropionate) Ointment/2006	Plaque psoriasis in patients 12 years of age and older	Use once daily for up to 4 weeks	1603 subjects with mild-to very severe plaque psoriasis on trunk and limbs were treated once daily for 4 weeks. Subjects were randomized to one of four treatment arms: Taclonex Ointment, calcipotriene hydrate 50 mcg/g in the same vehicle, betamethasone dipropionate 0.64 mg/g in the same vehicle, and vehicle alone. Treatment effect was 48%, 16.5%, 23.3% and 7.6%, respectively. Efficacy was assessed as the proportion of subjects with absent or very mild disease according to the Investigator's Global Assessment of Disease Severity at end of treatment (4 weeks).	Hypercalcemia and hypercalciuria and HPA axis suppression have been observed. Patients aged 12 to 17 years should not use more than 60 g per week. Treatment of more than 30% body surface area is not recommended.

Product Class	Example Product/ Year Approved	Relevant Indication[1]	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Retinoid	Tazorac (tazarotene) cream, 0.05%, 0.1%/ 2000	Plaque psoriasis	Apply a thin film once daily.	Improvements in plaque elevation, scaling, and erythema were generally significantly greater with tazarotene 0.05% and 0.1% than with vehicle. The number of patients with none, minimal or mild overall disease was significantly greater with tazarotene 0.05% and 0.1% vs. vehicle.	Retinoids may cause fetal harm when administered to a pregnant woman.
Retinoid / Cortico-steroid combination product	Duobrii (halobetasol propionate and tazarotene lotion, 0.01%/0.045%) / 2019	Plaque psoriasis	Apply a thin film once daily.	In 2 Phase 3 trials, 276 adult subjects with moderate to severe plaque psoriasis (baseline IGA =3, 4) were treated with Duobrii and 142 with vehicle lotion. Duobrii lotion achieved treatment success, compared to vehicle (Trial -301: 35.8% vs. 7.0% and in Trial -302: 45.3% vs. 12.5%); Treatment success was defined by an IGA score of clear (0) or almost clear (1) with at least 2-grade improvement from baseline at Week 8.	Risks from corticosteroids and Retinoids: Embryofetal risk in pregnant patients, Photosensitivity and risk of sunburn, Reversible HPA axis suppression and AEs from corticosteroids

Product Class	Example Product/ Year Approved	Relevant Indication[1]	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Aryl hydrocarbon receptor (AhR) modulating agonist	Vtama (tapinarof) (5/2022)	Plaque psoriasis in adult Patients (≥18 years of age)	Apply a thin layer once daily	In 2 Phase 3 Trials in adult subjects with mild-to-severe plaque psoriasis (baseline IGA =2, 3, 4 on a 5-point IGA scale), 683 subjects were treated with tapinarof cream, 1% QD, and 342 subjects were treated with the vehicle cream. The primary efficacy endpoint was defined as a Physician's Global Assessment (PGA) score of 0 ("clear") or 1 ("almost clear") with at least a two-grade reduction from baseline, assessed at Week 12. For both trials, tapinarof cream, 1% was superior to vehicle on the primary efficacy endpoint (Study 3001: 35% vs. 6% and in Study 3002: 40% vs. 6%; p-values <0.001).	The most common cutaneous adverse drug reactions were folliculitis (20%) and contact dermatitis (7%). Urticaria and drug eruptions were reported in ≤1% of patients in a long-term safety trial.

Source: Modified from Table 1, NDA 207589/S-010 (Enstilar: calcipotriene and betamethasone dipropionate Foam), Multidisciplinary Review and Evaluation by Dr. Melinda McCord. [Duobrii and Vtama examples added by this reviewer].
Abbreviations: AE, adverse event; CSRD, corticosteroid-responsive dermatoses; IGA, Investigator's Global Assessment

Regulatory Background

U.S. Regulatory Actions and Marketing History

Roflumilast cream has not been approved for marketing in any country. Oral roflumilast tablets (Daliresp) was approved under NDA 022522 by the FDA in 2011 for the indication of treatment to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

Summary of Presubmission/Submission Regulatory Activity

The Applicant developed roflumilast cream for topical treatment of plaque psoriasis under IND 135681 and submitted their marketing application for NDA 215985 under 505(b)(1) regulatory pathway. Milestone interactions with the Applicant included the following:

Pre-IND Meeting (9/13/2017)

Requirements for drug development under a 505 (b)(2)Regulatory pathway and the design of a potential clinical bridging study were discussed.

Type C Guidance Meeting-Written Response Only (7/19/2018)

Advice regarding patient-reported outcome measures, including Psoriasis Symptom Diary (PSD), psoriasis symptom inventory, itch-related sleep loss, fatigue, and work limitations attributable to psoriasis were conveyed to the Sponsor.

End of Phase (EOP)2 Meeting (10/23/2019)

Phase 3 development plans were discussed, including:

1. Inclusion of subjects ≥12 years of age
2. General design of Phase 3 trials
3. Treatment of intertriginous psoriasis and its potential inclusion in label
4. Primary efficacy endpoint (IGA success) and secondary efficacy endpoint of pruritus responders (4-point reduction in Worst Itch-Numerical Rating Scale [WI-NRS])
5. Safety assessments to include psychiatric assessments (Columbia-Suicide Severity Rating Scale [C-SSRS], Patient Health Questionnaire depression scale (PHQ-8)/Modified Patient Health Questionnaire-9 for Adolescents) and dermal safety studies; the FDA agreed that no electrocardiogram (ECG) monitoring would be required for Phase 3 trials
6. Size of the safety database

Agreed iPSP (5/20/2020)

An agreed iPSP agreement letter was conveyed to the Sponsor, which included the following:

1. Plan to request a waiver for ages 0 to less than <2 years
2. No requests for deferral
3. Inclusion of subjects between 2 years to <17 years of age in Phase 3 trials.

Pre-NDA Meeting (5/3/2021)

1. Applicant's plan for pooling data in the integrated summary of effectiveness and integrated summary of safety (ISS) were discussed. Statistical comments regarding the Sponsor's proposed pooling of safety data in the ISS (the pivotal Phase 3 pool, the vehicle-controlled pool and the long-term open-label pool) were conveyed.
2. For the long term open-label study ARQ-151-306, submission of available safety data at the time of the NDA submission, followed by 120-day safety update and final clinical study report (CSR) submission with the pediatric supplement (following the initial NDA approval) was deemed acceptable.
3. The presentation of safety data, including exposure-adjusted incidence rates (EAIRs) were discussed.
4. Contents and format for the integrated summary of effectiveness and ISS to include subject narratives, case-report forms for all deaths, serious adverse events (SAEs), severe adverse events (AEs), all subject discontinuations, AEs resulting in permanent discontinuation, pregnancies, and hypersensitivity reactions were discussed.

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

Office of Scientific Investigations

The overall quality of the clinical information contained in this submission was adequate. All Phase 3 trials were conducted at sites in the U.S. and Canada.

The Division requested that the Office of Scientific Investigations conduct clinical inspections of 2 domestic sites. The criteria used to select these sites were high enrollment, high efficacy, and low deviations (Study ARQ-151-302, Site 244); high enrollment, high efficacy, and financial interest > $25,000 (Study ARQ-151-301, Site 116).

Table 2. Planned Clinical Site Inspections

(Name, Address, Phone Number, Email, Fax #)	Site #	Protocol ID	Number of Subjects (SAFPOP)	Study Title
Alonso-Llamazares, Javier 201 Madeira Ave Coral Gables, FL 33134 USA United States phone:+1 305.225.0400 fax: 305-200-5587 email:jalonso@drivenclinicalresearch.com	244	ARQ-151-302	25	A Phase 3, 8-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-151 Cream 0.3% Administered QD in Subjects with Chronic Plaque Psoriasis
Stewart, Daniel 43900 Garfield Rd Suite 106 Clinton Township, MI 48038 USA United States phone:+1 586.286.7325 fax: 586-286-2549 email:dstewart@skincareresearch.com	116	ARQ-151-301	19	

Source: Reviewer's Table with data from CDER's Clinical Investigator Site Selection Tool Generated 11/3/2021.
Abbreviations: FL, Florida; ID, identification; MI, Michigan; QD, once daily; SAFPOP, safety population

In the Clinical Inspection Summary, the review team concluded that the conduct of the Trials appears to be adequate, and that the data generated appear to be acceptable to support the use of this product for the proposed indication. In her Clinical Inspection Summary of 6/21/2022, Elena Boley, MD, MBA, made the following overall assessment of findings and recommendations regarding the findings of the Clinical Site Inspections:

> *"Drs. Stewart and Alonso-Llamazares were inspected in support of NDA 215985, covering Protocols ARQ-151-301 and ARQ-151-302. Despite some protocol deviations at the two sites, the study overall appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.*
>
> *During the clinical investigator inspections, the records related to the primary efficacy endpoint of "Investigator's Global Assessment (IGA) success," defined as an IGA score of 'Clear' or 'Almost Clear' plus a 2-grade improvement from Baseline to Week 8, were reviewed and verified against the Sponsor's data line listings for all 44 subjects randomized at these 2 sites.*
>
> *No discrepancies were noted. There was no evidence of under-reporting of adverse events."*

The Clinical Review Team for NDA 215985 concurs with the conclusions by the Office of Scientific Investigation clinical inspection team that the data quality from the inspected sites are acceptable in support of this application and did not identify any safety concerns that would preclude a recommendation for an "Approval Action" for this NDA.

Product Quality

Based on our evaluation of the available information, the Applicant provided sufficient information to support an approval recommendation from the product quality perspective. The Applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

Thus, the Office of Pharmaceutical Quality recommends APPROVAL of NDA 215985 for commercialization of Zoryve (roflumilast) cream, 0.3%.

The complete Integrated Quality Review dated July 13, 2022, is archived in the CDER Informatics Platform.

Clinical Microbiology

There is no information needed or related to clinical microbiology for this application.

Nonclinical Pharmacology/Toxicology

Executive Summary

Roflumilast is a small molecule phosphodiesterase 4 (PDE4) inhibitor. The inhibition of PDE4 activity leads to accumulation of intracellular cyclic 3,5-adenosine monophosphate (AMP). Increased phosphodiesterase activity in inflammatory cells has been associated with dermatologic disease. Daliresp® (roflumilast) oral tablets have been approved under NDA 22522 for the treatment of COPD, with the maximum recommended human daily dose of 0.5 mg. The Applicant obtained a right of reference letter for Daliresp (NDA 22522) that allows use of the nonclinical data available for Daliresp to support the nonclinical safety for their topical roflumilast cream being developed for the treatment of plaque psoriasis in patients 12 years of age and older.

Oral repeat-dose toxicity studies were conducted in mice, rats, hamsters, dogs, and monkeys, with treatment durations up to 6, 6, 3, 12, and 10 months, respectively. The target organs of toxicity for roflumilast included nasal cavity, cardiovascular system, gastrointestinal tract, and reproductive system. A pivotal 9-month chronic dermal toxicity study was conducted in minipigs. Topical doses up to 1% roflumilast cream applied at 2 mL/kg to 10% body surface area (BSA) of minipigs (the maximum feasible dose) were well tolerated with no significant toxicity.

In genotoxicity testing, roflumilast was positive in an in vivo mouse micronucleus test, but negative in the following assays: the Ames test, an in vitro chromosome aberration assay, an in

vitro hypoxanthine phosphorybosyl transferase (HPRT) test, an in vitro micronucleus test, a deoxyribonucleic acid (DNA) adduct formation assay in rat nasal mucosa, liver and testes, and an in vivo mouse bone marrow chromosome aberration assay.

Three carcinogenicity studies were conducted with roflumilast, including a 2-year oral carcinogenicity study in hamsters, a 2-year oral carcinogenicity study in mice, and a 2-year dermal carcinogenicity study in mice. In 2-year oral gavage carcinogenicity studies, roflumilast treatment resulted in dose-related, statistically significant increases in the incidence of undifferentiated carcinomas of nasal epithelium in hamsters at doses ≥8 mg/kg/day. The tumorigenicity of roflumilast appears to be attributed to a reactive metabolite of 4-amino-3,5-dichloropyridine (ADCP) N-oxide. No evidence of tumorigenicity was observed in mice at oral doses up to 12 and 18 mg/kg/day in female and male mice, respectively. No evidence of carcinogenicity was observed in mice at dermal doses up to 1% roflumilast cream applied at 2 mL/kg/day.

In a fertility study, roflumilast decreased fertility rates in male rats at 1.8 mg/kg/day. The male rats also showed increases in the incidence of tubular atrophy, degeneration in the testis and spermatogenic granuloma in the epididymides. No effect on rat fertility rate or male reproductive organ morphology was observed at 0.6 mg/kg/day. In a female fertility study, no effect on fertility was observed up to the highest roflumilast dose of 1.5 mg/kg/day in rats.

In an embryofetal development study, pregnant rats were dosed orally during the period of organogenesis with up to 1.8 mg/kg/day roflumilast. No evidence of structural abnormalities or effects on survival rates were observed. Roflumilast did not affect embryofetal development at a maternal oral dose of 0.2 mg/kg/day. In a fertility and embryofetal development study, male rats were dosed orally with up to 1.8 mg/kg/day roflumilast for 10 weeks and females for two weeks prior to pairing and throughout the organogenesis period. Roflumilast induced pre- and post-implantation loss at maternal oral doses ≥0.6 mg/kg/day. Roflumilast did not cause fetal structural abnormalities at maternal oral doses up to 1.8 mg/kg/day.

In an embryofetal development study in rabbits, pregnant does were dosed orally with 0.8 mg/kg/day roflumilast during the period of organogenesis. Roflumilast did not cause fetal structural abnormalities at the maternal oral dose of 0.8 mg/kg/day.

In pre- and post-natal developmental studies in mice, dams were dosed orally with up to 12 mg/kg/day roflumilast during the period of organogenesis and lactation. Roflumilast induced stillbirth and decreased pup viability at maternal doses ≥2 mg/kg/day and 6 mg/kg/day, respectively. Roflumilast induced delivery retardation in pregnant mice at maternal doses ≥2 mg/kg/day. Roflumilast decreased pup rearing frequencies at a maternal dose of 6 mg/kg/day during pregnancy and lactation. Roflumilast also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at a maternal dose of 12 mg/kg/day.

In a juvenile toxicity study in rats, oral doses up to 0.8 mg/kg/day roflumilast were administered to juvenile rats (3 weeks old) once daily for 3 months. Target organs of toxicity included liver,

epididymis, heart, lung, and spleen (hemosiderosis). No-observed adverse effect level (NOAELs) of 0.2 mg/kg/day in males and 0.5 mg/kg/day in females were identified. The NOAELs in this study are comparable to that identified in a previous 3-month adult oral toxicity study in rats (0.2 mg/kg/day). There was no increased sensitivity in terms of male reproductive organ toxicity compared to the previous study.

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

This NDA is approvable from a pharmacology/toxicology perspective. There is no recommended nonclinical postmarketing commitment/requirement for this NDA.

Referenced NDAs, BLAs, DMFs

For pivotal nonclinical data that have been reviewed under NDA 22522 and associated INDs, summary pharmacology/toxicology information is provided in this review. In nonclinical studies, ARQ-151 and B9302-107 were used as code names for roflumilast and B9502-044 was used as a code name for roflumilast N-oxide.

Pharmacology

Primary Pharmacology

Roflumilast and its active metabolite (roflumilast N-oxide) are inhibitors of phosphodiesterase 4 (PDE4), which is a major cyclic AMP-metabolizing enzyme. Roflumilast and roflumilast N-oxide inhibition of PDE4 activity leads to accumulation of intracellular cyclic AMP. Inflammatory conditions such as psoriasis are related to a dysregulated immune system governed by a pro-inflammatory cytokine network. Literature shows that increased phosphodiesterase activity in inflammatory cells has been associated with dermatologic disease and treatment with PDE inhibitors may have therapeutic effects.

Secondary Pharmacology

The binding of roflumilast on non-PDE4 enzyme related receptors was evaluated. Receptor binding screen studies in vitro showed that neither roflumilast nor roflumilast N-oxide interacted with muscarinic M1-, M2-, or M3- receptors, histamine H1-receptors, α1A-, α1B-, or α2- adrenoceptors, β-adrenoceptors, adenosine A1- (roflumilast N-oxide only), A2A-, or A2B-receptors, or Dopamine DA2-receptors (roflumilast only). The study results did not indicate significant risk of unintended pharmacological activity of roflumilast due to binding to non-specific receptors.

Safety Pharmacology

Safety pharmacology studies were conducted to evaluate effects of roflumilast on behavior, cardiovascular function, respiratory function, neuromuscular function, stomach acid secretion, gastrointestinal motility, body temperature, locomotor activity, pupil diameter and renal function. Roflumilast at 3-100 mg/kg (orally [PO]) decreased grip strength by up to 89% in mice. Roflumilast at 3-30 mg/kg (PO) reduced the threshold for pentetrazol-induced seizures by 30-93%; the no effect dose level was 1 mg/kg. At 30 mg/kg, mice also exhibited increased tonic convulsions and lethality in a potentiation test and shortened time to tonic convulsions and death. Roflumilast at 3-30 mg/kg prolonged hexobarbital-induced loss of righting reflex (up to 590%) and a dose-dependent increase in ethanol-induced sleeping time (up to 368%) in rats.

Roflumilast at 10 mg/kg (PO) caused a significant increase in heart rate (62%) and a decrease in blood pressure (12-26 mm Hg) in male normotensive rats. A cumulative IV injection in anesthetized male rats of roflumilast at 0.3-20 µmol/kg increased systolic arterial pressure (16%) and dP/dt max (9%) at the high dose and decreased diastolic pressure (24-29%). Cats at 0.1-7 mg/kg showed sustained increase in blood pressure (46-63%), heart rate (up to 18%), and cardiac contractility (3-fold). The cats also showed a rise in the ST-phase (two highest doses) and increased breathing rate and respiratory minute volume (33 and 32%). Bolus injections (10^{-11} to 10^{-7} M) increased coronary flow (21-47% at 10^{-8} to 10^{-7} M) in male guinea pig Langendorff hearts. In renal function studies, male rats received 3-10 mg/kg roflumilast N-oxide (PO) showed increases in urine potassium and ketone bodies (~200%). At 10 mg/kg, increases of urine sodium, pH, and osmolality and decreases of urine chloride and volume and serum urea were noted.

ADME/PK

Table 3. Summary of PK/TK Data for Roflumilast and Its Active Metabolite Roflumilast N-Oxide

Type of Study	Major Findings	
Absorption		
ARQ-151: A 7-day dermal tolerability study in minipigs (Study# MPI-2621-001)	IV, 0.03 mg/kg Topical, CL: 36 mL/min/kg V_z: 1.25 l/kg $t_{1/2}$: 0.39 hr	1.0% cream, 20 mg/kg C_{max} 13.6 ng/ml (Day 7) T_{max} 1.3 hr (Day 7) AUC_{last} 95 ng•hr/ml
Distribution		
Summary information from nonclinical review for NDA 22522	Following oral dosing, roflumilast is widely distributed in the body. Highest drug concentrations were found in the liver and adrenals in mice and hamsters, and in the nose and liver in rats. Other organs with relatively high roflumilast concentrations were (in a descending order) kidney, fat, lung, heart, testes, and brain. Roflumilast in the plasma is predominantly protein-bound. The free drug represents only up to 3.7% of the drug in plasma in animals used in the toxicology program and humans. Specifically, the free fraction was 3.7%, 2.0%, 2.9%, 2.2%, 1.6% and 2.1% in mice, rats, hamsters, rabbits, dogs and monkeys, respectively.	

Type of Study	Major Findings
Metabolism	
Summary information from nonclinical review for NDA 22522	Roflumilast metabolism was studied in vitro and in vivo. Roflumilast is metabolized by CYP3A4, CYP1A2 and CYP2G1 to form at least 17 roflumilast metabolites in animals and humans. The metabolites were formed through N-oxidation, odealkylation, or oxidative mono-dichlorination followed by conjugation. Roflumilast is metabolized to three major metabolites: roflumilast N-oxide, 4-amino-3,5-dichloropyridine (ADCP) and ADCP N-oxide. Roflumilast N-oxide is the most abundant among all species.
Excretion	
Summary information from nonclinical review for NDA 22522	Roflumilast is excreted via feces and urine. The proportion of excretion by each route varied significantly with species. After oral administration, fecal excretion is predominant in mice and dogs while urine excretion is predominant in humans. Other species were somewhere in between. The major route of excretion was fecal in rats and hamsters, and urine in monkeys and rabbits, respectively. Roflumilast was excreted in rat milk. Roflumilast and/or its metabolite concentrations measured 8 hours after an oral dose of 1 mg/kg given to lactating rats were 0.32 and 0.02 µg/g in the milk and pup liver, respectively.
TK data from general toxicology studies	Roflumilast: R Roflumilast N-oxide: RN
A 6-month oral (gavage) toxicity study in B6C3F1 mice (Study# RCC 798096)	<u>Mouse (oral daily dosing for 6 months)</u> $AUC_{0-\infty}$ (µg•hr/l) at Week 26: 4 mg/kg/day: 153 (R), 513 (RN) 12 mg/kg/day: 690 (R), 2197 (RN) 36 mg/kg/day: 6123 (R), 15929 (RN) Dose proportionality: The AUC increase was more than dose-proportional
A 6-month oral toxicity study in Wistar rats (Study# 14/96)	<u>Rat (oral daily dosing for 6 months)</u> AUC_{0-8hr} (µg•hr/l) at Week 26: 0.5 mg/kg/day: 10 (R) 1.5 mg/kg/day: 41 (R) 2.5 mg/kg/day: 79 (R) Dose proportionality: The AUC increase was more than dose-proportional
A second 6-month oral toxicity study in Wistar rats (Study# 97/96)	<u>Rat (oral daily dosing for 6 months)</u> AUC (µg•hr/l) at Week 26 (extrapolated): 0.8 mg/kg/day: 35 (R)
A 12-month oral toxicity study in beagle dogs (Study# 132/2000)	<u>Dog (oral daily dosing for 12 months)</u> AUC_{0-24hr} (µg•hr/l) at Week 52: 0.2 mg/kg/day: 160 (R), 15 (RN) 0.6 mg/kg/day: 510 (R), 66 (RN) 2 mg/kg/day: 919 (R), 54 (RN) Accumulation: not noted Dose proportionality: The AUC increase was less than dose-proportional between 0.6 and 2 mg/kg/day.

Type of Study	Major Findings
Combined 4-week/42-week oral gavage toxicity study in adult cynomolgus monkeys (Study# 0382-047)	Monkey (oral daily dosing for 42 weeks) $AUC_{0-\infty}$ (µg•hr/l) at Week 42: 0.1 mg/kg/day: 80 (R), 340 (RN) 0.25 mg/kg/day: 205 (R), 835 (RN) 0.5 mg/kg/day: 556 (R), 1685 (RN) Dose proportionality: The AUC increase was more than dose-proportional
A 13-week dermal toxicity study in CD-1 mice (Study# 2621-006)	Mouse (dermal daily dosing for 13 weeks) AUC_{last} (ng•hr/ml) at Week 13 (sex-combined): 3 mg/kg/day (0.15% cream): 82 (R), 627 (RN) 10 mg/kg/day (0.5% cream): 149 (R), 862 (RN) 20 mg/kg/day (1% cream): 194 (R), 1277 (RN) Accumulation: not significant Dose proportionality: The AUC increase was less than dose-proportional
A 39-week dermal toxicity study in Göttingen minipigs (Study# 2621-012)	Minipig (dermal daily dosing for 39 weeks) AUC_{last} (ng•hr/ml) at Week 39 (sex-combined): 3 mg/kg/day (0.15% cream): 83 (R), 2.6 (RN) 10 mg/kg/day (0.5% cream): 211 (R), 8.2 (RN) 20 mg/kg/day (1% cream): 329 (R), 11.5 (RN) Accumulation: noted (up to ~14-fold comparing AUC values) Dose proportionality: The AUC increase was less than dose-proportional
TK data from reproductive toxicology studies	TK analysis was not conducted in reproductive toxicology studies.
TK data from carcinogenicity studies	
A 2-year oral (gavage) carcinogenicity study in B6C3F1 mice (Study# PR 97/2001)	Mouse (oral daily dosing for 2 years) AUC_{0-24h} (µg•hr/l) at Month 24: 0.5 mg/kg/day: not ascertained 2 mg/kg/day: 72 (R), 244 (RN) 6 mg/kg/day: 231 (R), 831 (RN) 12 mg/kg/day (female): 663 (R), 2145 (RN) 18 mg/kg/day (male): 961(R), 3736 (RN) Accumulation: not significant Dose proportionality: The AUC increase was slightly higher than dose-proportional
A 2-year oral (gavage) carcinogenicity study in Syrian hamster (Study# PR 7/2002)	Hamster (oral daily dosing for 2 years) AUC_{0-24h} (µg•hr/l) at Month 24: 0.25 mg/kg/day: not ascertained (R), 55 (RN) 1 mg/kg/day: not ascertained (R), 204 (RN) 4 mg/kg/day: 40 (R), 1234 (RN) 8 mg/kg/day: 53 (R), 2721 (RN) Accumulation: not noted after Month 3 Dose proportionality: The AUC increase was lower than dose-proportional for roflumilast and roughly dose-proportional for roflumilast N-oxide.

Type of Study	Major Findings
Complementary 2-year oral (gavage) carcinogenicity study in Syrian hamster (Study# 233/2003)	Hamster (oral daily dosing for 2 years) AUC (µg•hr/l) at Week 12: 16 mg/kg/day: 520 (R), 11336 (RN)
TK data from juvenile toxicology studies	TK analysis was not conducted in the 3-month juvenile toxicity study in rats.

Abbreviations: AUC, area under the concentration-time curve; CL, clearance; C_{max}, maximum plasma concentration; CYP, cytochrome P450; IV, intravenous; $t_{1/2}$, half-life; TK, toxicokinetic; T_{max}, time to maximum plasma concentration

Toxicology

General Toxicology

Oral repeat-dose toxicity studies were conducted in mice, rats, hamsters, dogs, and monkeys, with treatment durations up to 6, 6, 3, 12, and 10 months, respectively. These studies have been reviewed under NDA 22522. The target organs of toxicity for roflumilast included nasal cavity, cardiovascular system, gastrointestinal tract, and reproductive system. Significant non-neoplastic nasal lesions (epithelial disorganization, degeneration, necrosis, and nerve fiber atrophy of the olfactory area) were limited to the rodent species (mice, rats, and hamsters). Cardiovascular changes (focal hemorrhage, myocarditis, or vasculitis) were observed in mice, dogs, and monkeys. Changes in the gastrointestinal tract (serositis, inflammation, peritonitis, and stomach erosion) were observed in rats and monkeys. Changes in the male reproductive organs were observed in mice, rats, hamsters, and dogs. The affected organs may include the following: the prostate (atrophy), testes (tubular atrophy degeneration and atrophy, spermatogenic disturbances), epididymides (oligospermia and granuloma), and seminal vesicles (atrophy). Changes (uterine and cervical atrophy) in female reproductive organs were observed in mice. Disruption of female reproductive physiology (decreases in estrus events and estradiol levels) were observed in rats and monkeys. The overall NOAEL values in mice, rats, hamsters, dogs and monkeys were 4, 0.8, 4, 0.6 and 0.25 mg/kg/day, respectively. See Table 3 in Section 0 for toxicokinetic (TK) information.

A 39-week dermal toxicity study in minipigs was conducted (Study# 2621-012, previously reviewed under the associated IND). Topical doses of 0 (vehicle), 0.15%, 0.5%, and 1% roflumilast cream (3, 10, and 20 mg/kg/day roflumilast) were administered to Göttingen minipigs (4/sex/dose) once daily for 9 months (applied at 2 mL/kg to 10% BSA). The 1% strength is the maximum feasible concentration in this formulation and the high dose is considered the maximum feasible dose. Assessment of toxicity was based on mortality, clinical observations, dermal irritation scores, body weight, food consumption, ophthalmology, ECG, clinical pathology (hematology, clinical chemistry, and urinalysis), gross pathology, organ weights, and histopathology. No significant toxicity was noted in this study. The NOAEL was identified as the high dose, 1% roflumilast cream applied at 2 mL/kg once daily for 9 months. See Table 3 in Section 0 for TK information.

Genetic Toxicology

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

Carcinogenicity

Both oral and dermal carcinogenicity studies were conducted for roflumilast, including two 2-year oral carcinogenicity studies in hamsters, a 2-year oral carcinogenicity study in mice, and a 2-year dermal carcinogenicity study in mice. The oral carcinogenicity studies have been reviewed under NDA 22522. The dermal mouse carcinogenicity study is reviewed under this NDA.

In 2-year oral gavage carcinogenicity studies, roflumilast treatment resulted in dose-related, statistically significant increases in the incidence of undifferentiated carcinomas of nasal epithelium in hamsters at doses ≥8 mg/kg/day. The tumorigenicity of roflumilast appears to be attributed to a reactive metabolite of ADCP N-oxide. No evidence of tumorigenicity was observed in mice at roflumilast oral doses up to 12 and 18 mg/kg/day in females and males, respectively.

A 2-year dermal carcinogenicity study was conducted in mice with roflumilast cream. Topical doses of 0 (untreated control), 0 (vehicle control), 0.15%, 0.5%, and 1.0% roflumilast cream (applied at 2 mL/kg to 10% BSA; 3, 10, and 20 mg/kg/day roflumilast) were administered to CD-1 mice once daily for two years. There were no significant treatment-related effects on mortality. There were no significant treatment-related dermal observations at the administration sites. A decrease in body weight was noted in high dose males at the end of the treatment. A complete tissue list was examined for vehicle control group and high dose group. Target tissues and gross lesions were examined for the rest of the groups. There were no biologically significant test article-related neoplastic findings in this study. TK analysis was not conducted in this carcinogenicity study. However, the same topical doses were tested in a 13-week dermal mouse toxicity study and the TK data can be used for safety margin calculation. See Table 3 in Section 0 for TK information.

This 2-year dermal mouse carcinogenicity study has been reviewed by the Executive Carcinogenicity Assessment Committee (ECAC). The Committee concluded that this study was adequate and there was no evidence of drug-related neoplasms in this study. See Section 0 for the detailed review of the study.

Reproductive and Developmental Toxicology

Oral reproductive and developmental toxicity studies have been reviewed under NDA 22522. In a fertility study, roflumilast decreased fertility rates in male rats at 1.8 mg/kg/day. The male rats also showed increases in the incidence of tubular atrophy, degeneration in the testis and spermatogenic granuloma in the epididymides. No effect on rat fertility rate or male reproductive organ morphology was observed at 0.6 mg/kg/day. In a female fertility study, no effect on fertility was observed up to the highest roflumilast dose of 1.5 mg/kg/day in rats.

In an embryofetal development study, pregnant rats were dosed orally during the period of organogenesis with up to 1.8 mg/kg/day roflumilast. No evidence of structural abnormalities or effects on survival rates were observed. Roflumilast did not affect embryofetal development at a maternal oral dose of 0.2 mg/kg/day. In a fertility and embryofetal development study, male rats were dosed orally with up to 1.8 mg/kg/day roflumilast for 10 weeks and females for two weeks prior to pairing and throughout the organogenesis period. Roflumilast induced pre- and post-implantation loss at maternal oral doses ≥0.6 mg/kg/day. Roflumilast did not cause fetal structural abnormalities at maternal oral doses up to 1.8 mg/kg/day.

In an embryofetal development study in rabbits, pregnant does were dosed orally with 0.8 mg/kg/day roflumilast during the period of organogenesis. Roflumilast did not cause fetal structural abnormalities at the maternal oral dose of 0.8 mg/kg/day.

In pre- and post-natal developmental studies in mice, dams were dosed orally with up to 12 mg/kg/day roflumilast during the period of organogenesis and lactation. Roflumilast induced stillbirth and decreased pup viability at maternal doses ≥2 mg/kg/day and 6 mg/kg/day, respectively. Roflumilast induced delivery retardation in pregnant mice at maternal doses ≥2 mg/kg/day. Roflumilast decreased pup rearing frequencies at a maternal dose of 6 mg/kg/day during pregnancy and lactation. Roflumilast also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at a maternal dose of 12 mg/kg/day. See Table 3 in Section 0 for TK information.

Other Toxicology Studies

Juvenile Animal Toxicity

An oral juvenile toxicity study in Wistar rats was conducted (Study# WR0589, included in the nonclinical review for NDA 22522, complete review conducted under associated IND). Oral doses (administered via gastric cannula) of 0 (vehicle: 4% methocel), 0.2, 0.5, and 0.8 mg/kg/day roflumilast were administered to juvenile Wistar rats (3 weeks old, 10/sex/group) once daily for 3 months, with an 8-week recovery period (8/sex/group for vehicle control and high dose groups).

There was no drug-related mortality. Target organs of toxicity included liver (centrilobular hypertrophy), epididymis (lympho-histiocytic infiltration), heart (myocardial degeneration), lung (lympho-histiocytic infiltration, interstitial pneumonia), and spleen (hemosiderosis). NOAELs of

0.2 mg/kg/day in males and 0.5 mg/kg/day in females were identified. The NOAELs in this study are comparable to that identified in a previous 3-month adult oral toxicity study in rats (0.2 mg/kg/day). There was no increased sensitivity in terms of male reproductive organ toxicity compared to the previous study. The identified target organs in the 3-month adult study (nasal cavities, testes, epididymis, and the thymus) were not identified in juvenile animals with the exception of epididymis.

Ocular Irritation

A bovine corneal opacity and permeability test was conducted with 1% roflumilast cream (Study# 2441-03, reviewed under associated IND). Roflumilast cream was determined to be a non-irritant based on an in vitro irritancy score of -1.97.

Dermal Sensitization

The dermal sensitization potential of roflumilast was assessed using a Buehler assay in guinea pigs (Study# 2621-005, reviewed under associated IND). One group of female Hartley Albino guinea pigs was induced with 1% roflumilast cream. This group was administered with 1% roflumilast cream once a week for three weeks. Animals were challenged with 0.5% roflumilast cream which was administered two weeks after the third induction dose. No significant dermal effects were observed. Roflumilast cream was not a dermal sensitizer in this study.

Phototoxicity

The phototoxic potential of roflumilast was assessed in a neutral red uptake phototoxicity assay (Study# 20122622, reviewed under associated IND). The phototoxic potential was assessed using reduction in viability of BALB/c 3T3 mouse fibroblasts exposed to the test article and ultraviolet radiation compared to the viability of cells exposed to the test article in the absence of ultraviolet radiation. Concentrations of roflumilast tested included 0.1, 0.316, 1.00, 3.16, 10.0, 31.6, 100 and 178 µg/ml. Cells were exposed to 5 J/cm^2 UVA and 21 mJ/cm^2 UVB from a xenon arc solar simulator. Roflumilast did not show phototoxic potential in this assay.

Drug Excipient Evaluation

The drug excipient Crodafos CES is not listed in the FDA's inactive ingredients database (IID) for approved products. It's a mixture of cetearyl alcohol (b) (4), cetearyl phosphate (b) (4) and ceteareth-10 phosphate (b) (4). This proprietary blend has been widely used in personal care and cosmetic products since its market introduction in 1994. Its major component, cetearyl alcohol/ceteareth-20, is listed in the IID with a maximum approved level of 8% in a topical cream formulation. Computational toxicology evaluation using both rule-based DEREK and statistical-based Model Applier was conducted with the three components of Crodafos CES and the prediction for genotoxicity was all negative. The Ames II Mix and TA98 assay was performed using *Salmonella typhimurium* strains TA7001, TA7002, TA7003, TA7004, TA7005 and TA7006 in an equimolar mix, and strain TA98. No significant increase in revertants was observed in any strain. Crodafos CES was not mutagenic under the conditions of the assay.

The Applicant also provided 28-day dermal minipig toxicity data to support its safety. Topical doses of 0 (Crodafos CES vehicle control) or (b) (4)% Crodafos CES were applied to 10% BSA of minipigs (3/sex/group) at 2 mL/kg (200 mg/kg/day) once daily for 28 days. The study endpoints included mortality, clinical signs, body weight, food consumption, dermal observation, ophthalmology, ECG, clinical pathology, organ weights, gross pathology, and histopathology evaluation. No significant treatment-related effects were noted. The Applicant conducted a 39-week dermal minipig toxicity study and 2-year dermal mouse carcinogenicity study with the clinical formulation of roflumilast cream containing (b) (4)% Crodafos CES. No significant toxicity was noted in the vehicle control group of either study which provides additional nonclinical safety data for the Crodafos CES excipient. There is no safety concern for Crodafos CES at the proposed level of (b) (4)% in the clinical roflumilast cream formulation. All the proposed concentrations of other inactive ingredients are below maximum approved levels listed in the IID. Overall, there are no safety concerns for the inactive ingredients at the proposed levels in the Zoryve Cream formulation.

Potential Impurity Evaluation

The safety of (b) (4) a potential leachable from the proposed container closure system, is evaluated. Per the CMC reviewer, (b) (4) was detected at up to (b) (4) µg/day in the 4-week interim simulated leachable study.

The Applicant provided toxicology information of (b) (4) from the European Chemicals Agency database (b) (4) and the National Toxicology Program database. (b) (4) is negative in three bacterial mutagenicity tests, a drosophila germ cell mutagenicity test, a chromosome aberration test in CHO cells, and an in vivo micronucleus study in mice, and positive in an in vitro sister chromatid exchange test in CHO cells. The weight of evidence analysis suggests that there is no significant concern for its genotoxic potential. A structurally similar compound, (b) (4) was tested in National Toxicology Program for 2-year inhalation carcinogenicity studies. There was no evidence of carcinogenicity of (b) (4) in F344/N rats or B6C3F mice exposed to (b) (4) at (b) (4) ppm.

Oral (gavage) repeat-dose toxicity studies were conducted with (b) (4) in rats and mice. In 14-day studies, NOAELs were identified as (b) (4) and (b) (4) mg/kg/day in rats and mice, respectively. In 13-week studies, NOAELs were (b) (4) and (b) (4) mg/kg/day in rats and mice, respectively. Based on the study results of the repeat-dose toxicity studies and also considering that this drug product is for topical use with limited dermal absorption, the safety margin is adequate to support the safety of (b) (4) at its detected levels in the leachable study.

Clinical Pharmacology

Executive Summary

The Applicant is seeking approval of roflumilast cream 0.3% (Zoryve) for topical treatment of plaque psoriasis, including treatment of psoriasis in the intertriginous areas, in patients 12 years of age and older. Roflumilast and its active metabolite (roflumilast N oxide) are selective inhibitors of phosphodiesterase 4 (PDE 4). An oral formulation of roflumilast (Daliresp; NDA-022522) was approved by FDA in 2011 to reduce the risk of COPD exacerbations associated with chronic bronchitis. This Applicant has obtained right to refer all relevant clinical, non-clinical and CMC information submitted in NDA 022522 from AstraZeneca (The Applicant of NDA 022522).

The Clinical Pharmacology program in this submission consists of a maximal use study (MUsT) to evaluate pharmacokinetics (PK) and safety of once daily (QD) topical application of roflumilast cream 0.3% for two weeks in subjects 12 years of age and older with at least 10% and 20% BSA involvement in adolescents and adults, respectively (excluding the scalp) (Study ARQ-151-107).

Results from MUsT showed that in comparison to the adult exposure following repeat oral administration of roflumilast 500 µg (Bethke et al. 2007), the mean roflumilast area under the concentration-time curve $(AUC)_{0\text{-}24}$ values following repeat topical administration were 2.2-fold higher, while the mean roflumilast N-oxide $AUC_{0\text{-}24}$ values were 1.7-fold higher. When accounting for dose in adolescent and adult subjects, the mean C_{max} and AUC_{last} values were lower for adolescent subjects as compared to adult subjects and this could be due to lower % BSA and lower dose in adolescent subjects compared to adults.

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 label (NDA 022522). 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.

Plasma concentrations of roflumilast and roflumilast N-oxide were also collected at baseline, week 4 and week 8 during Phase III trials (ARQ-151-301, ARQ-151-302). Plasma exposure of roflumilast was observed at week 4 and week 8 in most subjects following daily administration of roflumilast 0.3% cream.

Recommendation

The office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology finds NDA 215985 acceptable.

Postmarketing Requirement (PMR) Recommendation

The following two (2) PMRs to conduct the following studies will be issued to the Applicant:

Study Protocol ARQ-151-215 (Ongoing)

An Open Label, 4-Week, Phase 2, Maximal Usage Pharmacokinetics and Safety Study of ARQ-151 Cream 0.3% Administered QD in 20 Pediatric Subjects (ages 6 to 11 years old) with Plaque Psoriasis. (b) (4)

Final Protocol Submission:	June 2020
Study Completion:	January 2022 (estimate)
Final Report Submission:	December 2022 (estimate)

Study Protocol ARQ-151-216 (Ongoing)

An Open Label, 4-Week, Phase 2, Maximal Usage Pharmacokinetics and Safety Study of ARQ-151 Cream 0.3% Administered QD in 10 Pediatric Subjects (ages 2 to 5 years old) with Plaque Psoriasis. (b) (4)

Final Protocol Submission:	July 2020
Study Completion:	April 2022 (estimate)
Final Report Submission:	December 2022 (estimate)

Summary of Clinical Pharmacology Assessment

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 cream 0.3% QD for 2 weeks to adolescent subjects (13 -17 years of age) with chronic plaque psoriasis involving at least 10% BSA and adult subjects with chronic plaque psoriasis involving at least 20% BSA. The MUsT study was conducted with the to-be-marketed formulation. It is noted that there were no subjects aged 12 years old in MUsT; however, their inclusion in Phase 3 trials and acceptable safety would support approval.

The Applicant in their study report compared the adult exposure assessed in MUsT with PK information following oral administration published in Bethke et al (Bethke et al. 2007). The Applicant noted that in adults, the systemic exposure (AUC_{0-24}) of roflumilast following topical application was 2.2-fold higher than the oral dose of 500 µg administered once daily for 12 days (72.7 versus 33.7 h*ng/mL), while the systemic exposure of roflumilast N-oxide following topical application was 1.7-fold higher than oral administration (628 versus 375.4 h*ng/mL). Following daily administration of roflumilast cream 0.3% at maximum use conditions, the

systemic exposure of roflumilast and roflumilast N-oxide after accounting for dose was lower in adolescent subjects than adult subjects and this could be because of lower % BSA and lower dose in adolescent compared to adults.

Summary of Safety in MUsT

Roflumilast cream 0.3% was well tolerated in this study, with no serious adverse events, no deaths, and few treatment-emergent adverse events (TEAEs), all of which were observed in adult subjects and were of mild or moderate intensity. No TEAEs were reported in the adolescent group. No discontinuation of investigational product due to AEs was reported for any subject. Nausea was the only TEAE reported in more than 1 subject (3/26 subjects [11.5%]; all observed in adults). Local tolerability was assessed based on both investigator-rated and subject-rated local tolerability assessments and the topical treatment was well tolerated. Overall, roflumilast cream 0.3% did not appear to have any influence on vital signs, clinical laboratory assessments, ECG parameters, or weight/body mass index. See Clinical review for further information on safety.

Pharmacokinetics of Roflumilast in Phase 3 Trials

Two identical Phase III studies (ARQ-151-301 and ARQ-151-302) were conducted by the Applicant to evaluate roflumilast cream 0.3% safety and efficacy in subjects 2 years of age and older with up to 20% BSA involvement with plaque psoriasis. Studies ARQ-151-301 and ARQ-151-302 were randomized, identical double-blind, vehicle controlled, parallel-group safety and efficacy study of roflumilast cream 0.3% and vehicle in subjects ≥2 years of age with chronic plaque psoriasis involving 2% to 20% (inclusive) BSA (excluding the scalp, palms, and soles) and an IGA of at least mild at baseline. Subjects were randomized 2:1 to receive roflumilast cream 0.3% or vehicle. Assigned treatment was applied topically QD to all lesions (excluding the scalp) for 8 weeks. Roflumilast plasma concentrations were measured predose at baseline and Weeks 4 and 8. The mean trough concentration at weeks 4 and 8 were similar for both roflumilast and roflumilast n-oxide. In study ARQ-151-301, mean trough concentrations for roflumilast were 2.05 ng/ml at week 4 and 1.82 ng/ml at week 8. Roflumilast N-oxide mean trough concentrations were 11.8 ng/ml and 10.10 ng/ml at week 4 and week 8, respectively. In study ARQ-151-302, mean trough concentrations for roflumilast were 1.99 ng/ml and 1.72 ng/ml at week 4 and week 8, respectively. Roflumilast n-oxide trough concentrations were 12.2 ng/ml and 10.2 ng/ml at week 4 and week 8, respectively.

Reviewer's comment: Due to limited number of subjects below the age of 12 years, data in subjects below the age of 12 years will not be considered in this review cycle.

Drug Interaction of Roflumilast

No drug interaction studies were conducted with roflumilast cream. However, a full complement of drug-interaction studies was 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 (CYP)3A4 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 increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should also be weighed carefully against benefit.

Dosing in Subjects With Renal or Hepatic Impairment

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.

Reviewer's comment: 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 27.5 and 12.9 in adults and adolescent subjects compared to 6.4% and 6.5% in Phase 3 trials, respectively. Also, the mean dose in the maximal use study was 6.5 gm and 3 gm respectively in adults and adolescent subjects compared to 2.24 g in the entire population in Phase 3 trials. 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.

General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen is to apply (b) (4) roflumilast 0.3% cream to the affected areas once a day.

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.

Comprehensive Clinical Pharmacology Review

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 cream 0.3% to be applied topically once daily for the treatment of plaque psoriasis, including treatment of psoriasis in the intertriginous areas, 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 cream 0.3% QD for 2 weeks to adolescent subjects (13 -17 years of age) with chronic plaque psoriasis involving at least 10% BSA and adult subjects with at least 20% BSA involved. The study was designed to ensure that a suitable number of subjects with plaque psoriasis at the upper range of severity would be evaluated, and PK would be adequately characterized. Summary of demographics is shown in Table 4.

Table 4. Summary of Demographics in Study ARQ-151-107

Variable Statistic or Category	Adolescents (N=6)	Adults (N=20)	Overall (N=26)
Age (years)			
N	6	20	26
Mean (SD)	14.7 (1.03)	52.6 (12.63)	43.8 (19.66)
Median	15.0	54.0	50.0
Min, max	13, 16	27, 74	13, 74
Gender, n (%)			
Male	4 (66.7)	14 (70.0)	18 (69.2)
Female	2 (33.3)	6 (30.0)	8 (30.8)
Child-bearing potential[a], n (%)			
Yes	2 (100)	0	2 (25.0)
No	0	6 (100)	6 (75.0)
Ethnicity, n (%)			
Hispanic or Latino	3 (50.0)	17 (85.0)	20 (76.9)
Not Hispanic or Latino	3 (50.0)	3 (15.0)	6 (23.1)
Race, n (%)			
Asian	1 (16.7)	0	1 (3.8)
Black or African-American	0	1 (5.0)	1 (3.8)
White	5 (83.3)	18 (90.0)	23 (88.5)
Height (cm)			
N	6	20	26
Mean (SD)	167.7 (23.87)	171.0 (9.21)	170.2 (13.43)
Median	173.8	172.7	172.7
Min, max	130.0, 195.6	153.0, 188.0	130.0, 195.6
Weight (kg)			
N	6	20	26
Mean (SD)	69.2 (27.22)	99.5 (24.91)	92.5 (28.07)
Median	69.1	97.9	95.2
Min, max	36.5, 103.9	63.5, 178.7	36.5, 178.7
Body Mass Index (kg/m^2)			
N	6	20	26
Mean (SD)	23.9 (6.21)	33.9 (7.59)	31.6 (8.36)
Median	22.2	33.2	30.1
Min, max	19.0, 35.9	24.0, 55.0	19.0, 55.0

Variable Statistic or Category	Adolescents (N=6)	Adults (N=20)	Overall (N=26)
Body Surface Area (%)			
N	6	20	26
Mean (SD)	13.0 (3.58)	27.5 (7.76)	24.1 (9.32)
Median	12.0	24.5	22.0
Min, max	10.0, 20.0	21.0, 45.0	10.0, 45.0
Baseline IGA, n (%)			
Moderate	6 (100)	19 (95.0)	25 (96.2)
Severe	0	1 (5.0)	1 (3.8)
Baseline PASI			
N	6	20	26
Mean (SD)	12.48 (5.403)	20.08 (5.685)	18.32 (6.406)
Median	13.20	19.20	18.00
Min, max	4.2, 18.9	7.2, 28.8	4.2, 28.8
Baseline mPASI			
N	6	20	26
Mean (SD)	11.878 (6.1947)	19.696 (5.6697)	17.892 (6.5869)
Median	12.885	19.200	18.000
Min, max	1.68, 18.90	7.20, 28.80	1.68, 28.80

Source: Table 14.1.2.1

Abbreviations: IGA = Investigator Global Assessment; max = maximum; min = minimum; mPASI = modified Psoriasis Area Severity Index; N = number of subjects; n = number of observations; PASI = Psoriasis Area Severity Index; SD = standard deviation

a. Only captured for female subjects; percentages are based on the number of female subjects in the Safety population.

Note: Percentages are n/number of subjects in the Safety population within age group and overall*100.

Source: 5.3.3.2: ARQ-151-107 Study Report; Table 10-1

Blood samples were taken at pre-dose, 1, 2, 4, 8 and 24 hours post dose administration on Day 1 and Day 15 from all subjects. Additional samples were collected at 1, 2, and 3 weeks post the last dose administered for the adult subjects (optional for adolescents). Systemic concentrations were at or near steady state by Day 15 based on fairly flat profile (Figure 1).

Following daily administration of roflumilast cream 0.3% at maximum use conditions, systemic pharmacokinetic results in ARQ-151-107 are provided in Table 5.

Table 5. Summary of Pharmacokinetic Results After Daily Treatment With Roflumilast 0.3% Cream in Adolescent and Adult Subjects in ARQ-151-107

Analyte Day	Age Group (years)	N	Statistic	BSA (%)	Target Dose (mg)	T_{max} (h)	C_{max} (ng/mL)	C_{max}/dose (ng/mL/mg)	AUC_{last} (h·ng/mL)	AUC_{last}/dose (h·ng/mL/mg)
Roflumilast										
1	Adolescent	3	Mean	14.7	13.9	24.0	0.826	0.0617	13.9	1.06
			SD	4.62	4.38	0.00	0.504	0.0450	9.40	0.870
	Adult	19	Mean	27.7	28.5	18.6	2.40	0.0812	41.3	1.38
			SD	7.86	8.06	9.41	2.21	0.0629	43.5	1.24
15	Adolescent	5	Mean	13.6	12.9	10.4	1.27	0.105	25.1	2.07
			SD	3.65	3.46	12.4	1.23	0.111	24.0	2.17
	Adult	18	Mean	26.8	27.5	11.3	3.72	0.137	72.7	2.74
			SD	6.80	6.98	10.8	2.49	0.0956	53.1	2.12
Roflumilast N-oxide										
1	Adolescent	2	Mean	16.0	15.2	24.0	2.97	0.222	31.4	2.32
	Adult	17	Mean	28.2	29.0	24.0	6.68	0.227	81.4	2.77
			SD	8.14	8.35	0.00	6.92	0.225	91.8	2.98
15	Adolescent	6	Mean	13.0	12.3	16.5	7.17	0.605	140	11.8
			SD	3.58	3.39	11.6	9.39	0.836	179	15.9
	Adult	18	Mean	26.8	27.5	12.9	30.6	1.11	628	23.2
			SD	6.80	6.98	10.5	29.4	1.12	648	24.8

AUC_{last} = area under the plasma concentration-time curve from time zero to last measurable concentration; BSA = body surface area; C_{max} = maximum concentration; SD = standard deviation; T_{max} = time to maximum concentration.
ARQ-151-107 CSR, Appendix 16.1.13 PK Report, Table 1

Source: 2.7.2: Summary of Clinical Pharmacology Studies; Table 7

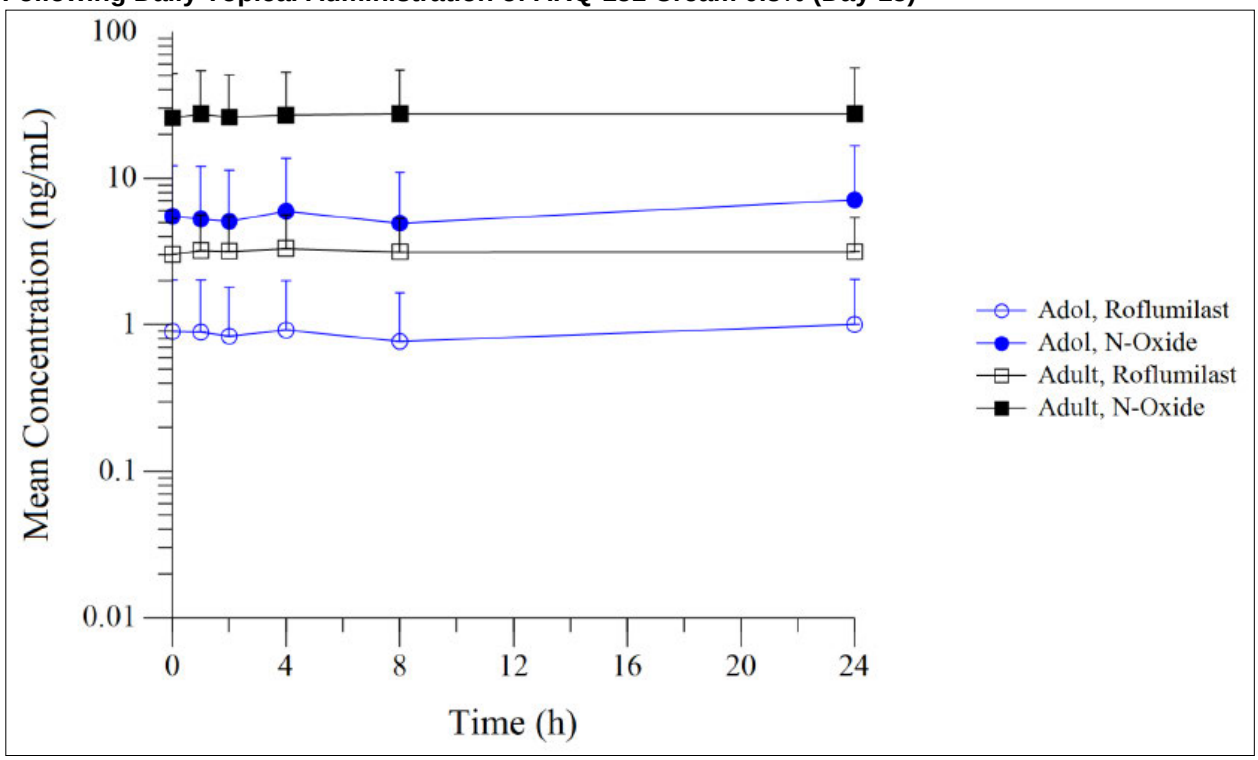
The Applicant in their study report compared the adult exposure reported in this study with PK information following oral administration published in Bethke et al. (Bethke et al. 2007). The Applicant noted that in comparison to the adult exposure following repeat oral administration of roflumilast 500 µg, the mean roflumilast AUC_{0-24} values following repeat topical administration were 2.2-fold higher (72.7 versus 33.7 h*ng/mL), while the mean roflumilast N-oxide AUC_{0-24} values were 1.7-fold higher (628 versus 375 h*ng/mL).

Table 6. Summary of Pharmacokinetic Results After Daily Treatment With Roflumilast 0.3% Cream in Adolescent and Adult Subjects and When Adjusted/Normalized for Dose at Day 15 in ARQ-151-107

Analyte	Age Group	N	BSA (%)	Target Dose (mg)	C_{max} (ng/ml/mg)	C_{max}/Dose (ng/ml/mg)	AUC_{last} (h*ng/ml)	AUC_{last}/Dose (h*ng/ml/mg)
Roflumilast	Adolescent	5	13.6 ± 3.65	12.9±3.46	1.27 ± 1.23	0.105 ± 0.111	25.1 ± 24.0	2.07 ± 2.17
	Adult	18	26.8 ± 6.80	27.5±6.98	3.72 ± 2.49	0.137 ± 0.0956	72.7 ± 53.1	2.74 ± 2.12
Roflumilast N-Oxide	Adolescent	6	13.0 ± 3.58	12.3±3.39	7.17 ± 9.39	0.605 ± 0.836	140 ± 179	11.8 ± 15.9
	Adult	18	26.8 ± 6.80	27.5±6.98	30.6 ± 29.4	1.11 ± 1.12	628 ± 648	23.2 ± 24.8

Source: 2.7.2: Summary of Clinical Pharmacology Studies; Adapted from Table 7
Abbreviations: AUC, area under the concentration-time curve; BSA, body surface area; C_{max}, maximum plasma concentration

Figure 1. Mean Plasma Concentration by Time Plots of Roflumilast and Roflumilast N-Oxide Following Daily Topical Administration of ARQ-151 Cream 0.3% (Day 15)

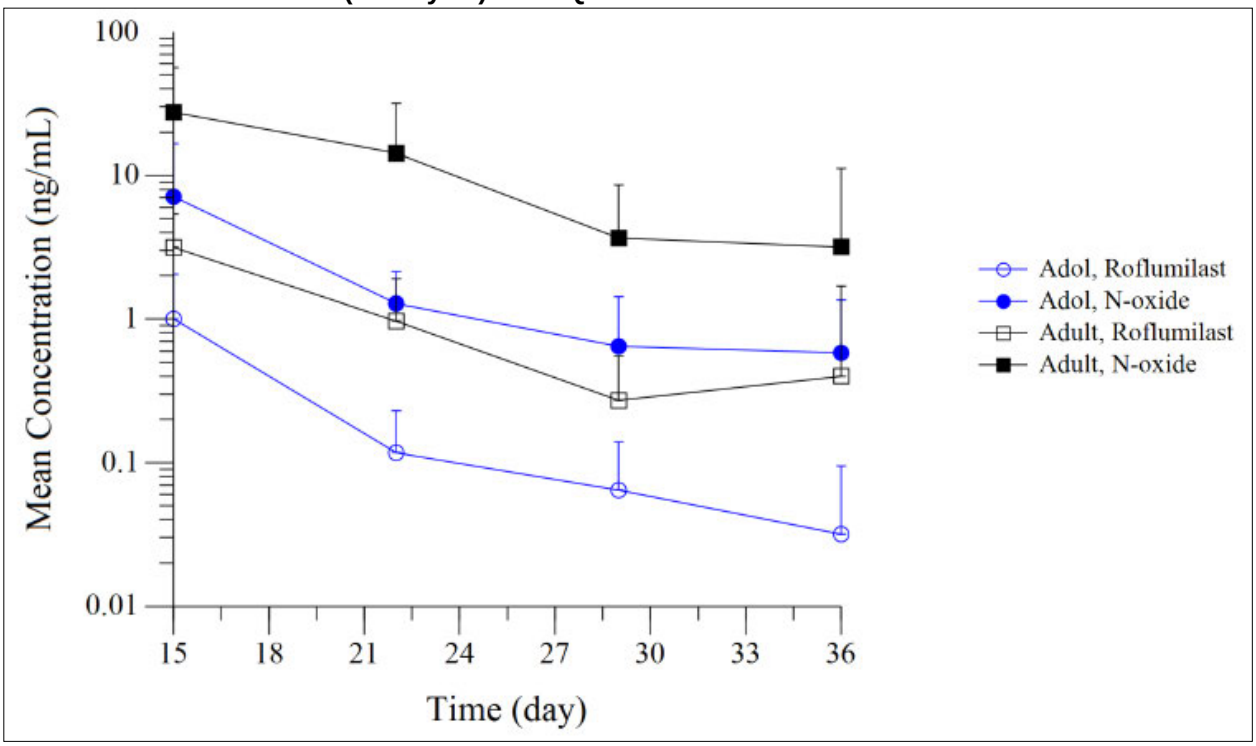


Source: 5.3.3.2:ARQ-151-107; Appendix 16.1.13 Pharmacokinetic Report: Figure 2

On Day 15, the mean roflumilast C_{max} values were 1.27±1.23 and 3.72±2.49 ng/mL in adolescent and adult subjects, respectively. The mean dose-normalized C_{max} values were 0.105±0.111 and 0.137±0.096 ng/mL/mg, respectively. The mean roflumilast N-oxide C_{max} values were 7.17±9.39 and 30.6±29.4 ng/mL in adolescent and adult subjects, respectively. The mean dose-normalized C_{max} values were 0.605±0.836 and 1.11±1.12 ng/mL/mg, respectively. These data demonstrate that when accounting for dose in adolescent and adult subjects, the mean C_{max} values were lower for adolescent subjects as compared to adults. On Day 15, the mean roflumilast AUC_{last} values were 25.1±24.0 and 72.7±53.1 h·ng/mL in adolescent and adult subjects, respectively. The mean dose-normalized AUC_{last} values were 2.07±2.17 and 2.74±2.12 h·ng/mL/mg, respectively. The mean roflumilast N-oxide AUC_{last} values were 140±179 and 628±648 h·ng/mL in adolescent and adult subjects, respectively. The mean dose-normalized AUC_{last} values were 11.8±15.9 and 23.2±24.8 h·ng/mL/mg, respectively. These data demonstrate that when accounting for dose in adolescent and adult subjects, the mean AUC_{last} values were lower for adolescent subjects as compared to adult subjects.

In summary when accounting for dose in adolescent and adult subjects, the mean C_{max} and AUC_{last} 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 for at least 20% BSA involved in adults and at least 10% BSA involved in adolescents and hence, the adolescent dose is expected to be lower than adult dose, thus producing an overall lower exposure.

Figure 2. Mean Roflumilast and Roflumilast N-Oxide Plasma Concentrations Following 1, 2 and 3 Weeks After the Last Dose (on Day 15) of ARQ-151 Cream 0.3%



Source: 5.3.3.2:ARQ-151-107; Appendix 16.1.13 Pharmacokinetic Report: Figure 3

Mean elimination concentration by time profile data at 1, 2 and 3 weeks following the last administration on Day 15 in ARQ-151-107 are presented in Figure 2. Half-life for roflumilast and roflumilast N-oxide were assessed using the week 2–24-hour, week 3, week 4 and week 5 plasma concentration values. In adult subjects, the mean roflumilast half-life was 4.0 days (N=16), and the mean roflumilast N-oxide half-life was 4.6 days (N=18). In adolescent subjects, the sample size was smaller, and the mean half-life of roflumilast and roflumilast N-oxide was lower, i.e., 2.9 days [N =1] and 2.8 days [N =2], respectively. The half-life estimation in adolescent subjects is not considered very reliable due to data in very few subjects.

Mean Dose Used in MUsT and Phase 3 Trials

The mean dose in the maximal use study was 6.5 gm and 3 gm respectively in adults and adolescent subjects compared to 2.24 g in the entire population in the Phase 3 trials. 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 III Trials

Two Phase 3 studies ARQ-151-301 and ARQ-151-302 evaluated the safety and efficacy of roflumilast cream 0.3% in a parallel, double-blind, vehicle-controlled study in subjects ≥2 years of age with chronic plaque psoriasis involving between 2% and 20% BSA. In both these studies, either roflumilast cream 0.3% or vehicle was applied QD over 8 weeks. Roflumilast plasma

concentrations were measured predose at baseline and weeks 4 and 8. Pharmacokinetic parameters for roflumilast and roflumilast N-oxide after daily administration of roflumilast cream 0.3% is provided in Table 6. Roflumilast and roflumilast N-oxide plasma concentration values seems to have reached steady state by the time of the first post-baseline PK assessment at Day 29 in both pivotal Phase III studies.

In Study ARQ-151-301, the mean (SD) trough roflumilast concentrations at week 8 in adolescents were 0.91±0.50 (N=3) and 1.82±2.41 (N=238) in adults. Trough roflumilast N-oxide concentrations at week 8 in adolescents (8.71±5.49 ng/mL) were lower than adult values 10.1±12.2 ng/mL (N=238). As the plasma concentration versus time profile at steady state was flat in nature, an AUC_{0-24} value was extrapolated by Applicant by multiplying the predose value by the dosing interval of 24 h. For adolescents at Week 8, the extrapolated roflumilast AUC_{0-24} values were 21.9±12.0 h·ng/mL and were lower than the adult value of 47.8±58.9 h·ng/mL. The extrapolated roflumilast N-oxide AUC_{0-24} in adults and adolescents was 247±293 and 209±132 h·ng/mL, respectively. These data demonstrate that exposure is lower in adolescents as compared to the adult populations similar to the results seen in MUsT study (ARQ-151-107).

Table 7. Summary of Pharmacokinetic Results on Day 29, and 57 After Repeat Dosing in ARQ-151-301, and ARQ-151-302

Study Analyte	Day	Treatment	Age	BSA[a] (%)		Trough Conc (ng/mL)		Conc/BSA (ng/mL/mg)		Extrapolated AUC_{0-24} (h·ng/mL)	
				N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
ARQ-151-301											
Roflumilast	29	0.3%	Adolescent	3	4.83 (1.26)	3	0.972 (0.226)	3	0.215 (0.0339)	3	23.3 (5.43)
		0.3%	Adult	241	5.97 (4.13)	241	2.05 (2.83)	223	0.400 (0.435)	223	53.3 (69.1)
	57	0.3%	Adolescent	3	4.83 (1.26)	3	0.911 (0.50)	3	0.188 (0.0776)	3	21.9 (12.0)
		0.3%	Adult	241	5.97 (4.13)	238	1.82 (2.41)	217	0.382 (0.486)	217	47.8 (58.9)
Roflumilast N-oxide	29	0.3%	Adolescent	3	4.83 (1.26)	3	8.42 (3.80)	3	1.81 (0.450)	3	202 (91.2)
		0.3%	Adult	241	5.97 (4.13)	241	11.8 (12.9)	236	2.17 (2.18)	236	288 (310)
	57	0.3%	Adolescent	3	4.83 (1.26)	3	8.71 (5.49)	3	1.77 (0.748)	3	209 (132)
		0.3%	Adult	241	5.97 (4.13)	238	10.10 (12.2)	233	1.91 (2.30)	233	247 (293)
ARQ-151-302											
Roflumilast	29	0.3%	Adolescent	5	8.26 (4.82)	5	0.331 (0.217)	4	0.0950 (0.0814)	4	9.92 (3.13)
			Adult	244	6.87 (4.83)	244	1.99 (2.22)	230	0.373 (0.460)	230	50.6 (53.5)
	57	0.3%	Adolescent	5	8.26 (4.82)	5	0.857 (0.895)	4	0.235 (0.190)	4	25.7 (21.0)
			Adult	244	6.87 (4.83)	238	1.72 (2.13)	225	0.312 (0.360)	225	43.7 (51.5)
Roflumilast N-oxide	29	0.3%	Adolescent	5	8.26 (4.82)	5	3.53 (2.44)	5	0.761 (0.783)	5	84.6 (58.4)
			Adult	244	6.87 (4.83)	244	12.2 (14.1)	242	2.12 (2.95)	242	294 (338)
	57	0.3%	Adolescent	5	8.26 (4.82)	5	6.72 (7.24)	5	1.30 (1.22)	5	161 (174)
			Adult	244	6.87 (4.83)	238	10.2 (12.8)	233	1.75 (2.19)	233	249 (308)

BSA = body surface area; conc = concentration; extrapolated AUC_{0-24} = trough concentration, represents the area under the plasma concentration-time curve from time zero to 24 hours; N =number of subjects.
[a] BSA to which roflumilast cream was applied.Subjects who had no quantifiable concentrations of roflumilast were excluded from the BSA analysis.
Source: ARQ-151-301 CSR, Appendix 16.1.13 PK Report, Table 1; ARQ-151-302 CSR, Appendix 16.1.13 PK Report, Table 1

Source: 2.7.2: Summary of Clinical Pharmacology Studies; Table 8

In Study ARQ-151-302, trough roflumilast concentrations on Week 8 were lower in adolescent (0.857±0.895 ng/mL, N=5) as compared to adult (1.72±2.13 ng/mL, N=238) populations. Trough N-oxide concentrations at Week 8 in adults and adolescents were 10.2±12.8 ng/mL and

6.72±7.24 ng/mL, respectively. The extrapolated roflumilast AUC_{0-24} values in adolescents and adults were 25.7±21.0 h·ng/mL and 43.7±51.5 h·ng/mL, respectively. The extrapolated roflumilast N-oxide AUC_{0-24} values in adults and adolescents were 249±308 h·ng/mL and 161±174 h·ng/mL, respectively. These data demonstrate that exposure is lower in adolescents as compared to the adult populations similar to the results seen in MUsT study (ARQ-151-107).

Following topical administration, difference in the pharmacokinetics of roflumilast and roflumilast N oxide were observed based on age (12 to 88 years), sex, race, or ethnicity.

Table 8. Mean (SD) Roflumilast and Roflumilast N-Oxide Trough Concentrations by Age Group From ARQ-151-301 and ARQ-151-302 Studies

Age	N	Roflumilast (ng/mL)	Roflumilast N-Oxide (ng/mL)
> 65 years	119	2.22 (2.69)	11.0 (11.8)
18 – 65 years	853	1.84 (2.36)	11.0 (13.1)

N = number of observations; SD = standard deviation.
Source: AD-21-078 Table 4
Source: 2.7.2: Summary of Clinical Pharmacology Studies; Adapted from Table 9

The mean systemic exposure of roflumilast was observed to be 1.2-fold higher in patients with age greater than 65 years as compared to the age group ≤65 years.

Table 9. Mean (SD) Roflumilast and Roflumilast N-Oxide Trough Concentrations by Sex From ARQ-151-301 and ARQ-151-302 Studies

Sex	N	Roflumilast (ng/mL)	Roflumilast N-Oxide (ng/mL)
Female	355	1.29 (1.55)	8.33 (9.80)
Male	617	2.23 (2.72)	12.5 (14.3)

N = number of observations; SD = standard deviation.
Source: AD-21-078 Table 3
Source: 2.7.2: Summary of Clinical Pharmacology Studies; Adapted from Table 10

The mean systemic exposure of roflumilast and n-oxide in females were observed to be lower than males.

Table 10. Mean (SD) Roflumilast and Roflumilast N-Oxide Trough Concentrations by Race From ARQ-151-301 and ARQ-151-302 Studies

Race	N	Roflumilast (ng/mL)	N-Oxide (ng/mL)
American-Indian or Alaska Native	8	1.54 (2.06)	10.3 (12.9)
Asian	74	2.36 (1.99)	15.6 (12.7)
Black or African-American	34	2.94 (6.25)	16.4 (24.2)
Native Hawaiian or Other Pacific Islander	10	3.58 (5.93)	19.3 (37.2)
White	798	1.76 (2.04)	9.99 (11.1)
Not Reported	12	3.85 (2.94)	28.1 (26.7)
Other	31	1.73 (1.92)	11.5 (12.2)
More than One Race	5	0.841 (0.570)	3.88 (3.01)

N = number of subjects; SD = standard deviation.
Source: AD-21-078 Table 1
Source: 2.7.2: Summary of Clinical Pharmacology Studies; Adapted from Table 11

The mean systemic exposure of roflumilast and N-oxide in the white population seems to be lower than any other race.

Table 11. Mean (SD) Roflumilast and Roflumilast N-Oxide Trough Concentrations by Ethnicity From ARQ-151-301 and ARQ-151-302 Studies

Race	N	Roflumilast (ng/mL)	Roflumilast N-Oxide (ng/mL)
Hispanic or Latino	227	2.19 (2.28)	14.2 (15.0)
Not Hispanic or Latino	743	1.79 (2.44)	10.0 (12.2)

N = number of observations; SD = standard deviation.
Source: AD-21-078 Table 2
Source: 2.7.2: Summary of Clinical Pharmacology Studies; Adapted from Table 12

The mean systemic exposure of roflumilast and n-oxide in Hispanic or Latino population seems to be higher than not Hispanic or Latino population.

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. In vitro studies and clinical drug-drug interaction studies suggest that the biotransformation of roflumilast to its N-oxide metabolite is mediated by CYP1A2 and 3A4. Together, roflumilast and roflumilast N-oxide account for 87.5% of the total dose administered in plasma 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 ADCP N-oxide were detected in urine. Following multiple topical applications of roflumilast cream, the roflumilast N-oxide metabolite appears to circulate at about

approximately 8-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. The N-oxide metabolite is about 3-fold less potent against inhibiting the PDE-4 isozyme relative to the parent.

Drug-Drug Interaction Studies

No drug interaction studies were conducted with roflumilast cream. However, a full complement of drug-interaction studies was conducted in support of the oral roflumilast. 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 has been 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 CYP 3A4 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) PK 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. Therefore, a warning in the label that the co-administration of roflumilast with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects and the risk of such concurrent use should be weighed carefully against benefit is indicated.

Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

No. For topical product, PK 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 a MUsT and in subjects aged 12 years and older with plaque psoriasis in the Phase 3 trials.

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 oral Roflumilast label indication.

Oral roflumilast was studied in 12 subjects with severe renal impairment 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 cream. Applicant is relying on the findings from drug-interaction studies conducted in support of the oral roflumilast program. Roflumilast is extensively metabolized by CYP3A4 and CYP1A2 to its primary active metabolite roflumilast N-oxide. In drug-drug interaction studies with oral roflumilast product it has been observed that AUC of roflumilast and roflumilast N-oxide decreased. While a similar reduction in exposure would be expected following topical administration of roflumilast, efficacy following topical administration of roflumilast is considered to be related to the local concentration of roflumilast in the skin and hence no warning has been included in the label regarding co-administration with CYP inducers.

In drug interaction studies with oral roflumilast product it has been observed that C_{max} and AUC increased after coadministration with CYP3A4 inhibitors e.g., erythromycin, ketoconazole and dual CYP3A4/1A2 inhibitors e.g., fluvoxamine, enoxacin, cimetidine. Hence, this product will be labeled that coadministration of roflumilast with systemic CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously may increase roflumilast systemic exposure and may result in increased adverse reactions and the risk of such concurrent use should be weighed carefully against benefit. Results from in vitro and in vivo drug-drug

interaction studies suggest that although roflumilast and the N-oxide metabolite have been shown to be the inhibitors of the CYP3A4 isozyme their inhibitor constant (Ki) values of about 1 and 60µM, respectively are much higher than the average plasma concentration of roflumilast and N-oxide metabolite of 3.0 ng/ml (7.4nM) and 26 ng/ml (62nM) and hence no impact on CYP3A4 substrates are expected after topical administration. 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. Hence, warning in the label stating that coadministration of roflumilast with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects and the risk of such concurrent use should be weighed carefully against benefit is added.

Sources of Clinical Data and Review Strategy

Table of Clinical Studies

The Applicant submitted safety data from the following studies:

- Two identical 8-week, Phase 3 (pivotal) trials (ARQ-151-301, ARQ-151-302)
- One 12-week, Phase 2 dose-ranging trial (ARQ-151-201)- excluding 0.15% dose group
- Two long-term, open-label studies (ARQ-151-202 [52-week], ARQ-151-306 [24-week])
- Four dermal safety studies (ARQ-151-108, -109, -110, and -111)

The ISS includes pooled safety data from the following pools:

1. Phase 3 pool: ARQ-151-301/-302
2. Vehicle-controlled (VC) pool: ARQ-151-201/-301/-302
3. Long-term (LT), open-label pool: ARQ-151-202/-306

Table 12. Listing of Clinical Trials Relevant to This NDA/BLA

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
ARQ-151-301 (DERMIS-1)	04211363	Phase 3, R (2:1), DB, VC, PG	Roflumilast cream, 0.3% or vehicle cream applied topically once daily (QD)	Primary Efficacy IGA success (a score of Clear (0) or Almost Clear (1) and a ≥2-grade improvement from baseline at Week 8 Secondary Efficacy -IGA success at Week 4 -I-IGA success (a score of Clear (0) or Almost Clear (1) and a ≥2-grade improvement from Baseline at Week 8 -WI-NRS success (≥4-point reduction in WI-NRS pruritus score from baseline at Weeks 8, 4, 2 (baseline NRS>=4) PASI-75 at week 8 Exploratory Efficacy -Change from Baseline in PSD total score at Weeks 8, 4 Pharmacokinetics Safety: TEAEs, local tolerability, clinical laboratories (chemistry/hematology,	8 weeks Roll-over to study -306 or 1-week follow-up	439	Subjects with chronic plaque psoriasis: Age ≥2 years IGA ≥2 PASI ≥2 2%≤BSA ≤20% (excluding scalp/palms/soles)	43 sites in the U.S. and Canada

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
				urinalysis), vital signs (SBP, DBP, HR, T), physical examination (skin, lungs, and heart), weight, height, BMI, C-SSRS, PHQ-8 /PHQ-A, and CDI-2				
ARQ-151-302 (DERMIS-2)	04211389	Same as in -301	Same as in -301	Same as in -301	Same as in -301	442	Same as in -301	43 sites in the U.S. and Canada
Studies to Support Safety								
ARQ-151-201		Phase 2b, R (1:1 excluding 0.15% arm), DB, VC, PG, DR	roflumilast Cream 0.3%, ARQ-151 Cream 0.15%, or vehicle cream applied QD	Primary Efficacy: IGA success at Week 6 Pharmacokinetics Safety: TEAEs, local tolerability, clinical laboratories (chemistry/hematology, urinalysis), ECGs, vital signs, body weights, PHQ-8, C-SSRS	12 weeks, 4-week follow-up	218 (excluding roflumilast 0.15%)	Age ≥18 years IGA ≥2 mPASI ≥2 2%≤BSA ≤20 (excluding scalp/palms/soles)	30 sites in the U.S. and Canada
ARQ-151-202		Phase 2b, OLE, LTS	roflumilast cream, 0.3% QD	Safety: TEAEs, local tolerability, clinical laboratory (chemistry/hematology, urinalysis), 12-lead ECGs, PHQ-8, C-SSRS	52 weeks	332, including: Cohort 1 (n=230) (roll-over from -201) Cohort 2 (n=102) (de novo)	Age ≥18 years Cohort 1 (roll-over from -201) Cohort 2 (de novo) IGA ≥2 2%≤BSA ≤25% (excluding scalp/palms/soles)	30 sites in the U.S. and Canada

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
ARQ-151-306		Phase 3, OLE, LTS	roflumilast cream, 0.3% QD	Safety: TEAEs, local tolerability, clinical laboratory (chemistry/hematology, urinalysis), PHQ-8, C-SSRS, CDI-2	24 weeks	267	Cohort 1 (roll-over from Studies -107, -215, -216, -301, -302) Age ≥2 years Cohort 2 (de novo) 2≤Age ≤17 years 2%≤BSA ≤25% (excluding scalp/palms/soles)	61 sites in the U.S. and Canada
Other Studies Pertinent to the Review of Efficacy or Safety (e.g., Clinical Pharmacological Studies)								
ARQ-151-108 (HRIPT)		Phase 1, R, C, EB, WS	roflumilast cream 0.3%, vehicle control, negative control (0.9% saline solution) occlusive patch applications to mid-back skin (x 3/ week)	TEAEs, Frequency of subjects with a sensitization reaction Mean and total cumulative irritancy scores	Induction: 3 weeks (x9 patches) Rest: 10-14 days Challenge: 48 hours (1 Patch) Rechallenge (1 patch) if needed	244	Healthy subjects Age ≥18 years	U.S.(1)

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
ARQ-151-109 (CIPT)		Phase 1, R, C, EB, WS	roflumilast cream 0.3%, vehicle control, positive control (0.2% sodium lauryl sulfate [SLS]), negative control (0.9% saline solution) occlusive patch applications to mid-back skin QD	TEAEs, Total and mean cumulative irritancy scores	3 weeks	45	Healthy subjects Age ≥18 years	U.S.(1)
ARQ-151-110 Phototoxicity		Phase 1, R, VC, WS	roflumilast cream 0.3%, vehicle cream Single dose, occlusive patch	TEAEs, Erythema (0-3) and edema (0-2 scores at patch sites	4 days	35	Healthy subjects Age ≥18 years	U.S.(1)
ARQ-151-111 Photoallergy		Phase 1, R, VC, WS	Occlusive patch application x 2/week x 3 weeks, selected sites irradiation	TEAEs, Erythema (0-3) and edema (0-2 scores at patch sites	Induction 3 weeks, Rest 10-14 days, challenge 3 days	71	Healthy subjects Age ≥18 years	U.S.(1)

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
ARQ-151-101		Phase 1/2a	roflumilast cream, 0.5% QD, roflumilast cream, 0.15% QD, vehicle cream QD	Primary: Safety, PK secondary: efficacy	4 weeks	91	≥18 years	Canada (7), and the U.S.(1)
ARQ-151-107		Phase 1, OL, MUsT	roflumilast cream, 0.3% QD	PK, safety	2 weeks	26	≥12 years	U.S.(8)

Source: Applicant
Abbreviations: BMI, body mass index; BSA, body surface area; C, controlled; CDI-2, Children's Depression Inventory 2;CIPT, cumulative irritation patch test; C-SSRS, Columbia-Suicide Severity Rating Scale; DB, double-blind; DBP, diastolic blood pressure; DR, dose-ranging; EB, evaluator-blinded; ECG, electrocardiogram; HR, heart rate; HRIPT, human repeat insult patch tests; IGA, Investigator's Global Assessment; I-IGA, Intertriginous-Investigator's Global Assessment; LTS, long-term safety; MUsT, maximal use study; OL, open-label; OLE, open-label extension; PASI, Psoriasis Area and Severity Index; PG, parallel-group; PHQ-8, Patient Health Questionnaire depression scale; PHQ-A, Modified Patient Health Questionnaire-9 for Adolescents; PK, pharmacokinetics; PSD, Psoriasis Symptom Diary; QD, once daily; R, randomized; SBP, systolic blood pressure; TEAE, treatment-emergent adverse event; U.S., United States; VC, vehicle-controlled; WI-NRS, Worst Itch-Numeric Rating Scale; WS, within-subject

Review Strategy

Data Sources

The data sources used for the evaluation of the efficacy and safety of roflumilast cream, 0.3% included the Applicant's CSRs, datasets, clinical summaries, and proposed labeling. The submission was submitted in electronic common technical document format and was entirely electronic. Both Study Data Tabulation Model and analysis datasets were submitted. The analysis datasets used in this review are archived at:

\\CDSESUB1\evsprod\NDA215985\0001\m5\datasets

Data and Analysis Quality

A consultation for review of data fitness was obtained from CDER Office of Computational Sciences (OCS) on 10/14/2021. The OCS Jump Start team performed exploratory safety analysis and data fitness analysis for trials ARQ-151-202, ARQ-151-301, and ARQ-151-302 for this NDA and found the data quality acceptable. In collaboration with the OCS/Jump Start team, the Statistical and Clinical reviewers held the following meetings with the JumpStart team:

- 11/1/2021 Annotated Core DF assessment
- 11/5/2021 ISS overview assessment
- 11/8/2021 SDTM to ADaM traceability assessment
- 11/10/2021 ISS traceability assessment
- 11/16/2021 Exploratory safety analysis assessment

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

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

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

Additionally, at the request of the Statistical and Clinical reviewers, OCS conducted additional SPS analyses [related to the EAIR, or weighted EAIR for the long-term open-label pool (pool 3) and the vehicle-controlled pool (pool 2)] which showed results consistent with those reported by the Applicant in Table 9 of M.2.7.4.

Statistical and Clinical and Evaluation

Review of Relevant Individual Trials Used to Support Efficacy

Trial Design

The Applicant conducted two identically designed, randomized, parallel-group, double-blind, vehicle-controlled, Phase 3 trials (ARQ-151-301/302) to evaluate the safety and efficacy of roflumilast (ARQ-151) cream 0.3% administered QD in subjects with mild to severe plaque psoriasis. For enrollment, the protocols specified the following key inclusion criteria:

- Male or female, 2 years or older
- Clinical diagnosis of psoriasis vulgaris of at least 6 months duration as determined by the Investigator; stable disease for the past 4 weeks
- Psoriasis vulgaris on the face, extremities, trunk, and/or intertriginous areas involving 2% to 20% of BSA (excluding the scalp, palms and soles)
- Investigator's Global Assessment (IGA) score of at least 'mild' (2) at baseline; see Table 13 for details on the IGA scale
- Psoriasis Area and Severity Index (PASI) score of at least 2 (excluding the scalp, palms and soles) at baseline

Each trial was designed to enroll and randomize approximately 400 subjects from approximately 40 sites in Canada and United States in a 2:1 ratio to roflumilast cream 0.3% (N=267) or vehicle cream (N=133), applied once daily. According to the statistical analysis plans (SAPs), randomization was stratified by site, baseline IGA score (IGA =2 versus IGA ≥3), and intertriginous involvement at baseline (I-IGA ≥2, yes versus no). All psoriasis lesions on a subject were to be treated including the face, trunk, genitals/skin folds, or limbs (excluding the scalp). The palms and soles were treated but were not counted towards any measurements of efficacy.

The trials consisted of a screening period, an 8-week treatment period and a follow-up period. Subjects had clinic visits at screening, baseline and Weeks 2, 4, 6, 8 and 9 (follow-up visit). Upon completion of the trials, participants had the opportunity to participate in the open-label, long-term safety trial ARQ-151-306 of up to 6 months. The Week 8 visit of the present trials (ARQ-151-301/302) is the Day 1 visit for Trial ARQ-151-306 and there would not be a Week 9 follow-up visit.

Trial Endpoints

The protocol-specified primary endpoint is IGA success at Week 8, where success is defined as IGA score of 'clear' (0) or 'almost clear' (1) and a 2-grade improvement from baseline.

The protocols specified the following secondary efficacy endpoints:

1. PASI 75 (subjects who achieve a 75% reduction in PASI from baseline) at Week 8.
2. Intertriginous area IGA (I-IGA) score of 'clear' (0) or 'almost clear' (1) with a 2-grade improvement from baseline to Week 8, for subjects with intertriginous area involvement and with severity of the intertriginous lesions at least 'mild' (I-IGA ≥2) at baseline.
3. A 4-point reduction from baseline in WI-NRS pruritus score at Week 8 among subjects with WI-NRS pruritus score ≥4 at baseline.
4. A 4-point reduction from baseline in WI-NRS pruritus score at Week 4 among subjects with WI-NRS pruritus score ≥4 at baseline.
5. A 4-point reduction from baseline in WI-NRS pruritus score at Week 2 among subjects with WI-NRS pruritus score ≥4 at baseline.
6. Change from baseline in PSD total score at Week 8
7. Change from baseline in PSD total score at Week 4
8. Time to achieving PASI 50 (subjects who achieve a 50% reduction in PASI from baseline)
9. I-IGA score of 'clear' at Week 8 for subjects with intertriginous area involvement and with severity of the intertriginous lesions at least 'mild' (I-IGA ≥2) at baseline
10. PASI 90 (subjects who achieve a 90% reduction in PASI from baseline) at Week 8 (removed from multiplicity testing procedure in the SAP)

The Agency commented several times during the IND stage (End-Of-Phase 2 meeting dated 10/23/2019; advice letter dated 1/20/2020 and Pre-NDA meeting dated 5/3/2021) that endpoints based on PASI and the change from baseline in total PSD, may not be clinically meaningful for mild psoriasis and recommended removal of such endpoints from the multiplicity testing procedure (MTP). (b) (4)

Table 13. Investigator's Global Assessment (IGA)

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: Protocol Amendment 1 for Trial ARQ-151-301; Appendix 5, page 113
Note: This IGA (whole body) was the first efficacy measure at clinic visits and prior to the application of any Investigational Product.

Psoriasis Area and Severity Index

PASI is a weighted sum score endpoint that typically ranges from 0 to 72. The body is divided into four sections: head (h), arms (a), trunk (t) and legs (l). The extent of psoriatic involvement for each of the three areas was determined using the following scale:

- 0=0% of involved area
- 1 = <10% of involved area
- 2=10–29% of involved area
- 3=30–49% of involved area
- 4=50–69% of involved area
- 5=70–89% of involved area
- 6=90–100% of involved area

Within each area, the severity is estimated by three clinical signs: erythema ('E'; redness), induration ('T'; thickness) and desquamation ('S'; scaling). Severity parameters are measured on a scale of 0 to 4, from none to maximum severity possible. To calculate the PASI, the sum of the severity rating for the three main signs are multiplied with the numerical value of the area affected and with the various percentages of the four body areas. These values are then added to complete the formula as follows:

PASI =0.1 (Eh + Th + Sh) Ah +0.2 (Ea + Ta + Sa) Aa +0.3 (Et + Tt + St) At +0.4 (El + Tl + Sl) Al

Worst Itch-Numerical Rating Scale

The WI-NRS was 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") completed by subjects at screening, baseline, and Weeks 2, 4, 6, 8 and 9 (if applicable).

Psoriasis Symptoms Diary

The PSD was completed by adult subjects at screening, baseline, and Weeks 2, 4, 6 and 8. The PSD questionnaire comprises of 16 questions, assessing signs and symptoms of psoriasis on a 0-10 numeric rating scale.

Statistical Methodology

Analysis Sets

The SAPs specified that the primary efficacy analysis set is the intent-to-treat (ITT) population, defined as all randomized subjects. The SAPs also specified the following analysis populations:

- Modified intent-to-treat population (mITT): all randomized subjects with the exception of subjects who missed the Week 8 IGA assessment specifically due to coronavirus disease 2019 (COVID-19) disruption. This population was used for sensitivity of the primary endpoint.
- I-IGA ITT Population (I-IGA-ITT): subjects with intertriginous area involvement, and with severity of the intertriginous lesions at least 'mild' (intertriginous IGA (I-IGA) ≥2) at baseline in the ITT population.
- I-IGA mITT Population (I-IGA-mITT): subjects with intertriginous area involvement, and with severity of the intertriginous lesions at least 'mild' (intertriginous IGA (I-IGA) ≥2) at baseline in the mITT population.
- Pruritus ITT Population (PRU4-ITT): subjects with WI-NRS pruritus score ≥4 at baseline in the ITT population. This population will be used for the analysis of achievement of a 4-point reduction in WI-NRS pruritus score as compared to baseline.
- Pruritus mITT Population (PRU4-mITT): subjects with WI-NRS pruritus score ≥4 at baseline in the mITT population.

A Per Protocol population described in the protocol was removed with its associated analyses from the SAP.

Analysis Methods for the Primary and Secondary Endpoints

The protocols/SAPs specified analyzing the primary endpoint (IGA success at Week 8) using the Cochran-Mantel-Haenszel (CMH) test stratified by site, IGA at baseline, and intertriginous involvement at baseline. According to the CSR, pooled site was used as a stratification factor in the statistical models.

The protocols/SAPs specified analyzing binary secondary endpoints using the same analysis method with that for the primary endpoint. Continuous secondary endpoints were analyzed using analysis of covariance with the factors of treatment, site, baseline IGA, baseline intertriginous involvement, and visit as independent variables. Time-to-event endpoints were analyzed using the Kaplan-Meier estimator. Treatment group comparisons were performed using the log-rank statistic.

The SAPs specified that all analyses that include the stratification factors (site, baseline IGA, and baseline intertriginous involvement) will use the data as collected in the interactive voice response system (IVRS). If the overall number of discrepancies between the IVRS and the electronic case report form (eCRF) database exceeds 10%, the SAPs specified a sensitivity analysis in which the stratification factors are based on the values as collected in the eCRF database.

Pooling Sites

The SAPs specified that sites are pooled for statistical analysis as follows: For analysis, sites should have a minimum of 10 randomized subjects. The smallest sites will be grouped sequentially in order of smallest to largest, restricting to those sites that did not meet the minimum enrollment of 10, until each pooled site has a minimum of 10 subjects with at least one subject in each treatment group.

Estimand Framework

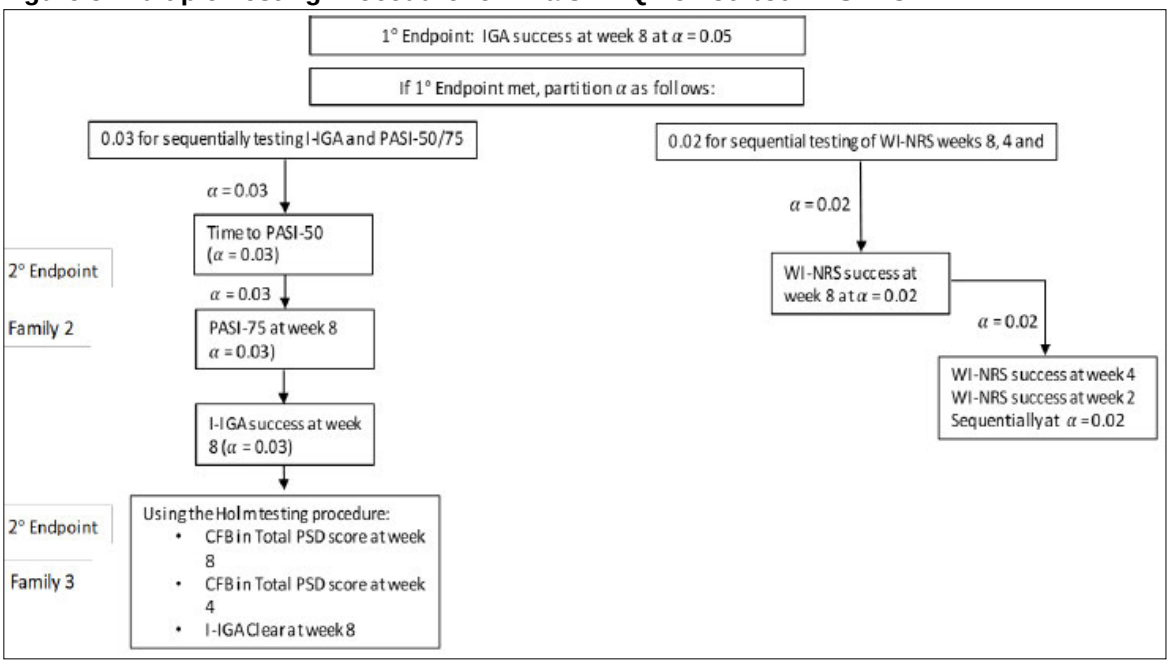
The SAPs specified the primary estimand of the ratio of the odds of achieving IGA success after 8 weeks of using roflumilast cream 0.3%, relative to the odds of success after 8 weeks of using vehicle cream. The SAP specified adopting the "Treatment Policy Strategy" for handling all known or unknown intercurrent events in this trial, i.e., the odds ratio of achieving IGA success for roflumilast cream 0.3% relative to vehicle after 8 weeks are evaluated regardless of the occurrence of any such intercurrent event. This estimand shall be estimated using the CMH approach.

Multiplicity Testing Procedure

According to the SAPs, secondary endpoints were to be tested statistically if the primary endpoint was considered statistically significant. To control for multiple comparisons among the secondary endpoints, the SAPs specified using the MTP summarized in Figure 3. The Applicant stated that there was a typographical error in the SAPs for the tested secondary endpoints: I-IGA of Clear at Week 8 was not intended to be tested using the Holm method; instead, IGA success at Week 4 was intended to be tested at the α =0.03 level and using the Holm testing procedure. According to the Applicant, the error was detected on 20-Jan-2021, after database lock, but before unblinding the data. This error was corrected in a memorandum to file and the MTP was modified as summarized in Figure 4. The memorandum to file describes that the Applicant's team decided to modify the MTP on 8/26/2020; however, on 1/21/2021, they realized that the contract research organization company did not make the update to change

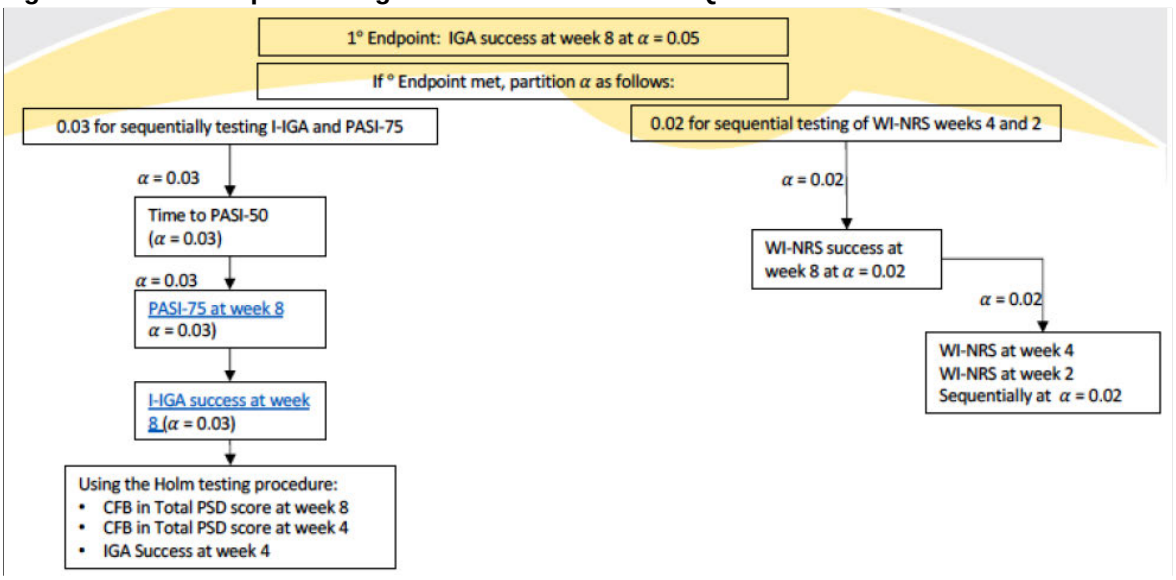
the endpoint. The Applicant noted that upon identification of such error, they directed the contract research organization company to use the MTP summarized in Figure 4. However, the Agency was not informed for this error until the submission of the NDA on 9/29/2021.

Figure 3. Multiple Testing Procedure for Trials ARQ-151-301/302 – SAPs



Source: Sponsor's SAP for Trial ARQ-151-301; page 14
Abbreviations: CFB, change from baseline; IGA, Investigator's Global Assessment; I-IGA, Intertriginous-Investigator's Global Assessment; IP, Investigational Product; PASI, Psoriasis Area and Severity Index; PSD, Psoriasis Symptom Diary; SAP, statistical analysis plan; WI-NRS, Worst Itch-Numeric Rating Scale

Figure 4. Final Multiple Testing Procedure for Trials ARQ-151-301/302



Source: Memordum to file
Abbreviations: CFB, change from baseline; IGA, Investigator's Global Assessment; I-IGA, Intertriginous-Investigator's Global Assessment; IP, Investigational Product; PASI, Psoriasis Area and Severity Index; PSD, Psoriasis Symptom Diary; WI-NRS, Worst Itch-Numeric Rating Scale

Methods for Handling the Missing Data

The protocols/SAPs specified the regression-based multiple imputation (MI) method as the primary method for handling the missing data for the analysis of the primary and secondary endpoints intended for hypothesis testing. Step Process for the MI method:

1. If the data set does not have monotone missing pattern, the monotone data augmentation method using Markov-Chain Monte-Carlo (MCMC) described below is used to impute the small amount of missing data that may be missing at the intermediate visits that is required to make the missing data pattern monotone before applying the multiple imputation algorithm. This method uses a non-informative Jeffreys prior to derive the posterior mode from the expectation-maximization (EM) algorithm as the starting values for the MCMC method. The MCMC method uses the seed 59726314. The IGA score is treated as a continuous variable for this step. To avoid values that could not be observed in practice, imputed values are constrained to be integers in the range of 0 to 4. The number of imputed monotone datasets are determined based on the amount of missing data that is required to be imputed to make the original dataset monotone per Table 14.

Table 14. Number of Imputed Databases Based on Amount of Non-Monotone Missing Data

Non-monotone Missing Data	Number of Imputed Datasets
≤ 2%	1
> 2% to ≤ 5%	3
> 5%	10

Source: SAP for Trial ARQ-151-301; page 20

2. Imputation algorithm is implemented using the predictive mean matching method. For subjects with complete data up to a particular visit, a predictive mean matching model is fit that includes the outcome at that visit as the dependent variable and as independent variables, IGA score outcomes at previous visits, baseline IGA score, treatment group, and investigational site, using a seed of 461903. This process is repeated 25 times, resulting in a total of 25 to 250 complete analysis datasets, depending on the number of imputed monotone datasets that are required.
3. For each completed dataset, compute the necessary derived variables. The dichotomous success rate (clear or almost clear with at least a 2-point change from baseline) is derived using these datasets. The results obtained are analyzed using the CMH test. Analysis is performed separately for each of the 25 to 250 complete analysis data sets, and the results are combined into one multiple imputation inference.

The SAPs stated that the primary efficacy analysis and the sensitivity analyses are based on the ITT/mITT population. The analysis of the mITT population uses the MI datasets already created for the ITT population (i.e., no new MI datasets will be generated).

The SAPs also specified the following sensitivity analyses of the primary endpoint analysis:

- Repeated measures logistic regression model (GEE) with IGA success as the dependent variable and treatment, site, and visit as the independent variables.
- Tipping point analysis: The sensitivity analysis is performed by using a specified sequence of shift parameters, which adjusts the imputed values for observations in the active treatment group. The range of shift parameters to be included in this analysis are -1.5 to 1.5 by 0.2. Once the likely point of the shift is determined, the analysis is rerun using an expanded range around the suspected tipping point, with greater precision (i.e., to 2 decimal places, by 0.01). Thus, the value at which the results of the analysis are shifted from significant (i.e., $\alpha \leq 0.05$) to non-significant (i.e., $\alpha > 0.05$) is determined. Steps 1 and 3 of the analysis will be the same as for the multiple imputation analysis described above. However, Step 2 of the analysis is where the shift parameters is applied.

Subject Disposition, Demographics, and Baseline Disease Characteristics

Trial ARQ-151-301 enrolled and randomized a total of 439 subjects at 43 investigational sites in Canada and United States. Trial ARQ-151-302 enrolled and randomized a total of 442 subjects at 42 investigational sites in Canada and United States. All randomized subjects in both trials had at least dose of investigational product. Table 15 presents the disposition of subjects for the two pivotal trials. In both trials, the discontinuation rate was slightly lower in roflumilast arm compared to vehicle arm. The most common reasons for discontinuation were lost to follow-up and withdrawal by the subject. Only a small proportion of subjects discontinued the trial due to COVID-19 (1%-2%).

Table 15. Subject Disposition – Trials ARQ-151-301/302 (ITT*)

	Trial ARQ-151-301		Trial ARQ-151-302	
Subject Disposition	**Roflumilast Cream, 0.3% (N=286)**	**Vehicle Cream (N=153)**	**Roflumilast Cream, 0.3% (N=290)**	**Vehicle Cream (N=152)**
Completed	254 (89%)	132 (86%)	261 (90%)	128 (84%)
Discontinued	32 (11%)	21 (14%)	29 (10%)	24 (16%)
Reasons for discontinuation				
Adverse event	5 (2%)	2 (1%)	1 (<1%)	2 (1%)
Lost to follow-up	11 (4%)	3 (2%)	13 95%)	6 (4%)
Physician decision	0 (0%)	1 (1%)	-	-
Pregnancy	1 (<1%)	0 (0%)	-	-
Protocol violation	1 (<1%)	0 (0%)	-	-
Non-compliance	-	-	2 (1%)	2 (1%)
Withdrawal by subject	11 (4%)	10 (6%)	8 (3%)	12 (8%)
Other	0 (0%)	3 (2%)	-	-
Due to COVID-19	3 (1%)	2 (1%)	5 (2%)	2 (1%)

Source: Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt
* Intent-to-treat (ITT) Population: all randomized subjects
Abbreviations: COVID-19, Coronavirus Disease 2019

Table 16 presents the demographics and baseline disease characteristics for the two pivotal trials. The demographics and baseline disease characteristics were generally balanced across the treatment arms within each trial and were comparable across trials. The majority of

subjects were White and male. The subjects in the vehicle cream arm were on average slightly older than those in the roflumilast cream arm. Only a small proportion of subjects had mild or severe IGA score at baseline. Furthermore, only a small proportion of subjects (about 20%) had psoriasis at the intertriginous involvement at baseline (I-IGA score of at least 2 – mild). The majority of subjects (above 75%) had worst-itch NRS score of at least 4 at baseline.

Table 16. Demographics and Baseline Disease Characteristics – Trials ARQ-151-301/302 (ITT[1])

	Trial ARQ-151-301		Trial ARQ-151-302	
Characteristic	**Roflumilast Cream, 0.3% (N=286)**	**Vehicle Cream (N=153)**	**Roflumilast Cream, 0.3% (N=290)**	**Vehicle Cream (N=152)**
Age (years)				
Mean (SD)	47.6 (14.1)	48.7 (15.8)	46.9 (15.1)	47.1 (14.1)
Median	46	49	47	49
Range	9 – 86	13 – 88	6 – 82	8 – 82
Age group, n (%)				
2-<12	1 (0)	0 (0)	2 (1)	1 (1)
12-<18	3 (1)	3 (2)	5 (2)	3 (2)
18-<65	247 (86)	125 (82)	241 (83)	131 (86)
≥65	35 (12)	25 (16)	42 (14)	17 (11)
Sex, n (%)				
Female	97 (34)	57 (37)	114 (39)	52 (34)
Male	189 (66)	96 (63)	176 (61)	100 (66)
Race, n (%)				
White	234 (82)	124 (81)	240 (83)	126 (83)
Black or African American	8 (3)	8 (5)	13 (4)	9 (6)
American Indian or Alaska Native	4 (1)	1 (1)	0 (0)	1 (1)
Asian	21 (7)	11 (7)	20 (7)	9 (6)
Native Hawaiian or Other Pacific Islander	2 (1)	0 (0)	3 (1)	1 (1)
Multiple	2 (1)	1 (1)	1 (0)	0 (0)
Other	11 (4)	5 (3)	8 (3)	4 (3)
Not Reported	4 (1)	3 (2)	5 (2)	2 (1)
Country, n (%)				
US	214 (75)	110 (72)	230 (79)	121 (80)
Canada	72 (25)	43 (28)	60 (21)	31 (20)
IGA, n (%)				
2 – Mild	51 (18)	20 (13)	50 (17)	24 (16)
3 – Moderate	206 (72)	122 (80)	220 (76)	118 (78)
4 – Severe	29 (10)	11 (7)	20 (7)	10 (7)
PASI				
Mean (SD)	6.3 (3.1)	6.8 (3.7)	6.5 (3.2)	7.0 (3.5)
Median	5.6	6	5.6	6
Range	2 – 18	2 – 24.6	2 – 18.9	2 – 20.4
% BSA				
Mean (SD)	6.3 (4.4)	7.4 (4.8)	7.1 (4.8)	7.7 (5.1)
Median	5	6	5	6
Range	2 - 20	2 - 20	2 – 20	2 – 20
I-IGA, n (%)				
Missing	218 (76)	120 (78)	234 (81)	120 (79)
<2	5 (2)	1 (1)	3 (1)	1 (1)
≥2	63 (22)	32 (21)	53 (18)	31 (20)

Characteristic	Trial ARQ-151-301 Roflumilast Cream, 0.3% (N=286)	Trial ARQ-151-301 Vehicle Cream (N=153)	Trial ARQ-151-302 Roflumilast Cream, 0.3% (N=290)	Trial ARQ-151-302 Vehicle Cream (N=152)
WI-NRS, n (%)[2]				
Missing	1 (1%)	0 (0%)	2 (1)	1 (1)
<4	67 (23)	38 (25)	59 (20)	35 (23)
≥4	218 (76)	115 (75)	229 (79)	116 (76)

Source: Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt, ADEFF.xpt
[1] Intent-to-treat (ITT) Population: all randomized subjects
[2] One subject (roflumilast arm) in Trial ARQ-151-301 and three subjects (two in roflumilast arm and 1 in vehicle arm) in Trial ARQ-151-302 did not have a WI-NRS assessment at baseline.
Abbreviations: BSA, body surface area; IGA, Investigator's Global Assessment; I-IGA, Intertriginous-Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index; SD, standard deviation; US, United States; WI-NRS, worst itch numerical rating scale

Results for the Primary Endpoint

Table 17 presents the results for the primary efficacy endpoint of IGA success at Week 8 for Trials ARQ-151-301 and ARQ-151-302 in both ITT and mITT populations. Roflumilast cream was statistically superior to vehicle cream (p-values <0.001) in both trials. A higher treatment effect is observed in Trial ARQ-151-301 compared to Trial ARQ-151-302. In addition to the pre-specified odds ratios, the statistical reviewer also presents the difference in response rates between the two treatment arms since it is easier for interpretation, and therefore, is preferred for labeling. Furthermore, as noted in Section 0, the Applicant's analyses considered the stratification factors using the data as collected in the IVRS despite discrepancies with the values in the eCRF database (<10%). We note that such discrepancies should not occur in well-designed clinical trials, and therefore, the reviewer considered the actual baseline values (i.e., based on eCRF) in efficacy analyses. Table 17 presents both Applicant's and Reviewer's analyses; the results in the two analyses were very similar.

Table 17. Primary Endpoint Results at Week 8 – Trials ARQ-151-301/302 (MI[1])

Population	Trial ARQ-151-301 Roflumilast Cream, 0.3% (N=286)	Trial ARQ-151-301 Vehicle Cream (N=153)	Trial ARQ-151-302 Roflumilast Cream, 0.3% (N=290)	Trial ARQ-151-302 Vehicle Cream (N=152)
ITT Population[2]	N=286	N=153	N=290	N=152
Treatment Success[3]	41.5%	5.8%	36.7%	7.1%
Applicant's Analysis				
Difference (95% CI)[4]	39.6% (32.3%, 46.9%)		28.8% (20.8%, 36.9%)	
Odds Ratio (95% CI)[4]	20.7 (7.6, 56.5)		6.6 (3.2, 13.7)	
P-Value[4]	<0.001		<0.001	
Reviewer's Analysis				
Difference (95% CI)[5]	39.7% (32.4%, 47.0%)		29.5% (21.5%, 37.6%)	
Odds Ratio (95% CI)[5]	21.7 (8.1, 58.2)		6.8 (3.3, 14.1)	
P-Value[5]	<0.001		<0.001	
mITT Population[6]	N=281	N=151	N=285	N=149
Treatment Success[3]	41.8%	5.7%	37.1%	7.2%
Applicant's Analysis				
Difference (95% CI)[4]	40.2% (32.9%, 47.6%)		29.2% (21.1%, 37.3%)	
Odds Ratio (95% CI)[4]	20.7 (7.7, 56.1)		6.6 (3.2, 13.8)	
P-Value[4]	<0.001		<0.001	

	Trial ARQ-151-301		Trial ARQ-151-302	
Population	Roflumilast Cream, 0.3% (N=286)	Vehicle Cream (N=153)	Roflumilast Cream, 0.3% (N=290)	Vehicle Cream (N=152)
Reviewer's Analysis				
Difference (95% CI)[5]	40.4% (33.0%, 47.7%)		29.9% (21.7%, 38.0%)	
Odds Ratio (95% CI)[5]	21.8 (8.2, 57.9)		6.8 (3.3, 14.1)	
P-Value[5]	<0.001		<0.001	

Source: Statistical Reviewer's Analysis; ADEFF.xpt
[1] Missing data were imputed using multiple imputation; the rates displayed are the averages over the imputed datasets.
[2] Intent-to-treat (ITT) population defined as all randomized subjects.
[3] Treatment success is defined as a IGA score of 0 (clear) or 1 (almost clear) with at least a two-grade reduction from baseline.
[4] Estimate, 95% CI, and p-value are based on CMH test stratified by site, baseline IGA (based on IVRS), and baseline intertriginous involvement (based on IVRS); p-value for odds ratio obtained using the Wilson Hilferty transformation.
[5] Estimate and 95% CI, and p-value are based on CMH test stratified by site, baseline IGA (based on eCRF), and baseline intertriginous involvement (based on eCRF); p-value for odds ratio obtained using the Wilson Hilferty transformation.
[6] Modified Intent-To-Treat Population (mITT): all randomized subjects excluding subjects who missed the Week 8 IGA assessment due to COVID-19 disruption.
Abbreviations: CI, confidence interval; CMH, Cochran–Mantel–Haenszel; IGA, Investigator's Global Assessment; IVRS, interactive voice response system; MI, multiple imputation

Table 18 presents the number of subjects with missing data for the primary efficacy endpoint by week, treatment arm, and trial up to Week 8. The amount of missing data at Week 8 was slightly higher in the vehicle arm compared to the roflumilast arm in both trials. The amount of missing data at Week 8 due to COVID-19 is very small (1%-2%).

Table 18. Missing Data for the Primary Endpoint Up to Week 8 – Trials ARQ-151-301/302 (ITT*)

	Trial ARQ-151-301		Trial ARQ-151-302	
Week	Roflumilast Cream, 0.3% (N=286)	Vehicle Cream (N=153)	Roflumilast Cream, 0.3% (N=290)	Vehicle Cream (N=152)
Week 2	17 (6%)	10 (7%)	16 (6%)	7 (5%)
Week 4	24 (8%)	21 (14%)	23 (8%)	13 (9%)
Week 6	34 (12%)	22 (14%)	32 (11%)	23 (15%)
Week 8	31 (11%)	21 (14%)	26 (9%)	21 (14%)
Missing Week 8 due to COVID-19	5 (2%)	2 (1%)	5 (2%)	3 (2%)

Source: Statistical Reviewer's Analysis; ADEFF.xpt
* Intent-to-treat (ITT) population, defined as all randomized subjects
Abbreviations: COVID-19, Coronavirus Disease 2019

The primary method of handling missing data specified in the protocol was the regression-based MI method. The protocols/SAPs also specified two sensitivity analyses for the handling of missing data: (i) Repeated measures logistic regression model (GEE) with IGA success as the dependent variable and treatment, site, and visit as the independent variables, and (ii) tipping point analysis. The Applicant also conducted post hoc analyses using observed data. The statistical reviewer conducted additional analyses using the non-responder imputation and the worst-case scenario (i.e., missing data for roflumilast is imputed as non-responders and missing data for vehicle is imputed as responders). Table 19 presents the results for the primary endpoint (i.e., IGA success at Week 8) by the various imputation methods for handling the missing data (GEE is not presented here). The results were generally similar across the various methods in both trials. Roflumilast cream, 0.3% remained statistically superior to vehicle cream for the worst-case scenario in both trials, and therefore, the tipping point analysis was not performed.

Table 19. Results of the Primary Endpoint at Week 8 With Different Approaches for Handling Missing Data (ITT[1])

Approach to Missing Data	Roflumilast Cream, 0.3%	Vehicle Cream	Difference (P-Value)[2]
Trial ARQ-151-301	N=286	N=153	
MI (primary)	41.5%	5.8%	39.7% (<0.001)
NRI	37.8%	5.2%	36.7% (<0.001)
Observed cases	42.4%	6.1%	40.7% (<0.001
Worst-case scenario	37.8%	18.9%	22.4% (<0.001)
Trial ARQ-151-302	N=290	N=152	
MI (primary)	36.7%	7.1%	29.5% (<0.001)
NRI	34.1%	5.9%	27.8% (<0.001)
Observed cases	37.5%	6.9%	30.9% (<0.001)
Worst-case scenario	34.1%	19.7%	13.0% (0.0080)

Source: Statistical Reviewer's Analysis; ADEFF.xpt
[1] Intent-to-treat (ITT) Population: all randomized subjects
[2] Estimate for the difference is based on CMH test stratified by site, IGA at baseline (based on eCRF), and intertriginous involvement at baseline (based on eCRF). P-value for odds ratio is based on the same analysis.
Abbreviations: IGA, Investigator's Global Assessment; MI, multiple imputation; NRI, non-responder imputation

Results for the Secondary Efficacy Endpoints

The time to achieve PASI-50 was the first secondary endpoint to be tested in the first family of secondary endpoints. However, as noted in Section 0, the Agency commented several times during the IND stage (EOP 2 meeting dated 10/23/2019; advice letter dated 1/20/2020 and Pre-NDA meeting dated 5/3/2021) that endpoints based on PASI may not be clinically meaningful for mild psoriasis and recommended removal of such endpoints from the MTP. (b) (4) Therefore, this review does not present results for time to PASI-50. Results for PASI-75 (viewed as exploratory endpoint in this review) are included in the Appendix 0.

Table 20 presents the results for the secondary endpoint of I-IGA score of 'clear' (0) or 'almost clear' (1) with a 2-grade improvement from baseline to Week 8 based on reviewer's analysis (i.e., using eCRF values). This analysis includes only subjects with a baseline I-IGA score of at least 2 (I-IGA population). Only about 22% and 19% of subjects had I-IGA score ≥2 at baseline and were included in the analysis for Trials ARQ-151-301 and ARQ-151-302, respectively. In both trials, roflumilast cream, 0.3% was statistically superior to vehicle cream (p-values <0.001) for this endpoint at Week 8. Results based on I-IGA-mITT (not presented herein) are very similar to those based on the I-IGA-ITT. Results based on Applicant's analysis (i.e., using IVRS values) are presented in the Appendix 0 and are similar to those based on reviewer's analysis.

Table 20. I-IGA Success at Week 8 – Trials ARQ-151-301/302 (MI[1])

	Trial ARQ-151-301		Trial ARQ-151-302	
	Roflumilast Cream, 0.3% (N=286)	Vehicle Cream (N=153)	Roflumilast Cream, 0.3% (N=290)	Vehicle Cream (N=152)
I-IGA-ITT Population[2]	N=63	N=32	N=53	N=31
Treatment Success[3]	71.5%	13.8%	67.5%	17.4%
Difference (95% CI)[4]	63.6% (43.7%, 83.4%)		52.7% (30.9%, 74.5%)	
Odds Ratio (95% CI)[4]	16.7 (2.1, 131.6)		11.9 (2.5, 57.3)	
P-Value[4]	<0.001		<0.001	

Source: Statistical Reviewer's Analysis; ADEFF.xpt
[1] Missing data were imputed using multiple imputation; the rates displayed are the averages over the imputed datasets.
[2] I-IGA-ITT population, defined as randomized subjects with intertriginous area involvement of at least 'mild' (I-IGA ≥2) at baseline
[3] Treatment success is defined as an Intertriginous area IGA (I-IGA) score of 0 (clear) or 1 (almost clear) with at least a two-grade reduction from baseline
[4] Estimate, 95% CI, and p-value are based on CMH test stratified by site and IGA at baseline (based on eCRF); p-value for odds ratio obtained using the Wilson Hilferty transformation.
Abbreviations: CI, confidence interval; CMH, Cochran–Mantel–Haenszel; I-IGA, Intertriginous-Investigator's Global Assessment; ITT, intent-to-treat

As noted in Section 0, the Agency was not informed regarding the change of the endpoint of I-IGA clear at Week 8 to IGA success at Week 4 in the MTP until the NDA. To maintain the integrity of the trials, the reviewer does not consider testing for this endpoint (i.e., IGA success at Week 4) pre-specified. Analysis of such endpoint is considered post hoc, (b) (4) Table 21 presents the results for IGA success at Week 4 for ITT population based on reviewer's analysis (i.e., using values based on eCRF). Results based on mITT (not presented herein) are very similar to those based on the ITT. Results based on Applicant's analysis (i.e., using values based on IVRS) are presented in the Appendix 0 and are similar to those based on reviewer's analysis.

Table 21. IGA Success at Week 4 – Trials ARQ-151-301/302 (ITT; MI[1])

	Trial ARQ-151-301		Trial ARQ-151-302	
	Roflumilast Cream, 0.3% (N=286)	Vehicle Cream (N=153)	Roflumilast Cream, 0.3% (N=290)	Vehicle Cream (N=152)
Treatment Success[2]	19.8%	2.6%	18.6%	5.5%
Difference (95% CI)[3]	18.8% (12.9%, 24.6%)		13.5% (7.1%, 19.9%)	
Odds Ratio (95% CI)[3]	12.6 (3.5, 44.8)		3.8 (1.7, 8.3)	
P-Value[3]	<0.001		0.001	

Source: Statistical Reviewer's Analysis; ADEFF.xpt
[1] Intent-to-treat (ITT) population, defined as all randomized subjects; Missing data were imputed using multiple imputation; the rates displayed are the averages over the imputed datasets.
[2] Treatment success is defined as a IGA score of 0 (clear) or 1 (almost clear) with at least a two-grade reduction from baseline.
[3] Estimate, 95% CI, and p-value are based on CMH test stratified by site, baseline IGA (based on eCRF), and baseline intertriginous involvement (based on cCRF); p-value for odds ratio obtained using the Wilson Hilferty transformation.
Abbreviations: CI, confidence interval; CMH, Cochran–Mantel–Haenszel; IGA, Investigator's Global Assessment; MI, multiple imputation

Table 22 presents the results for the 4-point reduction from baseline in WI-NRS score at Weeks 2, 4 and 8 based on reviewer's analysis (i.e., using eCRF values). The analysis of these endpoints was prespecified to include only subjects with WI-NRS score ≥4 at baseline. About 75% and 78% of the subjects had WI-NRS score ≥4 at baseline and were included in such analysis for Trials ARQ-151-301 and ARQ-151-302, respectively. In both trials, roflumilast cream, 0.3% was statistically superior to vehicle cream (p-values <0.001) for the 4-point reduction from baseline in WI-NRS at Weeks 4 and 8 in both trials. However, results at Week 2 were not statistically

significant for Trial 301 (p-value=0.1346) but were statistically significant for Trial 302 (p-value=0.0016). Results based on PRU4-mITT (not presented here) are very similar to those based on the PRU4-ITT. Results based on Applicant's analysis (i.e., using IVRS values) are presented in the Appendix 0 and are similar to those based on reviewer's analysis.

Table 22. Response Rates for ≥4-Point Improvement From Baseline on Worst Itch NRS – Trials ARQ-151-301/302 (PRU4-ITT; MI[1])

	Trial ARQ-151-301		Trial ARQ-151-302	
Week	Roflumilast Cream, 0.3% (N=218)	Vehicle Cream (N=115)	Roflumilast Cream, 0.3% (N=229)	Vehicle Cream (N=116)
Week 8				
Treatment Success[2]	66.7%	25.7%	68.6%	33.3%
Difference (95% CI)[3]	41.1% (30.0%, 52.3%)		30.3% (18.1%, 42.5%)	
Odds Ratio (95% CI)[3]	8.2 (4.0, 16.9)		3.5 (2.0, 6.0)	
P-Value[3]	<0.001		<0.001	
Week 4				
Treatment Success[2]	49.4%	18.7%	55.8%	21.2%
Difference (95% CI)[3]	31.0% (20.0%, 41.9%)		34.4% (23.6%, 45.2%)	
Odds Ratio (95% CI)[3]	4.6 (2.4, 8.8)		4.9 (2.7, 9.1)	
P-Value[3]	<0.001		<0.001	
Week 2				
Treatment Success[2]	34.9%	22.7%	41.5%	21.9%
Difference (95% CI)[3]	10.6% (<0%, 21.4%)		20.0% (9.1%, 30.8%)	
Odds Ratio (95% CI)[3]	1.7 (1.0, 3.1)		2.6 (1.5, 4.6)	
P-Value[3]	0.1346		0.0016	

Source: Statistical Reviewer's Analysis; ADEFF.xpt
[1] Pruritus ITT Population (PRU4-ITT) defined as randomized subjects with WI-NRS pruritus score ≥4 at baseline; the rates displayed are the averages over the imputed datasets; missing data were imputed using multiple imputation; the rates displayed are the averages over the imputed datasets.
[2] Treatment success is defined as ≥4-point Improvement from baseline on worst itch NRS score
[3] Estimate, 95% CI, and p-value are based on CMH test stratified by site, baseline IGA (based on eCRD), and baseline intertriginous involvement (based on eCRF); p-value for odds ratio obtained using the Wilson Hilferty transformation.
Abbreviations: CI = confidence interval; CMH, Cochran–Mantel–Haenszel; ITT, intent-to-treat; MI, multiple imputation; NRS, numeric rating scale

Patient-Reported Outcomes

In addition to the endpoints based on the patient-reported outcome of worst itch NRS already presented in Section 0, the protocols/SAPs also specified secondary endpoints based on the total PSD score: change from baseline in PSD total score at Week 8 and at Week 4. As stated in Section 0, the PSD was completed by adult subjects only at screening, baseline, and Weeks 2, 4, 6 and 8. The PSD questionnaire comprises of 16 questions, assessing signs and symptoms of psoriasis, such as itching, pain, and scaling, on a 0-10 numeric rating scale. The Agency commented several times during the IND stage (EOP 2 meeting dated 10/23/2019; advice letter dated 1/20/2020 and Pre-NDA meeting dated 5/3/2021) that endpoints based on the change from baseline in total PSD score may not be clinically meaningful for mild psoriasis and recommended removal of such endpoints from the MTP. The results for these endpoints are presented in Table 23.

The reviewer further explored the proportion of subjects with PSD total score of 0. For Trial ARQ-151-301, 18.1% of subjects in roflumilast cream arm versus 2.4% of subjects in vehicle

cream arm had PSD Total score of 0 at Week 8; at Week 4: 8.7% versus 1.4%. For Trial ARQ-151-302, 17.1% of subjects in roflumilast cream arm versus 7.2% of subjects in vehicle cream arm had PSD total score of 0 at Week 8; at Week 4: 9.9% versus 2.8%.

Table 23. Results for Endpoints Based on PSD – Trials ARQ-151-301/302 (ITT; MI[1])

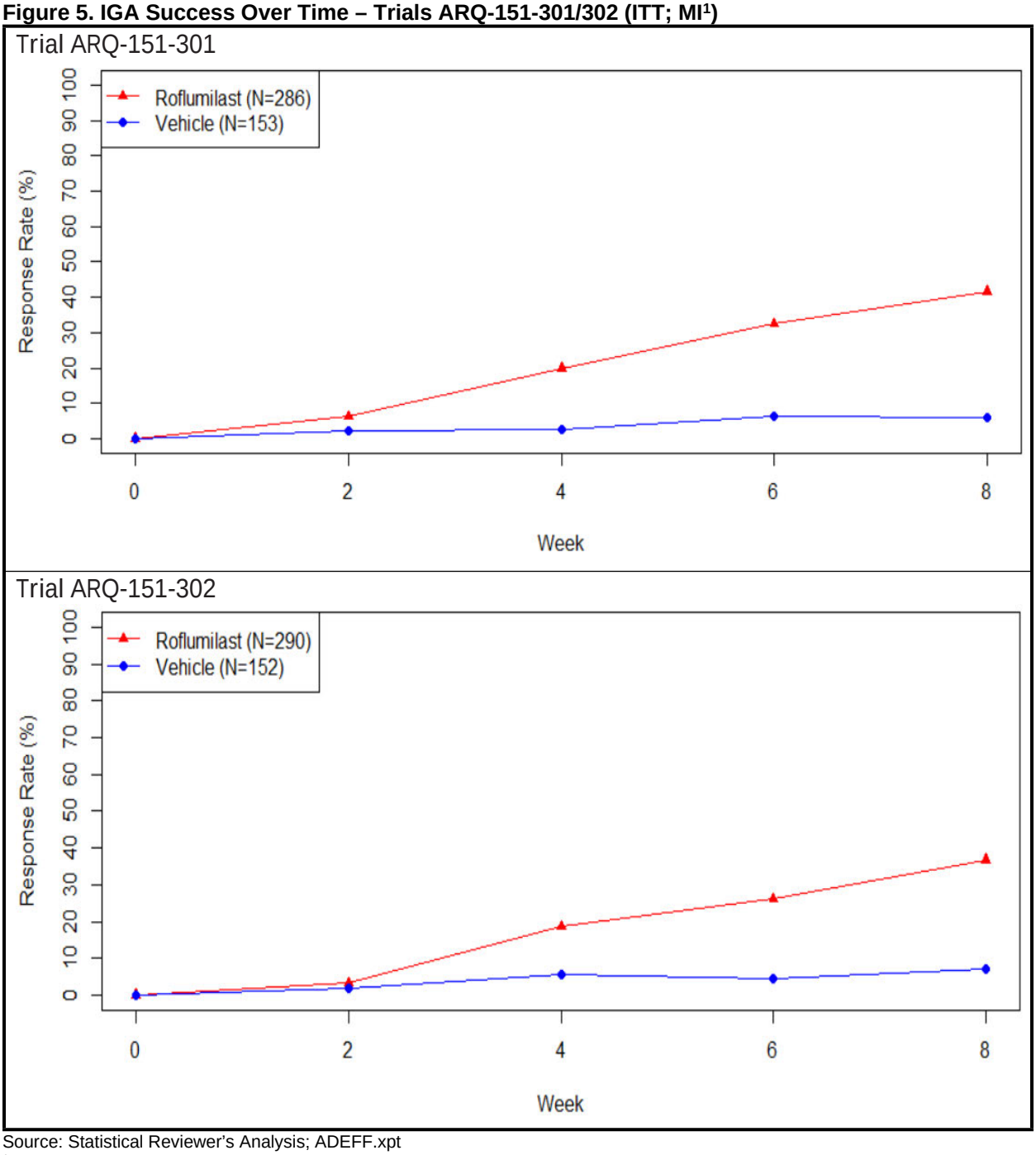
	Trial ARQ-151-301		Trial ARQ-151-302	
Absolute Change From Baseline in PSD Total Score at	**Roflumilast Cream, 0.3% (N=286)**	**Vehicle Cream (N=153)**	**Roflumilast Cream, 0.3% (N=290)**	**Vehicle Cream (N=152)**
Week 8				
Mean[2]	-48.9	-20.2	-45.8	-22.8
LS mean[3]	-49.2	-18.3	-48.8	-22.3
Difference (95% CI)[4]	-30.9 (-37.2, -24.6)		-26.5 (-33.3, -19.8)	
P-value[4]	<0.001		<0.001	
Week 4				
Mean[2]	-41.9%	-17.8	-40.7	-18.4
LS mean[3]	-42.5	-16.6	-41.9	-15.9
Difference (95% CI)[4]	-25.9 (-31.7, -20.0)		-26.0 (-31.9, -20.0)	
P-value[4]	<0.001		<0.001	

Source: Statistical Reviewer's Analysis; ADEFF.xpt
[1] Intent-to-treat (ITT) Population: all randomized subjects; the rates displayed are the averages over the imputed datasets.
[2] Average over the imputed datasets.
[3] LS mean based on ANCOVA with factors of site, baseline PSD score, baseline IGA (based on eCRF), and baseline intertriginous involvement (based on eCRF).
[4] Estimate, 95% CI, and p-value for the difference in LS means are based on ANCOVA with factors of site, baseline PSD score, IGA (based on eCRF), and baseline intertriginous involvement (based on eCRF).
Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; MI, multiple imputation; NRS, numeric rating scale; PSD, psoriasis symptom diary

Efficacy Over Time

Figure 5 presents the results for the IGA success (i.e., IGA score of 0 or 1 with at least a two-grade reduction from baseline) over time for Trials ARQ-151-301 and ARQ-151-302.

Figure 5. IGA Success Over Time – Trials ARQ-151-301/302 (ITT; MI[1])



Source: Statistical Reviewer's Analysis; ADEFF.xpt
[1] Intent-to-treat (ITT) Population: all randomized subjects; the rates displayed are the averages over the imputed datasets. IGA success is defined as a IGA score of 0 (clear) or 1 (almost clear) with at least a two-grade reduction from baseline.
Abbreviations: MI, multiple imputation

Findings in Special/Subgroup Populations

Age, Sex, Race, and Baseline Disease Severity

Table 24 presents the results for the primary efficacy endpoint (i.e., IGA score of 0 or 1 at Week 8 with at least 2-grade improvement) by age (<18, 18-64 and ≥65 years), sex, race (White, Black

or African American, Asian, Other) and baseline IGA score for Trial ARQ-151-301. The same results for Trial ARQ-151-302 are presented Table 25.

In both trials, the majority of subjects were White (approximately 82%) and adults less than 65 years of age (approximately 84%); therefore, it would be difficult to detect any differences in efficacy for the Non-White (i.e., Black of African American, Asian and Other) and subjects <18 or ≥65 years of age subgroups. For sex, the treatment effect was in general comparable between males and females in both trials. For baseline disease severity, treatment effect tended to be higher for subjects with moderate disease at baseline (i.e., IGA score of 3) in both trials; however, it should be noted that the sample size for the mild (IGA score of 2) and severe (IGA score of 4) disease was relatively small.

Table 24. IGA Success Rates at Week 8 by Age, Sex, Race and Baseline IGA Score – Trial ARQ-151-301 (ITT; MI[1])

Subgroups (n[ROFL], n[VEH])	Roflumilast Cream, 0.3% (N=286)	Vehicle Cream (N=153)	Difference (95% CI)
Age (years)			
<18 (4, 3)	50.0%	33.3%	16.7% (NA, NA)
18-64 (247, 125)	39.8%	6.3%	33.6% (25.7%, 41.4%)
≥65 (35, 25)	52.4%	<1%	52.0% (34.8%, 69.3%)
Sex			
Male (189, 96)	40.5%	6.0%	34.5% (25.6%, 43.4%)
Female (97, 57)	43.4%	5.5%	37.9% (26.1%, 49.8%)
Race			
White (234, 124)	42.9%	5.4%	37.5% (29.7%, 45.4%)
Black or African American (8, 8)	24.0%	0.0%	24.0% (-6.3%, 54.3%)
Asian (21, 11)	37.2%	0.5%	36.7% (14.4%, 59.0%)
Other (23, 10)	37.1%	21.3%	15.8% (-17.4%, 49.0%)
Baseline IGA			
Mild (51, 20)	17.8%	<1%	17.8% (6.4%, 29.1%)
Moderate (206, 122)	49.2%	6.5%	42.8% (34.3%, 51.2%)
Severe (29, 11)	28.3%	9.1%	19.2% (-4.5%, 43.0%)
Overall	**41.5%**	**5.8%**	**35.7% (28.5%, 42.8%)**

Source: Statistical Reviewer's Analysis; ADEFF.xpt
[1] Intent-to-treat (ITT) Population: all randomized subjects; the rates displayed are the averages over the imputed datasets.
Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; MI, multiple imputation; NA, not applicable; ROFL, roflumilast; VEH, vehicle

Table 25. IGA Success Rates at Week 8 by Age, Sex, Race and Baseline IGA Score – Trial ARQ-151-302 (ITT; MI[1])

Subgroups (n[ROFL], n[VEH])	Roflumilast Cream, 0.3% (N=290)	Vehicle Cream (N=152)	Difference (95% CI)
Age (years)			
<18 (7, 4)	14.3%	0.0%	14.3% (NA, NA)
18-64 (241, 131)	36.9%	7.4%	29.5% (21.3%, 37.6%)
≥65 (42, 17)	39.3%	6.1%	33.2% (14.3%, 52.1%)
Sex			
Male (176, 100)	39.1%	7.5%	31.6% (22.4%, 40.8%)
Female (114, 52)	32.9%	6.2%	26.7% (14.8%, 38.7%)

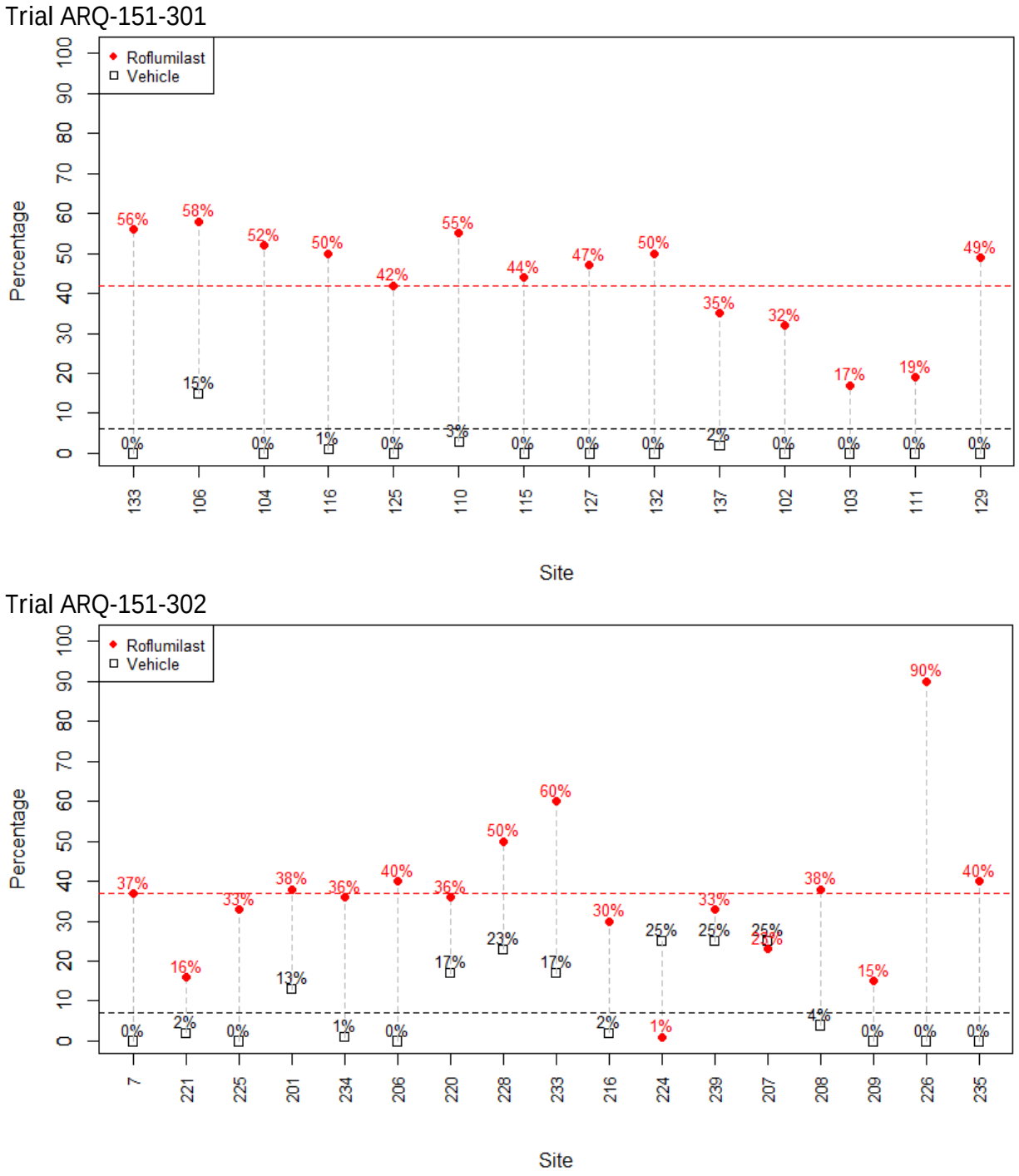
Subgroups (n[ROFL], n[VEH])	Roflumilast Cream, 0.3% (N=290)	Vehicle Cream (N=152)	Difference (95% CI)
Race			
White (240, 126)	36.1%	5.9%	30.3% (22.5%, 38.1%)
Black or African American (13, 3)	30.5%	1.3%	29.1% (-1%, 58.8%)
Asian (20, 9)	55.0%	13.3%	41.7% (9.4%, 74.0%)
Other (17, 8)	27.3%	25.0%	2.3% (-35.4%, 40.0%)
Baseline IGA			
Mild (50, 24)	13.1%	0.0%	13.1% (3.5%, 22.7%)
Moderate (220, 118)	43.5%	8.2%	35.3% (26.5%, 44.1%)
Severe (20, 10)	20.6%	10.8%	9.8% (-17.2%, 36.8%)
Overall	**36.7%**	**7.1%**	**29.6% (22.2%, 37.0%)**

Source: Statistical Reviewer's Analysis; ADEFF.xpt
[1] Intent-to-treat (ITT) Population: all randomized subjects; the rates displayed are the averages over the imputed datasets.
Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; MI, multiple imputation; NA, not applicable; ROFL, roflumilast; VEH, vehicle

Geographic Location (Investigational Site)

Trial ARQ-151-301 enrolled and randomized 439 subjects from 43 investigational sites in the United States and Canada. Trial ARQ-151-302 enrolled and randomized 442 subjects from 42 investigational sites in the United States and Canada. Figure 6 presents the results for the primary endpoint at Week 8 by investigational site in the ITT population for both clinical trials. The sites are ordered by total sample size from the left to the right. Due to the large number of sites, only the results for sites with at least 10 subjects are presented. Across the two trials, the treatment effect varied across the sites; however, this may be due to the relatively small sample sizes in many of the investigational sites. The response rate for roflumilast cream was higher than that for vehicle cream at all but two sites.

Figure 6. IGA Success Rates at Week 8 by Site - Trials ARQ-151-301/302 (ITT; MI[1])



Source: Statistical Reviewer's Analysis; ADEFF.xpt
[1] Intent-to-treat (ITT) Population: all randomized subjects; the rates displayed are the averages over the imputed datasets.
Note: 2 Dotted horizontal line denotes the overall result for each treatment group (red for roflumilast cream, black for vehicle cream).
Abbreviations: IGA, Investigator's Global Assessment; MI, multiple imputation

Review of Safety

Safety Review Approach

The safety evaluation of roflumilast cream, 0.3% QD for topical treatment of subjects with mild to severe chronic plaque psoriasis relied on safety data from two (pivotal) Phase 3 trials (ARQ-151-301/-302) included in the Phase 3 pool, one Phase 2b dose-ranging trial (ARQ-151-201 [excluding roflumilast 0.15% cream arm]) included in the VC pool [together with the Phase 3 trials -301/-302], two open-label long-term safety studies ARQ-151-202/-306 included in the LT, open-label pool, and four Phase 1 dermal safety studies (ARQ-151-108/-109/-110/-111).

The review of safety for roflumilast cream, 0.3% under NDA 215985 relied on the evaluation of pooled safety data from two Phase 3 randomized, double-blind, placebo-controlled trials (-301/-302) that comprised the Applicant's pivotal Phase 3 data pool in the ISS database, and shared identical inclusion/exclusion criteria, study designs, dosing regimen, and primary and secondary efficacy endpoints.

The VC pool (ARQ-151-201/-301/-302) included 1097 subjects, 881 of whom were also included in the Phase 3 pool; thus, the frequency of TEAEs reported in ≥1% of subjects treated with roflumilast cream, 0.3% were quite similar in both the Phase 3 pool and the VC pool (Refer to NDA Summary of Clinical safety (M. 2.7.4), Table 10).

The comparative analyses of the weighted EAIRs of TEAEs between the VC pool and the LT pool was used to assess the incidence of reported AEs for subjects exposed to roflumilast cream, 0.3% over time (Refer to NDA Summary of Clinical safety (M. 2.7.4), Table 9).

The results of dermal safety studies are discussed in a separate section of this review.

The safety population included all randomized subjects who used the study drug at least once. Of the 1097 subjects in the VC pool, 685 subjects received roflumilast with a mean number of drug applications of 59.2. In the LT pool, 598 subjects received roflumilast with a mean number of drug applications of 224.4.

To determine the safety profile of roflumilast cream, 0.3% for the treatment of mild to severe psoriasis, the review team analyzed the data for exposure, demographics, baseline characteristics, TEAEs [including severe TEAEs, SAEs, adverse events leading to discontinuation (AELD)], local tolerability assessments (by investigator [Berger and Bowman Scoring Scale] and by subject [burning/stinging]), directed physical examinations, clinical laboratory measurements (chemistry, hematology, urinalysis, and serum or urine pregnancy tests for female subjects of child-bearing potential), vital signs (blood pressure, heart rate, T) including weight (and baseline height), ECGs (excluding Phase 3 trials), and psychiatric and suicidality assessment (C-SSRS/ PHQ-8/Modified Patient Health Questionnaire-9 for Adolescents/Children's Depression Inventory 2). No adverse events of special interest were prespecified in the protocols.

Review of the Safety Database

Overall Exposure

Overall exposure to roflumilast in terms of frequency, duration and target population was adequate for the evaluation of safety.

In the VC pool, 621 (90.7%) subjects in the roflumilast group and 350 (85.0%) subjects in the vehicle group completed the trials (remaining subjects discontinued the trials). In the LT pool, 466 (77.9%) subjects completed, 120 (20.1%) subjects discontinued, and 12 (2.0%) subjects were continuing in the ongoing trials at the time of NDA submission.

The Demographic Characteristics of the VC pool at baseline were well-balanced across treatment groups and representative of the target population. Refer to Section 0 above 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 for the treatment of subjects with mild to severe plaque psoriasis. Safety assessments were reasonable and consistent with known adverse events for roflumilast in the target population:

- The size of safety database is adequate: A total of 1452 subjects (including 1057 subjects with psoriasis and 395 healthy subjects) received at least one dose of roflumilast cream 0.3%; of which 486 subjects treated for ≥24 weeks, 195 subjects treated for ≥52 weeks, and 41 subjects treated for ≥64 weeks.
- The total subject exposure to roflumilast cream, 0.3% in the VC and LT pools provides adequate data for the evaluation of safety. The Mean (SD) for the number of study drug applications were 59.2 (15.90) in the roflumilast arm and 59.7 (19.82) in the vehicle arm in the VC pool, and 224.4 (120.14) in the (open-label) roflumilast arm of the LT pool.
- The demographics of the study population are sufficiently representative of the target population as presented in Table 26.

Table 26. Demographic and Baseline Characteristics by Safety Data Pools (Safety Population)

Data Pool	Vehicle-Controlled Pool		Long-Term Pool
Treatment Arm	Roflumilast Cream, 0.3% (n=685)	Vehicle Cream (n=412)	Roflumilast Cream, 0.3% (N=598)
Age (years)			
Mean (SD)	48.0 (14.60)	49.9 (14.98)	51.4 (15.43)
Median	48.0	51.0	53.0
Minimum to maximum	6, 86	8, 89	6, 88
Sex, n(%)			
Male	421 (61.5)	262 (63.6)	340 (56.9)
Female	264 (38.5)	150 (36.4)	258 (43.1)

Data Pool	Vehicle-Controlled Pool		Long-Term Pool
Treatment Arm	Roflumilast Cream, 0.3% (n=685)	Vehicle Cream (n=412)	Roflumilast Cream, 0.3% (N=598)
Race, n(%)			
American Indian or Alaska native	4 (0.6)	3 (0.7)	1 (0.2)
Asian	49 (7.2)	25 (6.1)	32 (5.4)
Black or African American	33 (4.8)	24 (5.8)	44 (7.4)
Native Hawaiian or other Pacific Islander	5 (0.7)	1 (0.2)	3 (0.5)
White	556 (81.2)	340 (82.5)	492 (82.3)
Other/unreported	38 (5.5)	19 (4.6)	26 (4.3)
Ethnicity, n(%)			
Hispanic or Latino	164 (23.9)	109 (26.5)	124 (20.7)
Not Hispanic or Latino	520 (75.9)	303 (73.5)	473 (79.1)
Unknown/unreported	1 (0.1)	0	1 (0.2)
Weight (kg)			
Mean (SD)	91.5 (23.45)	92.9 (22.6)	92.3 (23.49)
Median	88.5	90.0	89.5
Minimum to maximum	18, 205	28, 187	18, 187
BMI (kg/m^2)			
Mean (SD)	31.7 (8.35)	32.6 (12.02)	32.1 (7.65)
Median	30.4	30.8	30.8
Minimum to maximum	14, 130	12, 175	13, 62
BSA(%)			
Mean (SD)	6.6 (4.53)	7.2 (4.61)	6.4 (4.42)
Median	5.0	6.0	5.0
Minimum to maximum	2, 20	2, 20	0, 30
Baseline IGA, n (%)			
Almost clear (1)	0	0	18 (3.0)
Mild (2)	118 (17.2)	55 (13.3)	130 (21.7)
Moderate (3)	510 (74.5)	328 (79.6)	410 (68.6)
Severe (4)	57 (8.3)	29 (7.0)	40 (6.7)

Source: adapted from NDA 215985, M 2.7.4 (SCS) Section 1.3.1, Tables 5, 6 (Pages 40, 42-43). Consistent with Clinical Reviewer's JMP Clinical 8.1 analysis.
Abbreviations: BMI, body mass index; BSA, body surface area; IGA, Investigator's Global Assessment; SD, standard deviation

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 cream, 0.3% for the treatment of mild to severe plaque psoriasis. 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 were recorded from the time the informed consent was signed. TEAEs were AEs that occurred after the first administration of the study drug. TEAEs

were followed up to 1 month (at the Investigator's discretion) until resolved or deemed clinically stable in all psoriasis trials, or (for local dermal safety studies in healthy subjects) until TEAEs resolved or subjects resumed care under their primary care physician. TEAEs were documented at each study visit (in person or by telephone) 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 23.0. 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 included in the VC and LT safety data pools, 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 toxicity grading scale 5-point severity scale [Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), and Grade 5 (death)].

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

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

The Applicant's assessment of adverse events conducted for the VC and LT safety data pools 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) at screening, baseline, Week 4 (and week 8 in trial -301/-302, week 12 in trial -201) visits for the VC data pool; and at screening, Day 1, weeks 4, 12, 24 (and weeks 36, 52 in trial -202) visits for the LT data pool. Laboratory assessments were not conducted for Dermal Safety studies (ARQ-151-108/ -109/ -110, -111).

Safety Results

Deaths

No deaths were reported in clinical trials of the roflumilast cream development program.

Serious Adverse Events

In the Phase 3 data Pool, SAEs were reported in 2/576 (0.3%) subjects in the roflumilast group and 2/305(0.7%) subjects in the vehicle group. In the VC data pool, SAEs were reported for 3 subjects (2.7/100 patient years of exposure [PYE]) in the roflumilast cream, 0.3% and 4 subjects (5.5/100 PYE) in the vehicle group. In the LT open-label pool, SAEs were reported for 15 subjects (3.8/100 PYE) treated with roflumilast cream, 0.3%.

Four(4) subjects treated with the vehicle cream in the VC data pool reported the following SAEs: basal ganglia infarction (1), Abortion spontaneous (1), plasma cell myeloma (1), and cervical radiculopathy (1).

In both the VC pool and the LT data pools, the investigators assessed all SAEs in roflumilast-treated subjects as not related to the study drug (or unlikely related to the study drug in 1 subject (b) (6). No PTs were reported as an SAE in >1 subject (or in >1% of subjects in any group) or were included in the category of AEs typically associated with the PDE-4 inhibitors class. The following subjects in the roflumilast cream, 0.3% treatment groups were reported with SAEs in the VC and LT data pools:

Table 27. Serious Adverse Events in Subjects Treated With Roflumilast Cream, 0.3% in the Vehicle-Controlled (VC) and Open-Label Long-Term (LT) Data Pools

Study/Subject ID/ Age (Years)/Sex	PT(s)	Severity	Outcome	Action taken
VC Pool				
(b) (6)	Chest pain	Severe	Recovered/resolved	Dose unchanged
	Concussion	Moderate	Recovered/resolved	Dose unchanged
	Foot fracture, deformity thorax, pneumothorax	Severe, life-threatening	Recovered/resolved	Drug interrupted
LT Pool				
(b) (6)	Myocardial Infarction, Hyponatremia	Severe, mild	Recovered/resolved	Drug interrupted
	Alcohol withdrawal syndrome	severe	Recovered/resolved	Dose unchanged
	Atrioventricular block	severe	Recovered/resolved	Not applicable
	SARS-COV-2 test positive	severe	Not recovered/not resolved	Drug interrupted
	Ileus, Urinary retention; Gastrointestinal Carcinoma	Moderate, severe	Recovered/resolved; Not recovered/not resolved	Drug discontinued
	Cardiac Failure Congestive	severe	Recovered/resolved	Drug discontinued
	Rectal cancer	severe	Not recovered/not resolved	Drug discontinued
	Transient ischemic attack, Cerebrovascular accident	severe	Recovered/resolved, Not recovered/not resolved	Not applicable
	Femur fracture; sepsis, acute kidney injury	severe	Recovering/resolving; Recovered/resolved	Drug discontinued
	Lung neoplasm malignant	severe	Not recovered/not resolved	Drug discontinued
	Supraventricular tachycardia	moderate	Recovered/resolved	Dose unchanged
	Device failure	severe	Recovered/resolved with sequelae	Drug interrupted
	Polycythemia Vera	severe	Recovering/resolving	Drug interrupted
	COVID-19 pneumonia	severe	Recovered/resolved	Dose unchanged
	Palpitation, Dehydration, Syncope	severe	Recovered/resolved	Drug interrupted

Source: Adapted from NDA 215985, M. 2.7.4, Tables 14-17. Consistent with Clinical Reviewer's JMP Clinical 8.1 analysis.
Abbreviations: COVID-19, Coronavirus Disease 2019; SARS-COV-2, severe acute respiratory syndrome coronavirus 2

Dropouts and/or Discontinuations Due to Adverse Effects

In the Phase 3 data Pool, AELDs were reported with similar frequency for 6/576 (1.0%) subjects in the roflumilast group and 4/305(1.3%) subjects in the vehicle group.

In the VC data pool, AELDs were reported with similar frequency for 7 subjects (6.0/100 PYE) in the roflumilast group and 7 subjects (9.8/100 PYE) in the vehicle group. The only AELDs reported in >1 subjects were Application site urticaria (2) in the roflumilast group and Application site dermatitis (2) in the vehicle group. The following AELDs were reported for 1 subject each in the roflumilast group: Psoriasis, Depression, Gastroenteritis, Application site dryness/pruritus/folliculitis, alanine aminotransferase/aspartate aminotransferase increased, nausea/dizziness, and SARS-COV-2 test positive.

In the open-label LT data pool, AELDs were reported for 14 subjects (3.6/100 PYE) treated with roflumilast cream. The only PT reported as an AELD in >1 subject were Psoriasis (2), and Pulmonary mass (2). Three subjects reported malignancy-related AELDs (gastrointestinal carcinoma, lung neoplasm malignant, and rectal cancer; all considered severe intensity and unrelated to study drug). Three subjects reported AELDs (urticaria, weight increased, and application site irritation) considered as mild in severity and possibly/probably/likely related to study drug by the investigators.

Significant Adverse Events

The Applicant proactively assessed the frequency of Depression and Weight Decrease in clinical trials of roflumilast cream because oral PDE-4 inhibitors (roflumilast and apremilast) have been associated with increased frequency of Psychiatric and Gastrointestinal AEs. Diarrhea, Nausea, and Insomnia are proposed by the Applicant as Adverse Drug Reactions of the roflumilast cream.

Psychiatric AEs

In the Phase 3 data pool, AEs for the SOC of Psychiatric disorders were reported in 13 (2.3%) subjects in the roflumilast group compared to 2 (0.7%) subjects in the vehicle group. Insomnia was reported in 8 (1.4%) subjects in the roflumilast group compared to 2 (0.7%) of subjects in the vehicle group; and is the only AE in the SOC of Psychiatric disorders which was considered by the Applicant as an Adverse Reaction of the roflumilast cream. Anxiety and Depression were reported in 3 (0.5%) and 2 (0.3%) subjects respectively in the roflumilast group, compared to 0 subjects each in the vehicle group.

In the VC and LT data pools, the reported frequency of AEs of anxiety and depression were low. The reported frequencies of AEs in the SOC of Psychiatric disorders decreased overtime, based on comparison of their respective EAIRs between the VC and LT pools, as summarized in Table 28.

Table 28. Frequency of AEs in SOC Psychiatric Disorders in Vehicle-Controlled and Long-Term Open-Label Pools

Data Pool	Vehicle-Controlled Pool		Long-Term Open-Label Pool
SOC: Psychiatric Disorders- Preferred Term	Roflumilast Cream, 0.3% (N=685) n (EAIR/100 PYE)	Vehicle Cream (N=412) n (EAIR/100 PYE)	Roflumilast Cream, 0.3% (N=598) n (EAIR/100 PYE)
Insomnia	10 (8.6)	2 (3.2)	4 (1.0)
Anxiety	3 (2.5)	1 (1.2)	4 (1.0)
Depression	3 (2.7)	1 (1.2)	4 (1.0)

Source: Adapted from NDA 215985, ISS Tables 14.3.3.1 and 14.3.3.2. Consistent with OCS SPS and Clinical Reviewer's analysis.
Abbreviations: AEs, adverse events; EAIRs, exposure adjusted subject incidence rate; PYE, patient-years of exposure; SOC, system organ class

In the VC pool, no suicidal ideation or behavior were reported based on the C-SSRS. In the LT pool, one subject (b) (6) reported suicidal ideation [subject's enrollment was a protocol deviation because of a prior history of suicidal ideation and ongoing treatment for depression, and the AE was considered unrelated to study drug], and one subject (b) (6) reported a non-suicidal self-injurious behavior at Week 4 [PHQ-8 depression severity of none to minimal at baseline/duration of the trial, no AEs reported].

Gastrointestinal AEs

Diarrhea and nausea are two AEs in the SOC of Gastrointestinal disorders considered by the Applicant as Adverse Drug Reaction for the roflumilast cream.

In the Phase 3 data pool, Diarrhea was reported in 18 (3.1%) subjects in the roflumilast group compared to 0 subjects in the vehicle group. Nausea was reported in 7 (1.2%) subjects in the roflumilast group compared to 1 (0.3) subject in the vehicle group.

In the VC data pool, Diarrhea was reported for 19 subjects in the roflumilast cream, 0.3% group (18 mild, 1 moderate, 0 severe), occurred early (in the first 3 weeks of treatment), none reported as SAE or AELD, and the reported outcome was resolved (18) or resolving (1). No Diarrhea was reported in vehicle group. Nausea was reported for 8 subjects in the roflumilast cream, 0.3% group [compared to 1 subject in the vehicle group] including (5 mild, 3 moderate, 0 severe), no SAE, 1 AELD, 3 study drug interruptions, 2 not recovered/not resolved AEs, 1 recovering/resolving AE.

In the LT data pool, Diarrhea was reported for 9 subjects in the roflumilast group (6 mild, 3 moderate, 0 severe), none reported as SAE or AELD, study drug interruptions (2), and outcome as resolved (9). Nausea was reported for 4 subjects in the roflumilast group (3 mild, 1 moderate, 0 severe), including none reported as SAE or AELD, study drug interruptions (1), and outcome as resolved/recovered (3).

The reported frequencies of Diarrhea and Nausea decreased overtime, based on comparison of their respective EAIRs between the VC and LT pools, as summarized in Table 29.

Table 29. Frequency of AEs in SOC Gastrointestinal Disorders in Vehicle-Controlled and Long-Term Open-Label Pools

Data Pool	Vehicle-Controlled Pool		Long-Term Open-label Pool
SOC: Gastrointestinal Disorders- Preferred Term	Roflumilast Cream, 0.3% (N=685) n (EAIR/100 PYE)	Vehicle Cream (N=412) n (EAIR/100 PYE)	Roflumilast Cream, 0.3% (N=598) n (EAIR/100 PYE)
Diarrhea	19 (15.8)	0	9 (2.3)
Nausea	8 (6.8)	1 (1.6)	4 (1.0)

Source: Adapted from NDA 215985, ISS Tables 14.3.3.1 and 14.3.3.2. Consistent with OCS SPS and Clinical Reviewer's analysis.
Abbreviations: AEs, adverse events; EAIRs, exposure adjusted subject incidence rate; PYE, patient-years of exposure; SOC, system organ class

Weight Decrease

In the Phase 3/VC data pools respectively, at Week 8, the mean (SD) change from baseline in weight was -0.80 (2.171) kg/-0.68 (2.226) kg in the roflumilast group compared with 0.15 (2.227) kg/0.11 (2.100) kg in the vehicle group.

In the LT data Pool, the mean (SD) change from baseline in weight were -0.33 (1.327) kg (Week 2), -0.95 (3.623) kg (Week 24/28), and -0.82 (4.353) kg at week 48/52.

In general, the mean changes from baseline in subjects' weights were not considered clinically significant.

In the Phase 3/VC data Pools, most subjects maintained stable body weights at Week 8. One subject in each group reported (intentional) weight loss (≥10% from baseline) as a result of intentional diet or lifestyle modifications. At Week 8, the rate of clinically significantly weight loss (≥5% from baseline) was 23/576 (4.0%) in the roflumilast group [20/576 (3.5%) intentional] compared to 7/305 (2.3%) in the vehicle group [6/305 (2.0%) intentional].

In the LT data pool, weight loss (≥10% from baseline) was reported for 5/368 (1.4%) of subjects [4/5 intentional] at Week 24/28, and 5/254 (2.0%) of subjects [4/5 intentional]at Week 48/52. Weight loss (≥5% from baseline) was reported for 35/368 (9.5%) of subjects [25/35 intentional] at Week 24/28, and 34/254 (13.4%) of subjects [28/34 intentional] at Week 48/52.

In general, a similar proportion of subjects in each group reported comparable percent weight gains as weight loss.

In the Phase 3 and VC data pools, no AE (PT: Weight decreased) was reported in any subject. In the LT data pool, 6 subjects reported Weight decreased (4 mild, 1 moderate, 1 severe) with 2/4 mild AEs were considered related to the study drug.

One AE of Weight decreased was reported as severe (non-SAE, AELD) in 1 subject in the LT data pool (Subject (b) (6)). The Subject was a 64-year-old male with a history of anemia and hematochezia at baseline. At Week 12 of the LT Study -202, subject's weight decreased by 4.1 kg (5%) from baseline (82.1 kg), and reported anemia (Grade 3, hemoglobin

9.5 g/dL). At Week 13, subject's weight (77.1 kg) decreased by 5 kg (6.1%) from baseline. The investigator considered the AE of weight decreased unlikely related to study drug, and as ongoing. Subject discontinued study drug and withdrew from the study.

Pregnancy

Two subjects reported pregnancies in the clinical trials of roflumilast cream.

- Roflumilast group- Subject (b) (6) (not reported as a TEAE)
  - A 27-year-old female subject with (-) serum/urine pregnancy tests at screening/baseline used condoms/spermicide for contraception. A (+) pregnancy test led her to withdraw from the study on Day 28. The pregnancy was medically confirmed and a healthy male baby was delivered via induced vaginal delivery. No abnormalities, complications, or AEs were reported for the mother or the baby.
- Vehicle group- Subject (b) (6)
  - A 30-year-old female subject withdrew from the Trial due to pregnancy on Day 56 of treatment with vehicle cream. The pregnancy outcome was reported as an SAE of spontaneous abortion 37 days after early withdrawal from the study.

Severe (Grade 3) AEs

In the Phase 3 data pool, severe AEs were reported in 9/576 (1.6%) subjects in the roflumilast group compared to 8/305 (2.6%) subjects in the vehicle group. In the VC data pool, severe AEs were reported in 11/685 (9.4/100 PYE) subjects in the roflumilast group and 9/412 (13.8/100 PYE) subjects in the vehicle group. In the LT open-label data pool, severe AEs were reported in 29/598 (7.4/100 PYE) subjects in the roflumilast group.

Treatment Emergent Adverse Events and Adverse Reactions

For the Phase 3 Data Pool, the incidence of TEAEs were 147/576 (25.5%) in the roflumilast group, compared to 64/305 (21%) in the vehicle group. The PTs reported as TEAEs in ≥1% of subjects treated with roflumilast (and more frequently than in the vehicle group) included diarrhea, headache, insomnia, nausea, application site pain, upper respiratory tract infection, and urinary tract infection (with similar results reported for the VC pool) as summarized in Table 30.

Table 30. TEAEs (by PT) Occurring in ≥1% of the Subjects in Roflumilast Group and at a Higher Frequency Compared to Vehicle Group in the Phase 3 Trials and the Vehicle-Controlled Trials (Safety Population)

Data Pool	Phase 3 Pool		Vehicle-Controlled Pool	
Preferred Term	Roflumilast Cream, 0.3% (N=576) n (%)	Vehicle Cream (N=305) n (%)	Roflumilast Cream, 0.3% (N=685) n (weighted%)	Vehicle Cream (N=412) n (weighted%)
Diarrhoea	18 (3.1)	0	19 (2.7)	0
Headache	14 (2.4)	3 (1.0)	15 (2.1)	3 (0.8)
Insomnia	8 (1.4)	2 (0.7)	10 (1.5)	2 (0.5)
Nausea	7 (1.2)	1 (0.3)	8 (1.2)	1 (0.3)
Application site pain	6 (1.0)	1 (0.3)	8 (1.2)	4 (0.8)
Upper respiratory tract infection	6 (1.0)	1 (0.3)	14 (2.3)	1 (0.3)
Urinary tract infection	6 (1.0)	2 (0.7)	6 (0.8)	3 (0.7)

Source: NDA 215985 Submission (Module 2.7.4, Table 10, Page 50), consistent with Clinical Reviewer's JMP Clinical 8.1. analysis (TRT01A, PIVOTFL='Y' or VEHICLFL = 'Y').
For the VC Pool, Incidence is based on the weighted average incidence from each study in the pool. Weight is the proportion of sample size in each study.
Abbreviations: PT, preferred term; TEAEs, treatment-emergent adverse events

Comparison of the reported frequencies of the TEAEs of diarrhea, headache, insomnia, nausea, application site pain, upper respiratory tract infection, and urinary tract infection over time based on the weighted EAIRs demonstrated lower incidence for each of these TEAEs in the open-label LT pool compared to the VC pool, as summarized in Table 31.

Table 31. Summary of EAIR for Vehicle-Controlled and Long-Term Open-Label Pools for TEAEs Occurring in ≥1% of the Subjects in the Roflumilast Group in the Phase 3 Pool

Data Pool	Vehicle-Controlled Pool		Long-Term Open-Label Pool
Preferred Term	Roflumilast Cream, 0.3% (N=685) n (EAIR/100 PYE)	Vehicle Cream (N=412) n (EAIR/100 PYE)	Roflumilast Cream, 0.3% (N=598) n (EAIR/100 PYE)
Diarrhoea	19 (15.8)	0	9 (2.3)
Headache	15 (12.5)	3 (4.7)	8 (2.0)
Insomnia	10 (8.6)	2 (3.2)	4 (1.0)
Nausea	8 (6.8)	1 (1.6)	4 (1.0)
Application site pain	8 (7.0)	4 (5.0)	3 (0.8)
Upper respiratory tract infection	14 (13.1)	1 (1.6)	23 (5.9)
Urinary tract infection	6 (4.9)	3 (4.3)	13 (3.3)

Source: NDA 215985 Submission. Modified from Module 2.7.4 (Table 9, Page 48) and ISS Tables 14.3.3.1/14.3.3.2, consistent with OCS SPS Reviewer analysis.
Abbreviations: EAIRs, exposure adjusted subject incidence rate; PYE, patient-years of exposure; SOC, system organ class; TEAEs, treatment-emergent adverse events

Adverse Drug Reactions

For the Phase 3 pool, adverse drug reactions (ADRs; defined as possibly, probably, or likely related to the study drug) occurred in 23/576 (4.0%) subjects in the roflumilast group, compared to 11/305 (3.6%) subjects in the vehicle group. For the VC pool, ADRs occurred in 30/685 (4.5%) and 18/412 (4.2%) of subjects in the roflumilast and vehicle groups, respectively. For the LT pool, ADRs occurred in 13/598 (2.2%) subjects treated with roflumilast.

Laboratory Findings

Specimens for laboratory tests, including hematology, chemistry, urinalysis, and serum/urine pregnancy test were collected at the following timepoints:

- Trials -301/-302: screening, baseline, Week 4, and week 8 (end of trial [ET]) visits
- Trial -201: screening, baseline, Week 4, (urine pregnancy test at W 8), and Week 12 (ET) visit
- Study -202: screening, Day 1, Weeks 4, 12, 24, 36, 52 (ET)
- Study -306: screening, Day 1, Weeks 4, 12, 24 (ET)

For the Phase 3 and VC data pools, 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; and the proportion of subjects with clinically significant values for each laboratory parameter was <1% in each group. Similar results were reported for the roflumilast group in the LT data pool.

Vital Signs

For the Phase 3 data pool, mean (SD) changes from baseline to Week 8 for roflumilast group compared to vehicle group were -0.8 (11.19) versus -0.8 (12.36) mm Hg in systolic blood pressure, -0.7 (7.74) versus -0.5 (7.68) mm Hg in diastolic blood pressure, 1.8 (10.72) versus 0.8 (10.41) beats per minute in heart rate, and -0.01 (0.397) versus -0.03 (0.390) (°C) in Temperature, respectively.

The changes from baseline to week 8 in vital signs were small and not clinically significant. Results for the VC and LT data pools were similar to results for the Phase 3 data pool.

Electrocardiograms

ECG data were not collected in Phase 3 studies of roflumilast cream, 0.3%. ECG data were collected in the Phase 1 MUsT (ARQ-151-107), the Phase 1/2a study (ARQ-151-101), the Phase 2b study (ARQ-151-201), and the Phase 2 long-term open-label study (ARQ-151-202).

At the EOP2 meeting on 11/5/2019, the Agency agreed that ECG data collection would not be required for Phase 3 trials based on no evidence for an adverse effect on any ECG variable in the Phase 2b study.

QT

The Agency waived the requirement for a thorough QT study for roflumilast cream, 0.3% in an Advice letter dated 2/3/2020, based on the thorough QT study previously conducted with oral roflumilast, existing nonclinical and clinical cardiovascular safety data for the oral formulation, and the pharmacokinetics and safety profile to date of ARQ-151 cream.

Immunogenicity

Not applicable to roflumilast cream, 0.3% drug product.

Analysis of Submission-Specific Safety Issues

Refer to Section 0 of this review (significant adverse events) for a discussion of safety assessments of the AEs typically associated with (oral) PDE-4 inhibitors class (Weight decrease, Psychiatric AEs, and Gastrointestinal AEs).

Clinical Outcome Assessment Analyses Informing Safety/Tolerability

In addition to safety assessments for TEAE, clinical laboratory, physical examinations, weight, vital signs, and psychiatric assessments (PHQ-8/-A, C-SSRS); local safety and tolerability assessments (by investigator [Berger and Bowman Scoring Scale] and by subject [burning/ stinging]) were conducted for the Trials in the VC data pool (at baseline, weeks 4, 8, and 12 for Trial -201) and on Day 1, weeks 4, 12, 24, (and weeks 36, 52 for Trial -202) for Trials in the LT data pool. Local safety and tolerability assessments used the following scoring scales:

Table 32. Local Safety and Tolerability Assessments Scoring Scales

Investigator's (Berger and Bowman) Scoring Scale			
Score	**Definition**	**Score**	**Definition**
Dermal Response		**Other Effects**	
0	No evidence of irritation	A	Slight glazed appearance
1	Minimal erythema; barely perceptible	B	Marked glazing
2	Definite erythema, readily visible; or minimal edema; or minimal papular response	C	Glazing with peeling and cracking
3	Erythema and papules	D	Glazing with fissures
4	Definite edema	E	Film of dried serous exudates
5	Erythema, edema, and papules	F	Small petechial erosions and/or scabs
6	Vesicular eruption	G	No other effect
7	Strong reaction spreading beyond test site		
Subject Local Tolerability Assessment			
Grade	**Sensation Following Investigational Product Application**		
0 (none)	No sensation		
1 (mild)	Slight warm, tingling sensation; not really bothersome		
2(moderate)	Definite warm, tingling sensation that is somewhat bothersome		
3 (severe)	Hot, tingling/stinging sensation that has caused definite discomfort		

Source: NDA 215985 Submission. Modified from Module 2.7.4 (Tables 118, 119, Page 236)

Local Safety Assessment by Investigators

For the VC data pool, the proportion of subjects reported with a score of 0 at baseline and at weeks 4, 8, and 12 were 99.7%, 99.0%, 98.7%, and 99% respectively for the roflumilast group. Similar proportion of subjects in the roflumilast and vehicle groups respectively for each score between 0 to 3 were reported at the same timepoints. A similarly low score pattern was reported for subjects in the long-term studies -306 and -202 (up to week 64).

One subject (b) (6) in the roflumilast group was reported with a score of 5 at week 4 with improvement to a score of 2 (B: marked glazing) at Week 8. This subject reported a local tolerability score of at Week 4 and a score of 0 at Week 8. No AEs were reported for this subject.

Local Tolerability Assessment by Subjects

For the VC data pool, the proportion of subjects reported with a score of 0 at baseline and at weeks 4, 8, and 12 were 77.3%, 88.5%, 94.3%, and 95.6% respectively for the roflumilast group. Similar proportion of subjects in the roflumilast and vehicle groups respectively for each score between 0 to 3 were reported at the same timepoints. A score of >1 was reported for <1% of subjects in the roflumilast group at weeks 4, 8, and 12. Subjects' local tolerability assessments were not included in the long-term studies -202 and -306.

Reviewer's comment: This reviewer agrees with the Applicant's conclusion that the results of the local safety and tolerability assessments showed low scores and were similar between the roflumilast and vehicle treatment groups. This is consistent with findings from the Provocative Dermal Safety studies for this product.

Safety Analyses by Demographic Subgroups

The Applicant conducted safety analyses based on age category, sex, race (per 21 CFR 314.50 (d)(5)(vi)(a)), ethnicity, and baseline disease characteristics (IGA, BSA).

In general, the results indicated that there were no substantial differences in the risk of TEAEs in demographic subgroups. No trends were reported for severe TEAEs, AELDs, or AEs considered to be related to the study drug by the Applicant. However, because the trials were not powered for these analyses, the data must be interpreted with caution. TEAEs by demographic subgroups are presented below.

TEAEs by Age Group

Three (3) of the 4 subjects <12 years of age enrolled in the Phase 3 and VC data pools were treated with roflumilast and reported no AEs. One (1) of the 4 subjects <12 years of age in the LT Studies reported a Grade 1 Application site irritation, likely related to roflumilast, which led to discontinuation from Study.

For the Phase 3 data 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:

- 12 years ≤ age <18 years: 2/8 (25%) versus 0/6
- 18 years ≤ age <65 years: 127/495 (25.7%) versus 52/262 (19.8%)
- 65 years ≤ age: 18/70 (25.7%) versus 11/36 (30.6%)

Most AEs were Grade 1 (mild) to Grade 2 (moderate) in severity. A similar severity pattern for AEs were reported for the VC and the LT data pools.

Reviewer's comment: The Age subgroup analysis was not powered for safety analyses, and because of small number of subjects in the age groups <18 years or >65 years of age, no meaningful conclusions may be drawn by comparing the incidence of AEs between these age subgroups.

This reviewer agrees with the following conclusion by the Applicant: "These data do not suggest differences in the safety profile of roflumilast cream 0.3% by age group."

TEAEs by Gender

For the Phase 3 data 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: 87/365 (23.8%) versus 40/196 (20.4%)
- Female: 60/211 (28.4%) versus 24/109 (22.0%)

Most AEs were Grade 1 (mild) to Grade 2 (moderate) in severity. A similar severity pattern for AEs were reported for the VC and the LT data pool. For the LT data pool, a higher proportion of female subjects 119/258 (46.1%) compared to male subjects 114/340 (33.5%) treated with roflumilast were reported with AEs.

Reviewer's comment: The Gender subgroup analysis was not powered for safety analyses, and no meaningful conclusions may be drawn by comparing the incidence of AEs between the male and female subgroups. For the LT data pool, the absence of a control group does not allow for a meaningful interpretation of a higher frequency of AEs in female subjects (46.1%) compared to male subjects (33.5%).

*This reviewer agrees with the foll*owing conclusion by the *Applicant: "These data do not suggest any differences between the sexes in the safety profile of roflumilast cream 0.3%."*

TEAEs by Race

For the Phase 3 data 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:

- White: 123/474 (25.9%) versus 49/250 (19.6%)
- Black: 4/21 (19.0%) versus 4/17 (23.5%)
- Asian: 13/41 (31.7%) versus 5/20 (25.0%)
- Other Race: 7/40 (17.5%) versus 6/18 (33.3%)

Most AEs were Grade 1 (mild) to Grade 2 (moderate) in severity. A similar severity pattern for AEs were reported for the VC and the LT data pools.

Reviewer's comment: The Race subgroup analysis was not powered for safety analyses, and no meaningful conclusions may be drawn by comparing the incidence of AEs between the racial groups.

This reviewer agrees with the following conclusion by the Applicant: "These data do not suggest differences in the safety profile of roflumilast cream 0.3% by race."

TEAEs by Ethnicity

For the Phase 3 data pool, the following proportion of subjects in each Ethnicity group were reported with a TEAE for the roflumilast group compared to the vehicle group, respectively:

- Hispanic or Latino: 36/139 (25.9%) versus 15/84 (17.9%)
- Not Hispanic or Latino: 111/436 (25.5%) versus 49/221 (22.2%)

Most AEs were Grade 1 (mild) to Grade 2 (moderate) in severity. A similar severity pattern for AEs were reported for the VC and the LT data pools. For the LT data pool, a higher proportion of Not Hispanic or Latino subjects 206/473 (43.6%) compared to Hispanic or Latino subjects 26/124 (21.0%) treated with roflumilast were reported with AEs.

Reviewer's comment: The Ethnicity subgroup analysis was not powered for safety analyses, and no meaningful conclusions may be drawn by comparing the incidence of AEs between the Hispanic or Latino and Not Hispanic or Latino subgroups. For the LT data pool, the absence of a control group does not allow for a meaningful interpretation of a higher frequency of AEs in the Not Hispanic or Latino subjects (43.6%) compared to the Hispanic or Latino subjects (21.0%).

This reviewer agrees with the following conclusion by the Applicant: "These data do not suggest any differences in the safety profile of roflumilast cream 0.3% by ethnicity."

TEAEs by Baseline IGA

The Phase 3 data pool included 145 subjects with mild (IGA =2), 666 subjects with moderate (IGA =3), and 70 subjects with severe (IGA =4) at baseline.

For the Phase 3 data 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 (IGA =2): 28/101 (27.7%) versus 10/44 (22.7%)
- Moderate (IGA =3): 113/426 (26.5%) versus 50/240 (20.8%)
- Severe (IGA =4): 6/49 (12.2%) versus 4/21 (19.0%)

Most AEs were Grade 1 (mild) to Grade 2 (moderate) in severity. A similar severity pattern for AEs were reported for the VC and the LT data pools.

For the LT data pool, the frequency of AEs reported based on baseline IGA category [6/18 (33.3%) for almost clear (IGA =1), 49/130 (37.7%) for Mild (IGA =2), 169/410 (41.2%) for moderate (IGA =3), and 9/40 (22.5%) for severe (IGA =4)] did not suggest a pattern.

Reviewer's comment: The baseline IGA subgroup analysis was not powered for safety analyses, and no meaningful conclusions may be drawn by comparing the incidence of AEs between baseline IGA subgroups. For the LT data pool, the absence of a control group, as well as the small number of subjects in the Almost clear (IGA =1) and Severe (IGA =4) categories, does not allow for a meaningful interpretation of a lower frequency of AEs reported for the Severe (IGA =4) group.

This reviewer agrees with the following conclusion by the Applicant: "There were no meaningful differences between the baseline IGA groups in any data pool."

TEAEs by Baseline BSA

The Phase 3 data pool included 379 subjects with BSA <5%, 328 subjects with 5% ≤ BSA ≤10%, and 174 subjects with BSA >10% affected by psoriasis at baseline.

For the Phase 3 data pool, the following proportion of subjects in each BSA group were reported with a TEAE for the roflumilast group compared to the vehicle group, respectively:

- BSA <5%: 67/265 (25.3%) versus 31/114 (27.2%)
- 5% ≤ BSA ≤10%: 51/207 (24.6%) versus 19/121 (15.7%)
- BSA >10%: 29/104 (27.9%) versus 14/70 (20.0%)

Most AEs were Grade 1 (mild) to Grade 2 (moderate) in severity. A similar severity pattern for AEs were reported for the VC and the LT data pools.

For the LT data pool, the frequency of AEs reported based on baseline BSA category [106/273 (38.8%) for BSA <5%, 96/236 (40.7%) for 5% ≤ BSA ≤10%, and 31/89 (34.8%) for BSA >10%] were similar.

Reviewer's comment: The baseline BSA category subgroup analysis was not powered for safety analyses, and no meaningful conclusions may be drawn by comparing the incidence of AEs between baseline BSA subgroups.

This reviewer agrees with the following conclusion by the Applicant: "The overall incidence of AEs was not decreased in the BSA <5% group or increased in the BSA >10% group."

Specific Safety Studies/Clinical Trials

Dermal Safety and Photosafety Studies

The Applicant conducted 4 dermal safety and photosafety studies for roflumilast cream, 0.3%. In general, the number of subjects enrolled and the design and conduct of these studies were consistent with the typical requirements for dermal safety studies.

Refer to the Table 12in Section 0 of this review for further details of the dermal safety studies. A summary of the results of the dermal safety studies are presented below.

ARQ-151-108 (Human Repeat Insult Patch Test)

Of the 244 subjects enrolled, 205 completed the study. Two (2) subjects (0.8%) reported mild AEs of contact dermatitis (related to tape) and discontinued study; and 203 subjects had a negative sensitization reaction at challenge and rechallenge; 2 subjects (1%) had a positive sensitization (or irritation) reaction to both roflumilast cream, 0.3% and vehicle cream at challenge and rechallenge. No significant differences in cumulative irritancy potential between roflumilast cream 0.3%, the vehicle cream, and 0.9% saline were reported during the induction period.

The Applicant concluded that repeated topical applications of roflumilast cream 0.3% to the skin of healthy human subjects was well-tolerated and showed a low frequency (1%) of contact sensitization under the (exaggerated) occlusive or semi-occlusive conditions for patch applications in this study.

ARQ-151-109 (Cumulative Irritation Patch Test)

Of the 45 subjects enrolled, 40 completed the study. No AEs were reported during the study. The mean cumulative irritancy scores reported was low and the same (0.1) for the roflumilast cream 0.3%, vehicle cream, and the 0.9% saline negative control; compared to 2.8 for the sodium lauryl sulfate positive control 0.2%.

The total cumulative irritancy scores reported for roflumilast cream 0.3%, vehicle cream, and the 0.9% saline negative control were low (2.6, 3.0 and 1.1, respectively); compared to 59.1 for the sodium lauryl sulfate 0.2% positive control.

The Applicant concluded that repeated topical applications of roflumilast cream 0.3% to the skin of healthy human subjects was well-tolerated under the (exaggerated) occlusive or semi-occlusive patch applications.

ARQ-151-110 (Phototoxicity)

All 35 subjects enrolled completed the study. No AEs were reported during the study. All edema scores in the study were negative (numerical score of 0).

On Day 2, the combined mean response score for erythema and edema was 0.1 for all 4 treated sites, irrespective of irradiation, and (0) for the untreated control site.

On Days 3 and 4, results were similar between the 3 irradiated sites. On Day 4, the combined mean response score for erythema and edema was (0.3) for each of the 3 irradiated sites (roflumilast cream, 0.3%, vehicle cream, and untreated control), with a mean response score of (0) for both nonirradiated sites (roflumilast cream, 0.3% and vehicle cream).

The Applicant concluded that under the conditions of this study, a single application of roflumilast cream 0.3% or its vehicle cream followed by light exposure did not show phototoxic potential.

ARQ-151-111 (Photoallergy)

Of the 71 subjects enrolled, 51 completed the study. One (1) subject reported an AE of COVID-19 and was discontinued from the study. A 7-week extension of the rest period between the Induction and Challenge phases of this study occurred because of the study site closure related to the COVID-19 pandemic. Per Applicant, this was not considered to affect the validity of this Photoallergy study based on the scientific rationale and the judgement of the investigator.

During the Induction phase, all 49 subjects (100%) experienced at least 1 erythema reaction (score of 1) on irradiated sites, regardless of which study intervention was applied. For non-irradiated sites, 11 subjects (22.4%) had at least 1 erythema reaction for both roflumilast cream 0.3% and vehicle cream sites. No subject experienced an edema reaction (all scores =0).

During the Challenge phase, for irradiated sites, similar number of subjects had an erythema reaction on the roflumilast cream and untreated control sites (9 subjects [40.4%] each), and 20 subjects [42.6%] on the vehicle cream site. No subjects experienced an edema reaction on any of the roflumilast cream 0.3% sites, or the untreated irradiated control site.

The Applicant concluded that there was no clinically significant potential for photo irritation for the roflumilast cream 0.3% and vehicle cream applied to healthy skin with or without irradiation; and no photosensitivity reactions to roflumilast cream 0.3% or its vehicle cream occurred after topical application in healthy human subjects followed by light exposure under the controlled conditions in this study.

Reviewer's comment: This reviewer agrees with the Applicant's conclusions that roflumilast cream, 0.3% and its vehicle cream did not show a clinically significant potential for skin irritation or sensitization under the exaggerated conditions of the above dermal safety studies; and irritancy, sensitization, phototoxicity, and Photoallergy were unlikely to be clinically significant for the proposed daily topical applications of the roflumilast cream, 0.3%.

Additional Safety Explorations

Not applicable to roflumilast cream, 0.3% drug product.

Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Roflumilast cream, 0.3% has not been marketed in any country, and there are no postmarketing safety data available.

Expectations on Safety in the Postmarket Setting

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

Integrated Assessment of Safety

The safety profile of roflumilast cream, 0.3% was adequately characterized during the drug development program. The primary review of safety of the drug product for topical treatment of mild to severe plaque psoriasis relied on the evaluation of pooled safety data from 881 subjects enrolled in two Phase 3 Trials (ARQ-151-301/-302) which were identical in design, trial population, dosing regimen, and key primary and secondary endpoints. Eligible subjects were randomized in a 2:1 ratio to receive roflumilast cream or vehicle cream once daily for 8 weeks.

Additionally, the Applicant submitted safety data from a 12-week, Phase 2 randomized, double-blind, placebo-controlled dose-ranging Trial (ARQ-151-201) in adult subjects with plaque psoriasis, and safety data for (roll-over and de novo) subjects treated with roflumilast cream, 0.3% in two open-label, long-term safety studies (ARQ-151-202/-306) of 52 weeks and 24 weeks duration, respectively.

Supportive safety data from four Phase 1, provocative dermal safety/photosafety studies demonstrated only a low sensitization potential (1.0%) in subjects treated with roflumilast cream.

No deaths were reported during any clinical trials of roflumilast cream, 0.3%.

For Phase 3 Trials ARQ-151-301/-302, the following safety results were reported:

- SAEs were reported in 0.3% of subjects treated with roflumilast cream compared to 0.7% of subjects treated with the vehicle cream. None of the SAEs were deemed by the investigators to be related to roflumilast cream.
- AELDs were reported with similar frequency of 1.0% for subjects treated with roflumilast cream compared to 1.3% for subjects treated with the vehicle cream.
- TEAEs were reported in 25.5% of subjects treated with roflumilast cream compared to 21% of subjects treated with the vehicle cream. The PTs reported as TEAEs in ≥1% of subjects treated with roflumilast cream (and at a higher frequency than reported in subjects treated with the vehicle cream) included diarrhea (3.1% versus 0), headache (2.4% versus 1.0%), insomnia (1.4% versus 0.7%), nausea (1.2% versus 0.3%), application site pain (1.0% versus 0.3%), upper respiratory tract infection (1.0% versus 0.3%), and urinary tract infection (1.0% versus 0.7%) for subjects treated with roflumilast cream compared to the vehicle cream, respectively.
- Severe AEs were reported in 1.6% of subjects treated with roflumilast cream compared to 2.6% of subjects treated with the vehicle cream.

- ADRs: Adverse Drug Reactions (possibly, probably, or likely related to the study drug) were reported in 4.0% of subjects treated with roflumilast cream compared to 3.6% of subjects treated with the vehicle cream.
- PDE-4-related AEs: Psychiatric or Gastrointestinal-related AEs were reported at significantly lower frequencies for subjects treated with the roflumilast cream compared to subjects treated with oral PDE-4 inhibitors. Suicidal ideation and behavior was not reported, and weight decrease in subjects treated with roflumilast cream was not clinically significant.
- Local safety and tolerability assessments by investigators and by subjects demonstrated low scores and were similar in subjects treated with roflumilast cream or the vehicle cream.
- The long-term, open-label safety studies demonstrated a general trend of a lower frequency of occurrence of AEs over time, based on their EAIRs.

The available data from the Phase 3 Trials demonstrated that roflumilast cream, 0.3% was safe in the treatment of subjects ≥12 years of age with plaque psoriasis. Postmarketing risk management will include professional labeling and routine pharmacovigilance. Three (3) Pediatric Research Equity Act (PREA) PMRs will be issued for roflumilast cream, 0.3%.

120-Day Safety Update

Per 21 CFR 314.50(d)(5)(vi)(b), the Applicant submitted a 120-Day Safety Update Report (SDN 10 dated 21 January 2022). The review team identified no new safety signals in the safety update report.

Statistical Issues

There were no major statistical issues affecting the overall conclusions. The treatment effect was generally consistent across endpoints and analysis populations. The results for the primary efficacy endpoint of IGA success at Week 8 for the two pivotal trials (301 and 302) show that roflumilast cream, 0.3% was statistically superior to vehicle cream (p-values <0.001), with slightly, higher treatment effect is observed in Trial 301 compared to Trial 302. The Applicant's analyses considered the stratification factors using the data as collected in the (IVRS despite discrepancies with the values in the eCRF database (<10%); however, the statistical reviewer considered the actual baseline values (i.e., based on eCRF) in efficacy analyses. The results between Applicant's and reviewer's analysis were very similar.

The magnitude of missing data at Week 8 was slightly higher in the vehicle arm compared to the roflumilast arm in both trials (14% versus 10% for roflumilast versus vehicle, respectively).

In addition to establishing efficacy for the primary endpoint, the results from the two clinical trials also supported treatment of psoriasis in the intertriginous areas. For the two trials there were 22% and 19% of randomized subjects, respectively, with I-IGA score ≥2 at baseline. In both trials, roflumilast cream, 0.3% was statistically superior to vehicle cream (p-values <0.001) for this I-IGA success at Week 8. Furthermore, the results from the two trials supported

improvement of 4 points in WI-NRS score at Week 4 and Week 8 for the subjects who had WI-NRS score ≥4 at baseline (see results in Section 0).

There were no substantial differences in efficacy among subgroups. In terms of handling missing data, the magnitude of missing data at Week 8 was slightly higher in the vehicle arm compared to the roflumilast arm in both trials (14% versus 10% for roflumilast versus vehicle, respectively). Roflumilast cream, 0.3% was statistically superior to vehicle cream across the various methods for handling the missing data, even in the extreme case of 'worst case scenario'.

Conclusions and Recommendations

To establish the safety and efficacy of roflumilast cream, 0.3% in the treatment of plaque psoriasis, the Applicant submitted data from two adequate and well-controlled, randomized (2:1), double-blind, vehicle-controlled, parallel-group, identically-designed Phase 3 Trials (ARQ-151-301 and ARQ-151-302) [-301/-302, respectively]. Subjects applied roflumilast cream, 0.3% once daily to affected areas for 8 weeks. Trials -301/-302 enrolled a total of 881 subjects ≥2 years of age with mild to severe plaque psoriasis [BSA involvement of 2% to 20% (excluding scalp, palms, and soles); an IGA score of 2 (mild), 3 (moderate), or 4 (severe); and a PASI score of ≥2] at baseline. Trials -301/-302 evaluated the primary endpoint of "IGA success", defined as an IGA score of 0 ("clear") or 1 ("almost clear") and a ≥2-point improvement from baseline, at Week 8.

Secondary efficacy endpoints (intended for labeling) included "I-IGA success" (defined as a score of (0) "Clear" or (1) "Almost Clear" and a ≥2-grade improvement from baseline [in subjects with a baseline I-IGA ≥2 score]) at Week 8, and WI-NRS success (defined as a ≥4-point improvement in WI-NRS pruritus score from baseline [in subjects with a baseline NRS ≥4 score]) at Weeks 8, 4, and 2.

In both Trials -301/-302, roflumilast cream, 0.3%, was superior to the vehicle cream (41.5% versus 5.8% [p-value<0.001] and 36.7% versus 7.1% [p <0.001], respectively) for the primary efficacy endpoint of IGA success at Week 8. The results for the secondary efficacy endpoints were in alignment with the results for the primary efficacy endpoint. Efficacy data submitted by the Applicant demonstrated that roflumilast cream, 0.3%, is effective for its intended use in the target population.

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

The Applicant submitted safety data from 1097 subjects who participated in the vehicle-controlled Trials (-301, -302, and ARQ-151-201) and 598 subjects who participated in the open-label, LT safety Studies (ARQ-151-202 and ARQ-151-306 [ongoing]) to support the safety of

roflumilast cream, 0.3% for topical treatment of plaque psoriasis. In the Phase 3 Trials (-301 and -302) safety data pool, the most frequently reported adverse events were Diarrhea (3.1%), Headache (2.4%), Insomnia (1.4%), Nausea (1.2%), Application site pain (1.0%), Upper respiratory tract infection (1.0%), and Urinary tract infection (1.0%).

The safety results reported in the open-label, LT safety Studies (-202/-306) in the LT safety data pool were consistent with the safety results reported in the Phase 3 Trials and the vehicle-controlled Trials safety data pools; with a trend for decreasing frequencies of reported AEs over time for treatment beyond 8 weeks.

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

Advisory Committee Meeting and Other External Consultations

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

Additionally, roflumilast 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.

Pediatrics

Because roflumilast cream, 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 plaque psoriasis in pediatric patients unless this requirement is waived, deferred, or inapplicable.

In an Agreed iPSP letter (5/20/2020), the Agency agreed with the Applicant's plan to request a waiver for pediatric subjects between ages of 0 to <2 years of age (because necessary studies are impossible or highly impracticable), no request for deferral of pediatric studies, and inclusion of pediatric subjects between ages of 2 to <18 years of age in the Phase 3 clinical effectiveness and safety studies.

At the time of the NDA submission (9/29/2021), the Applicant submitted safety data for 14 pediatric subjects (between 12 and <18 years of age) and 4 pediatric subjects (between 2 to <12 years of age) enrolled in the Phase 3 Trials (ARQ-151-301/-302); and safety data for 12 pediatric subjects (12 to <18 years of age) and 4 pediatric subjects (between 2 to <12 years of age) enrolled in the LTS Study ARQ-151-306.

Although a relatively small number of pediatric subjects between 12 to <18 years of age were included in the Phase 3 and LTS Studies, the safety data for this age group was deemed to be adequate for inclusion of this age group in the Applicant's INDICATIONS AND USAGE Section of the proposed label, "topical treatment of plaque psoriasis in patients 12 years of age and older" at the time of the NDA Approval.

The Applicant plans to request a deferral to conduct clinical studies in pediatric subjects between 2 to <12 years of age (adult studies are completed and ready for approval), which deviates from the Agreed iPSP.

The Applicant's PREA Waiver/Deferral/Pediatric Plan request was presented and discussed at the Pediatric Review Committee (PeRC) meeting (on 19 July 2022). The PeRC agreed with the Division's recommendation to grant a partial waiver to subjects under 2 years of age, and a deferral for subjects between 2 to <12 years of age; and agreed with the Division's recommendation for issuing the three PMRs outlined in Section 0 of this review.

Labeling Recommendations

Prescription Drug Labeling

Prescribing Information

The Applicant submitted proposed prescribing information (PI), patient package insert (PPI; also known as patient information), container labels and carton labeling for Zoryve (roflumilast) cream, 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.

Madhuri R. Patel, PharmD from the Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed PI, PPI, carton and container labeling for Zoryve and identified areas for improvement. The DMEPA reviewer noted that the Applicant had implemented all DMEPA recommendations regarding the container labels and carton labeling (Review in DARRTS on 7/5/2022).

Other Prescription Drug Labeling

The Applicant submitted a patient information (PPI and instructions for use) for Zoryve (roflumilast) cream, 0.3%. The Division of Medical Policy Programs and the Office of Prescription Drug Promotion reviewed and provided comments to ensure consistency with the PI and clarity of the concepts and language of the patient labeling. Refer to the Patient Labeling Review by Ruth Mayrosh, PharmD and Laurie Buonaccorsi, PharmD (dated 6/1/2022).

The final labeling will reflect all recommendations from the review teams.

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.

Postmarketing Requirements and Commitment

The following three (3) PREA PMRs to conduct the following studies will be issued to the Applicant:

Study Protocol ARQ-151-215 (Ongoing)

An Open Label, 4-Week, Phase 2, Maximal Usage Pharmacokinetics and Safety Study of ARQ-151 Cream 0.3% Administered QD in 20 Pediatric Subjects (ages 6 to 11 years old) with Plaque Psoriasis. (b) (4)

Final Report Submission: December 2022 (estimate)

Study Protocol ARQ-151-216 (Ongoing)

An Open Label, 4-Week, Phase 2, Maximal Usage Pharmacokinetics and Safety Study of ARQ-151 Cream 0.3% Administered QD in 10 Pediatric Subjects (ages 2 to 5 years old) with Plaque Psoriasis. (b) (4)

Final Report Submission: December 2022 (estimate)

Study Protocol ARQ-151-306 (Ongoing)

A Phase 3, multicenter, open-label extension study of the long-term safety of ARQ-151 cream 0.3% in subjects (≥2 years of age) with chronic plaque psoriasis. (b) (4)

Final Report Submission: June 2025 (estimate)

Division Director (DPT-II) Comments

Not applicable.

Division Director (OCP) Comments

Division Director (OB) Comments

Division Director (Clinical) Comments

I concur with the review team's recommendation for approval of Zoryve (roflumilast cream, 0.3%) for the topical treatment of plaque psoriasis, including treatment in the intertriginous areas, in patients 12 years of age and older.

Roflumilast is a small molecule phosphodiesterase-4 inhibitor. An oral formulation of roflumilast, Daliresp (NDA 022522), was approved in 2011 to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and history of exacerbations. The Applicant for Zoryve has obtained a right to refer to relevant clinical, nonclinical and CMC information submitted in the Daliresp NDA.

Effectiveness of roflumilast was demonstrated in two identical randomized (2:1), double-blind, vehicle-controlled Phase 3 clinical trials (ARQ-151-301 and ARQ-151-302) where subjects with plaque psoriasis applied investigational product once daily to affected areas for 8 weeks. The primary endpoint was IGA success, defined as an IGA score of 0 (clear) or 1 (almost clear) and $\geq$2 point improvement from baseline, measured at Week 8. In both trials, roflumilast cream was superior to vehicle cream for IGA success (see Section 0 of this review). The treatment effect was generally consistent across endpoints and analysis populations. Results of intertriginous

IGA success (Week 8) and improvement in Worst Itch NRS score (Weeks 4 and 8) supported effectiveness of roflumilast.

The Applicant submitted safety data from 1097 subjects who participated in the vehicle-controlled Trials (-301, -302, and ARQ-151-201) and 598 subjects who participated in the open-label, long term safety Studies (ARQ-151-202 and ARQ-151-306 [ongoing]). In the pooled Phase 3 trials (-301 and -302), the most frequently reported adverse events (≥1% incidence in Zoryve and greater than vehicle treatment) were diarrhea (3.1%), headache (2.4%), insomnia (1.4%), nausea (1.2%), application site pain (1.0%), upper respiratory tract infection (1.0%), and urinary tract infection (1.0%). Analysis of the Phase 3 pooled safety database did not identify significant safety signals that impact approvability.

Based on the efficacy and safety data, Zoryve (roflumilast cream, 0.3%) has an acceptable risk-benefit profile and offers an alternative treatment option in patients with mild to severe plaque psoriasis. Additional data in pediatric subjects will be requested via PMR (see Section 0).

Office Director (or Designated Signatory Authority) Comments

Appendices

References

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Nassr, N, A Huennemeyer, R Herzog, O von Richter, R Hermann, M Koch, K Duffy, K Zech, and G Lahu, 2009, Effects of rifampicin on the pharmacokinetics of roflumilast and roflumilast N-oxide in healthy subjects, Br J Clin Pharmacol, 68(4):580-587.

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 cream. 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-151-301/-302, which provided the primary data to establish effectiveness and safety of this product. Refer to Section 0 of this review for the trial designs. The Applicant provided the following disclosures for significant payments of other sorts from the Applicant of the covered study [21 CFR 54.4 (a)(3) (ii), 54.2 (f)]:

- [redacted] participated in Trials ARQ-151-201/-202/-301/-306. Dr. [redacted] reported receiving $60,000 per year from Arcutis Biotherapeutics, Inc. for consulting fees on his financial disclosure form for each study he participated in as a clinical investigator. The following steps were taken to minimize the potential for bias:
  - Per request of the Institutional Review Board (IRB), [redacted], MD served as the principal investigator and Dr. [redacted] served as a sub-investigator for all studies he participated in as a clinical investigator.
  - Per request of the IRB, the following language was added to informed consent forms: 'Dr. [redacted] (a Sub-Investigator in this study) receives financial compensation as a consultant for Arcutis, Inc. (the study sponsor and developer of the ARQ-151 Cream being investigated in this study). If you have questions about paid relationships that your physician/researcher may have, we encourage you to talk to him or her or check for industry relationships posted on individual faculty pages on our website at [redacted]
  - The Applicant's clinical regulatory team reviewed the disclosure and, because of multiple clinical sites participation, clinical site monitoring, and randomized subject assignments (studies ARQ-151-201/-301), did not require any additional steps for the clinical investigator to participate in the studies.

- [redacted] participated in Trials ARQ-151-201/-202/-301/-306. Dr. Stewart reported the following details of a positive financial interest of equity in the Applicant on his financial disclosure forms for each study he participated in as a clinical investigator:

Table 33. Details of Financial Interest by Clinical Investigator [redacted]

Study Number	Number of Shares[a]	Stock Price	Value
ARQ-151-201	200,000	$3.0956	$619,120
ARQ-151-202	200,000	$3.0956	$619,120
ARQ-151-301	200,000	$5.8148	$1,162,960
ARQ-151-306	99,964[b]	$17.00	$1,699,388

[a] Series A preferred stock held in a revocable trust
[b] Share reduction due to stock split; no shares were sold

The following steps were taken to minimize the potential for bias:
- Per request of the IRB, the following language was added to informed consent forms: "Your Study Doctor owns significant stock with the Sponsor of this study."
- The Applicant's clinical regulatory team reviewed the disclosure and, because of multiple clinical sites participation, clinical site monitoring, and randomized subject assignments (studies ARQ-151-201/-301), did not require any additional steps for the clinical investigator to participate in the studies.

The Applicant adequately disclosed financial interests involving clinical investigators. Because the number of investigators with financial disclosures was limited (2) and assessments were

blinded (for Trials ARQ-151-201/-301/-302), the strategies employed by the Applicant to minimize potential bias arising from investigator financial interests/arrangements appear reasonable.

Covered Clinical Study (Name and/or Number): ARQ-151-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 143		
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): 2		
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: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): ARQ-151-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 119		
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: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)

Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): ARQ-151-201

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 74		
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): 2		
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: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Nonclinical Pharmacology/Toxicology

Review of the 2-Year Dermal Carcinogenicity Study Report

Table 34. Study ARQ-151: A 104-Week Dermal Oncogenicity Study In Mice Details

Parameter	Details
Study no.:	2621-013
Study report location:	SDN 1, NDA 215985
Conducting laboratory and location:	(b) (4)
Date of study initiation:	05/31/2018
GLP compliance:	Yes
Drug, lot #, and % purity:	ARQ-151 vehicle cream, lot# GLP-0095-02F13, GLP-0095-04F03, GLP-0095-04F05, and GLP-0095-04F09 ARQ-151 0.15% cream, lot# GLP-0095-02F15, GLP-0095-04F01, GLP-0095-04F06, and GLP-0095-04F10 ARQ-151 0.5% cream, lot# GLP-0095-02F12, GLP-0095-04F02, GLP-0095-04F07, and GLP-0095-04F11 ARQ-151 1.0% cream, lot# GLP-0095-02F16, GLP-0095-04F04, GLP-0095-04F08, and GLP-0095-04F12
Prior ECAC dose concurrence:	Yes
Basis for dose selection	Maximum feasible dose

Abbreviations: ECAC, Executive Carcinogenicity Assessment Committee; GLP, good laboratory practice

Reviewer Carcinogenicity Conclusion: Negative
ECAC Carcinogenicity Conclusion: Negative

Tumor Findings

A complete tissue list was examined for vehicle control group and high dose group. Targe tissues and gross lesions were examined for the rest of the groups. In male mice, statistical significance was achieved in the incidence of malignant bronchiolar alveolar carcinoma in the trend test if it is classified as a rare tumor, and in pairwise comparison tests of vehicle control versus low dose (if it is classified as a rare tumor), vehicle control versus high dose, and vehicle control versus untreated control. However, as the highest tumor incidence was noted in the untreated control group, such finding is not considered of biological significance. In addition, bronchiolar alveolar adenoma/carcinoma are not considered rare tumors.

In female mice, statistical significance was achieved in the incidences of benign harderian gland adenoma, benign bronchiolar alveolar adenoma, and benign ovarian sex-cord stromal tumor in the trend tests if these tumor types are classified as rare tumors. However, no statistical significance was achieved in pairwise comparison tests for these tumor types. These findings are not considered biologically significant.

Overall, there were no biologically significant test article-related neoplastic findings in either sex.

Table 35. Methods for Study ARQ-151

Method	Details
Doses:	For both males and females: 0 (untreated control), 0 (vehicle control), 0.15%, 0.5%, and 1.0% ARQ-151 cream (applied at 2 mL/kg; 3, 10, and 20 mg/kg/day ARQ-151)
Frequency of dosing:	Once daily, to ~10% BSA
Dose volume:	2 mL/kg
Route of administration:	Dermal, unoccluded
Formulation/Vehicle:	Clinical vehicle
Species/Strain:	CD-1 mouse
Number/Sex/Group:	60/sex/group
Age:	~8 weeks at the start of dosing
Comment on study design and conduct:	Animals were individually housed in solid bottom cages.
Dosing comments	None
Dosing solution analysis	Not conducted by the contract lab. The test articles were directly provided by the sponsor.

Abbreviations: BSA, body surface area

Observations and Results

Mortality

Per the statistical reviewer's analysis, there were no significant treatment-related findings in mortality in either males or females.

Table 36. Survival at the End of Study ARQ-151

		Group 1 (Untreated)	Group 2 (Vehicle)	Group 3 (Low Dose)	Group 4 (Mid Dose)	Group 5 (High Dose)
Male	Survival number	27	26	28	30	20
	Survival rate	45%	43%	47%	50%	33%
Female	Survival number	20	21	23	22	21
	Survival rate	33%	35%	38%	37%	35%

Source: NDA 215985 submission, nonclinical reviewer analysis

Clinical Signs

There were no significant treatment-related clinical signs.

Dermal Observations

There were no significant treatment-related dermal observations at the administration sites.

Body Weights

Body weight was measured weekly for the first 14 weeks, biweekly for the next 14 weeks, and every 4 weeks thereafter. A decrease in body weight was noted in high dose males at the end of treatment (-7.4% and -9.1% compared with vehicle and untreated controls, respectively).

Feed Consumption

Food consumption was measured weekly for the first 14 weeks, biweekly for the next 14 weeks, and every 4 weeks thereafter. There were no significant treatment-related effects on food consumption.

Gross Pathology

There were no significant treatment-related findings.

Histopathology

Peer Review: Yes
Historical Control Provided for Tumor Incidence: Not provided

Neoplastic

A complete tissue list was examined for vehicle control group and high dose group. Targe tissues and gross lesions were examined for the rest of the groups. The tumor incidence data were analyzed by the Agency statistical reviewer. A dose-response relation test (trend test) was conducted across the vehicle control group, low, mid, and high dose groups. Pairwise comparison tests were conducted for untreated control group and three dose groups against the vehicle control group. A Poly-k method was used for the data analysis (k =3).

According to the FDA guidance for statistical design and data analysis of carcinogenicity studies, significance levels of α =0.01 for common tumors and α =0.05 for rare tumors (with a background incidence rate of 1% or less) for both dose response relation test and multiple pairwise comparisons were used for this study.

Per Agency nonclinical statistical analysis, the tumor types with p-values less than or equal to 0.05 for dose response relationship and/or pairwise comparisons are shown in Table 37.

Table 37. Summary Table of Tumor Types With P-Values ≤0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Naïve/Vehicle Control Group in Mice

		Vehicle (VC)	Low (L)	Mid (M)	High (H)	Naïve (NC)
		0 mg	3 mg	10 mg	20 mg	0 mg
Organ Name	Tumor Name	P - Trend	P - VC vs. L	P - VC vs. M	P - VC vs. H	P - VC vs. NC
Male						
Lung	Adenoma, Bronchiolar Alveolar, Benign	8/60 (45) 0.5737	12/60 (47) 0.2589	7/60 (47) 0.7440	9/60 (44) 0.4793	9/60 (48) 0.5590
	Carcinoma, Bronchiolar Alveolar, Malignant	2/60 (45) 0.0124@	10/60 (49) 0.0200@	6/60 (46) 0.1405	12/60 (44) 0.0031$	16/60 (51) 0.0006$
	Adenoma/Carcinoma, Bronchiolar Alveolar	10/60 (46) 0.0617	18/60 (50) 0.0945	11/60 (47) 0.5225	19/60 (45) 0.0302@	25/60 (51) 0.0046$
Female						
Harderian Glands	Adenoma, Benign	2/60 (43) 0.0474@	1/60 (44) 0.8836	4/60 (42) 0.3267	5/60 (42) 0.2068	5/60 (43) 0.2166
Lung	Adenoma, Bronchiolar Alveolar, Benign	6/60 (43) 0.0388@	8/60 (45) 0.4222	7/60 (43) 0.5000	13/60 (44) 0.0660	11/60 (45) 0.1647
Ovaries	Sex-Cord/Stromal Tumor, Benign	3/60 (43) 0.0118@	3/60 (45) 0.6834	3/60 (42) 0.6507	9/60 (42) 0.0534	3/60 (42) 0.6507

Source: Agency nonclinical statistical review
& X/ZZ (YY): X = number of tumor bearing animals; YY = mortality weighted total number of animals; ZZ = unweighted total number of animals observed
$ = Statistically significant at 0.01 level in common tumor for test of pairwise comparisons
@ = Not statistically significant at 0.01 level in common tumor for test of dose response relationship or at 0.01 level in common tumor for test of pairwise comparisons;

In male mice, statistical significance was achieved in the incidence of malignant bronchiolar alveolar carcinoma in the trend test if it is classified as a rare tumor (p =0.0124), and in pairwise comparison tests of vehicle control versus low dose (if it is classified as a rare tumor, p =0.02), vehicle control versus high dose (p =0.0031), and vehicle control versus untreated control (p =0.0006). However, as the highest tumor incidence was noted in the untreated control group, such finding is not considered of biological significance. In addition, bronchiolar alveolar adenoma/carcinoma are not considered rare tumors.

In female mice, statistical significance was achieved in the incidence of benign harderian gland adenoma in the trend test if it is classified as a rare tumor (p =0.0474), in the incidence of benign bronchiolar alveolar adenoma in the trend test if it is classified as a rare tumor (p =0.0388), and in the incidence of benign ovarian sex-cord stromal tumor in the trend test if it is classified as a rare tumor (p =0.0118). However, no statistical significance was achieved in pairwise comparison tests for these tumor types. Usually for a neoplastic finding considered to be biologically significant, statistical significance should be achieved in both the trend test and pairwise comparison test. These findings are not considered biologically significant.

Overall, there were no biologically significant test article-related neoplastic findings in either sex.

Non-Neoplastic

Ovarian sex-cord stromal hyperplasia was noted in mid dose and high dose females. Vehicle-related epidermal hyperplasia was present in treated skin sites at all treatment groups in both sexes.

Discussion and Conclusion

Topical doses of 0 (untreated control), 0 (vehicle control), 0.15%, 0.5%, and 1.0% roflumilast cream (applied at 2 mL/kg/day) were tested in CD-1 mouse in this 2-year dermal carcinogenicity study. The tested doses were recommended by the ECAC based on the maximum feasible dose. There was no significant treatment-related effect on mortality. There were no biologically significant test article-related neoplastic findings in this study. Roflumilast cream up to 1.0% was not carcinogenic when administered topically to mice once daily for 2 years.

Multiples of Human Exposure Calculation

The multiples of human exposure based on area under the concentration-time curve (AUC) comparison between the no-observed adverse effect levels (NOAELs) identified in pivotal toxicology studies and the clinical dose tested in a maximum use clinical PK study (ARQ-151-107) are calculated.

In the clinical PK study ARQ-151-107, roflumilast cream 0.3% was applied once daily for 2 weeks to adolescent subjects with psoriasis involving at least 10% body surface area (BSA) and adult subjects with psoriasis involving at least 20% BSA. The mean BSA was 27% in adult subjects and 13% in adolescent subjects. The mean topical doses were 27.5 and 12.3 mg/day roflumilast in adult and adolescent subjects, respectively. The mean AUC_{last} values at Day 15 were 72.7 and 25.1 ng•hr/ml for roflumilast and 628 and 140 ng•hr/ml for roflumilast N-oxide, in adult and adolescent subjects, respectively.

Multiples of human exposure for NOAELs identified in chronic toxicology studies are shown in Table 38.

Table 38. Multiples of Human Exposure for NOAELs in Chronic Toxicology Studies

Study	Route	NOAEL (mg/kg/day)	AUC (ng•hr/ml)	Multiples of Human Exposure* (AUC Comparison)
6-month mouse study	Oral	4	153	2
6-month rat study	Oral	0.8	35	0.5
12-month dog study	Oral	0.6	510	7
10-month monkey study	Oral	0.25	205	2.8
9-month minipig study	Dermal	20	329	4.5

Source: NDA 215985 submission. Nonclinical reviewer analysis.
*Compared to the mean AUC_{last} value for roflumilast at Day 15 in adult subjects (72.7 ng•hr/ml) in the maximum use clinical PK study ARQ-151-107
Abbreviations: AUC, area under the concentration-time curve; NOAEL, no-observed adverse effect level

For labeling purposes, the multiples of human exposure shown in the approved Daliresp label were calculated based on mg/m^2 dose comparison of roflumilast for reproductive toxicology

studies and AUC comparison (based on summed AUC values of roflumilast and its metabolites) for carcinogenicity studies. Per the Daliresp label, while roflumilast is three times more potent than roflumilast N-oxide at inhibition of the PDE4 enzyme in vitro, the plasma AUC of roflumilast N-oxide on average is about 10-fold greater than the plasma AUC of roflumilast in humans.

The maximum recommended human oral dose under NDA 22522 is 0.5 mg/day, with $AUC_{0\text{-}24hr}$ values of 33.7 and 375 ng•hr/ml in humans for roflumilast and roflumilast N-oxide, respectively. The Applicant stated that the human dermal dose of roflumilast tested in adults in the maximum use clinical PK study is 27.5 mg/day (~9 g 0.3% cream), with $AUC_{0\text{-}24hr}$ values of 72.7 and 628 ng•hr/ml in humans for roflumilast and roflumilast N-oxide, respectively, which were 2.2 times and 1.7 times the corresponding $AUC_{0\text{-}24hr}$ values at the oral dose of 0.5 mg/day.

The Applicant proposed to calculate a total phosphodiesterase 4 (PDE-4) load value for exposure comparison to account for the difference in potency of roflumilast and roflumilast N-oxide. The concentration values for both roflumilast and roflumilast N-oxide were converted to molar equivalents, and the N-oxide molar concentration value was divided by 3 and then added to the roflumilast molar concentration value to give a total PDE-4 load value. This approach is considered reasonable. The total PDE-4 load $AUC_{0\text{-}24hr}$ values are 382 and 680nM•hr, for the 0.5 mg/day oral dose and 27.5 mg/day topical dose, respectively. The topical AUC value is 1.8 times the oral AUC value. Therefore, for the Zoryve label, the multiples of human exposure calculated by AUC comparison should be reduced to 1/1.8 of the multiples contained in the Daliresp label.

For the Zoryve label, the multiples of human exposure calculated by mg/m^2 comparison could be reduced to 1/55 (0.5/27.5) of those contained in the Daliresp label if direct mg/m^2 dose comparison is used. However, these calculated multiples would be somewhat misleading as such comparison is based on the assumption that the systemic absorption rate following oral dosing and dermal dosing is the same, while generally the dermal absorption rate would be much lower than the oral absorption rate. Per the Daliresp label, the absolute bioavailability of roflumilast following a 0.5 mg oral dose is approximately 80%. Assuming a systemic absorption rate of 5% for Zoryve Cream in humans, the multiples of human exposure calculated by mg/m^2 comparison should be reduced to 0.3 times the multiples contained in the Daliresp label (0.5/27.5 x 80%/5%) for the Zoryve labeling.

The multiples of human exposure for nonclinical studies contained in the Zoryve labeling based on the multiples contained in the Daliresp labeling are shown in Table 39.

Table 39. Multiples of Human Exposure for Nonclinical Studies

Study	Route	Dose (mg/kg/day)	Multiples in Daliresp Labeling	Multiples in Zoryve Labeling
Rat embryo-fetal development study	Oral	1.8	30[a]	9[b]
Rat embryo-fetal development study	Oral	0.2	3[a]	1[b]
Rat fertility and embryo-fetal development study	Oral	0.6	10[a]	3[b]
Rat fertility and embryo-fetal development study	Oral	1.8	29[a]	9[b]
Rabbit embryo-fetal development study	Oral	0.8	26[a]	8[b]
Mouse pre- and post-natal development study	Oral	2	16[a]	5[b]
Mouse pre- and post-natal development study	Oral	6	49[a]	15[b]
Mouse pre- and post-natal development study	Oral	12	97[a]	29[b]
2-year hamster carcinogenicity study	Oral	8	11[c]	6[d]
2-year mouse carcinogenicity study	Oral	12 (F) 18 (M)	10[c] 15[c]	6[d] 8[d]
Male rat fertility study	Oral	0.6	10[a]	3[b]
Female rat fertility study	Oral	1.5	24[a]	7[b]

Source: NDA 215985 submission. Nonclinical reviewer analysis.
[a] multiple based on mg/m^2 comparison
[b] multiple reduced to 0.3 times the multiple contained in the Daliresp labeling
[c] multiple based on AUC comparison
[d] multiple reduced to 1/1.8 of the multiple contained in the Daliresp labeling

For the 2-year dermal mouse carcinogenicity study, the AUC values from the 13-week dermal mouse toxicity study are used for the multiple calculation. The total PDE-4 load $AUC_{0\text{-}24hr}$ values are 1930 and 1070nM•hr in females and males, respectively. The sex-combined $AUC_{0\text{-}24hr}$ value of 1500nM•hr is used for the multiple calculation for the Zoryve labeling.

The multiple of human exposure for the 2-year mouse dermal carcinogenicity study is shown in Table 40.

Table 40. Multiples of Human Exposure for 2-Year Mouse Dermal Carcinogenicity Study

Study	Route	NOAEL (mg/kg/day)	AUC (nM•hr)	Multiples of Human Exposure*** (AUC Comparison)
2-year mouse carcinogenicity study	Dermal	20*	1500**	2

Source: NDA 215985 submission. Nonclinical reviewer analysis.
*The highest dose without significant carcinogenic findings; 1% roflumilast cream applied at 2 mL/kg/day
**The sex combined total PDE-4 load $AUC_{0\text{-}24hr}$ value at the same dose from the 13-week dermal mouse toxicity study
***Compared to the mean total PDE-4 load AUC_{last} value at Day 15 in adult subjects (680nM•hr) in the maximum use clinical PK study ARQ-151-107
Abbreviations: AUC, area under the concentration-time curve; NOAEL, no-observed adverse effect level; PK, pharmacokinetics

Recommended Revisions to the Nonclinical Portions of Labeling

Revisions to the Applicant's proposed wording for the nonclinical and related sections of the labeling are provided below. It is recommended that the underlined wording be inserted into and the ~~strikethrough~~ wording be deleted from the ZORYVE label proposed by the Applicant. The subheadings in Section 0 should be in underlined format. A clean copy of the recommended nonclinical portions of labeling is also provided.

(b) (4)

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Clean version of the recommended nonclinical portions of labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

ZORYVE is a phosphodiesterase-4 inhibitor indicated for topical treatment of plaque psoriasis, including treatment of psoriasis in the intertriginous areas, in patients 12 years of age and older.

8.1 Pregnancy

Risk Summary

There are no randomized clinical studies of oral or topical roflumilast in pregnant women. In animal reproduction studies, roflumilast administered orally to pregnant rats and rabbits during the period of organogenesis produced no fetal structural abnormalities at doses up to 9 and 8 times the MRHD, respectively. Roflumilast induced post implantation loss in rats at oral doses greater than or equal to 3 times the MRHD. Roflumilast induced stillbirth and decreased pup viability in mice at oral doses 5 and 15 times the MRHD, respectively. Roflumilast has been shown to adversely affect pup post-natal development when dams were treated with an oral dose 15 times the MRHD during pregnancy and lactation periods in mice (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study, pregnant rats were dosed orally during the period of organogenesis with up to 1.8 mg/kg/day roflumilast (9 times the MRHD on a mg/m^2 basis). No evidence of structural abnormalities or effects on survival rates were observed. Roflumilast did not affect embryo-fetal development at a maternal oral dose of 0.2 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis).

In a fertility and embryo-fetal development study, male rats were dosed orally with up to 1.8 mg/kg/day roflumilast for 10 weeks and females for 2 weeks prior to pairing and throughout the organogenesis period. Roflumilast induced pre- and post-implantation loss at maternal oral doses greater than or equal to 0.6 mg/kg/day (3 times the MRHD on a mg/m^2 basis). Roflumilast did not cause fetal structural abnormalities at maternal oral doses up to 1.8 mg/kg/day (9 times the MRHD on a mg/m^2 basis).

In an embryo-fetal development study in rabbits, pregnant does were dosed orally with 0.8 mg/kg/day roflumilast during the period of organogenesis. Roflumilast did not cause fetal structural abnormalities at the maternal oral dose of 0.8 mg/kg/day (8 times the MRHD on a mg/m^2 basis).

In pre- and post-natal developmental studies in mice, dams were dosed orally with up to 12 mg/kg/day roflumilast during the period of organogenesis and lactation. Roflumilast induced stillbirth and decreased pup viability at maternal oral doses greater than 2 mg/kg/day and 6 mg/kg/day, respectively (5 and 15 times the MRHD on a mg/m^2 basis, respectively). Roflumilast induced delivery retardation in pregnant mice at maternal oral doses greater than 2 mg/kg/day (5 times the MRHD on a mg/m^2 basis). Roflumilast decreased pup rearing frequencies at a maternal oral dose of 6 mg/kg/day during pregnancy and lactation (15 times the MRHD on a mg/m^2 basis). Roflumilast also decreased survival and forelimb grip reflex and

delayed pinna detachment in mouse pups at a maternal oral dose of 12 mg/kg/day (29 times the MRHD on a mg/m^2 basis).

8.2 Lactation

Risk Summary

There is no information regarding the presence of ZORYVE in human milk, the effects on the breastfed infant, or the effects on milk production.

Roflumilast and/or its metabolites are excreted into the milk of lactating rats (*see Data*). When a drug is present in animal milk, it is likely that the drug will present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZORYVE and any potential adverse effects on the breastfed infant from ZORYVE or from the underlying maternal condition.

Data

Animal Data

Roflumilast and/or its metabolite concentrations measured 8 hours after an oral dose of 1 mg/kg given to lactating rats were 0.32 and 0.02 mcg/g in the milk and pup liver, respectively.

12.1 Mechanism of Action

Roflumilast and its active metabolite (roflumilast N-oxide) are inhibitors of PDE-4. Roflumilast and roflumilast N-oxide inhibition of PDE-4 (a major cyclic AMP-metabolizing enzyme) activity leads to accumulation of intracellular cyclic AMP. The specific mechanism(s) by which roflumilast exerts its therapeutic action is not well defined.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted in hamsters and mice with roflumilast to evaluate its carcinogenic potential. In 2-year oral gavage carcinogenicity studies, roflumilast treatment resulted in dose-related, statistically significant increases in the incidence of undifferentiated carcinomas of nasal epithelium in hamsters at doses greater than or equal to 8 mg/kg/day (6 times the MRHD on an AUC basis). The tumorigenicity of roflumilast appears to be attributed to a reactive metabolite of ADCP N-oxide. No evidence of tumorigenicity was observed in mice at roflumilast oral doses up to 12 and 18 mg/kg/day in females and males, respectively (6 and 8 times the MRHD, respectively, on an AUC basis).

In a 2-year dermal mouse carcinogenicity study, no evidence of carcinogenicity was observed at topical doses of roflumilast cream up to 1% applied at 2 mL/kg/day (2 times the MRHD on an AUC basis).

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

In a human spermatogenesis study, oral roflumilast 500 mcg had no effects on semen parameters or reproductive hormones during the 3-month treatment period and the following 3-month off-treatment period. In a fertility study, oral roflumilast decreased fertility rates in male rats at 1.8 mg/kg/day (9 times the MRHD on a mg/m^2 basis). The male rats also showed increases in the incidence of tubular atrophy, degeneration in the testis, and spermiogenic granuloma in the epididymides. No effect on rat fertility rate or male reproductive organ morphology was observed at 0.6 mg/kg/day (3 times the MRHD on a mg/m^2 basis). In a female fertility study, no effect on fertility was observed up to the highest roflumilast dose of 1.5 mg/kg/day in rats (7 times the MRHD on a mg/m^2 basis).

OCP Appendices (Technical Documents Supporting OCP Recommendations)

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

The Applicant, Arcutis Biotherapeutics, Inc., and (b) (4) developed and validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) bioanalytical methods for determination of roflumilast, roflumilast N-oxide, ADCP, and ADCP N-oxide in human plasma. The lower limit of quantification and calibration range for the analytes are presented in Table 41.

Table 41. Lower Limit of Quantification and Calibration Range for Roflumilast, Roflumilast N-Oxide, ADCP, and ADCP N-Oxide in Human Plasma

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, 171410VEMB_ARCMC_R1Abbreviations: ADCP, 4-Amino-3,5-dichloropyridine; LLOQ, Lower limit of quantification

The performance characteristics of the developed bioanalytical assay is shown in Table 42.

Table 42. Precision and Accuracy of the Bioanalytical Method

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, 171410VEMB_ARCMC_R1
Abbreviations: CV, coefficient of variation; RE, relative error

Stability of the analytes under various conditions were analyzed are reported in Table 43.

Table 43. Sample Stability Under Listed Conditions

Analyte	Freeze-Thaw Cycle (-20 to -70 ºC)	Benchtop Stability in Human Plasma at Room Temp	Processed Sample (Autosampler) Room Temp	Long Term Stability - 20 ºC	Long Term Stability -70 ºC	Stock Solution Stability Room Temp	Stock Solution Stability 4 ºC
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, 171410VEMB_ARCMC_R1
Samples were stored at -70 C and analyzed within the freezer stability limit of 671 days for roflumilast and roflumilast N-oxide and the long-term storage stability was deemed adequate.
Abbreviations: ADCP, 4-Amino-3,5-dichloropyridine

Incurred sample reanalysis: The Applicant notes that two thirds of the repeated sample results for incurred sample reanalysis were within 20% of the original results for both roflumilast and roflumilast N-oxide in plasma, confirming the reproducibility of the methods. Applicant noted that ADCP and ADCP N-oxide did not qualify for incurred sample reanalysis.

Reviewer's comment: The bioanalytical method developed and validated for quantification of roflumilast and roflumilast N-oxide is acceptable.

Clinical/Biostatistics

Table 44. PASI-75 Response at Week 8 – Trials ARQ-151-301/302 (ITT; MI[1])

	Trial ARQ-151-301		Trial ARQ-151-302	
	Roflumilast Cream, 0.3% (N=286)	**Vehicle Cream (N=153)**	**Roflumilast Cream, 0.3% (N=290)**	**Vehicle Cream (N=152)**
Treatment Success[2]	41.2%	7.0%	37.8%	5.3%
Applicant's Analysis				
Difference (95% CI)[3]				
Odds Ratios (95% CI)[3]	16.7 (23, 123.0)		11.7 (1.6, 88.8)	
P-Value[3]	<0.001		<0.001	
Reviewer's Analysis				
Difference (95% CI)[4]	35.4% (27.7%, 43.0%)		32.7% (25.2%, 40.2%)	
Odds Ratios (95% CI)[4]				
P-Value[4]	<0.001		<0.001	

Source: Statistical Reviewer's Analysis; ADEFF.xpt
[1] Intent-to-treat (ITT) population, defined as all randomized subjects; Missing data were imputed using multiple imputation; the rates displayed are the averages over the imputed datasets.
[2] Treatment success is defined as at least 75% reduction in PASI score from baseline.
[3] Estimate, 95% CI, and p-value are based on CMH test stratified by site, baseline IGA (based on IVRS), and baseline intertriginous involvement (based on IVRS); p-value for odds ratio obtained using the Wilson Hilferty transformation.
[4] Estimate and 95% CI, and p-value are based on CMH test stratified by site, baseline IGA (based on eCRF), and baseline intertriginous involvement (based on eCRF); p-value for odds ratio obtained using the Wilson Hilferty transformation.
Note: Results based on the mITT population (not presented here) are similar to those based on the ITT population.
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; IGA, Investigator's Global Assessment; IVRS, interactive voice response system; MI, multiple imputation; PASI, Psoriasis Area and Severity Index

Table 45. IGA 0/1 Success at Week 4 Based on Applicant's Analysis – Trials ARQ-151-301/302 (ITT; MI[1])

	Trial ARQ-151-301		Trial ARQ-151-302	
	Roflumilast Cream, 0.3% (N=286)	Vehicle Cream (N=153)	Roflumilast Cream, 0.3% (N=290)	Vehicle Cream (N=152)
Treatment Success[2]	19.8%	2.6%	18.6%	5.5%
Difference (95% CI)[3]	19.3% (13.5%, 25.1%)		13.5% (7.2%, 19.9%)	
Odds Ratio (95% CI)[3]	13.4 (3.7, 48.6)		3.9 (1.8, 8.7)	
P-Value[3]	<0.001		0.0011	

Source: Applicant's Analysis; ADEFF.xpt
[1] Intent-to-treat (ITT) population, defined as all randomized subjects; Missing data were imputed using multiple imputation; the rates displayed are the averages over the imputed datasets.
[2] Treatment success is defined as a IGA score of 0 (clear) or 1 (almost clear) with at least a two-grade reduction from baseline.
[3] Estimate, 95% CI, and p-value are based on CMH test stratified by site, baseline IGA (based on IVRS), and baseline intertriginous involvement (based on IVRS); p-value for odds ratio obtained using the Wilson Hilferty transformation.
Note: Results based on the mITT population (not presented here) are similar to those based on the ITT population.
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; IGA, Investigator's Global Assessment; IVRS, interactive voice response system; MI, multiple imputation

Table 46. I-IGA Success at Week 8 Based on Applicant's Analysis – Trials ARQ-151-301/302 (MI[1])

	Trial ARQ-151-301		Trial ARQ-151-302	
	Roflumilast Cream, 0.3% (N=286)	Vehicle Cream (N=153)	Roflumilast Cream, 0.3% (N=290)	Vehicle Cream (N=152)
I-IGA-ITT Population[2]	N=63	N=32	N=53	N=31
Treatment Success[3]	71.5%	13.8%	67.5%	17.4%
Difference (95% CI)[4]	66.5% (47.1%, 85.8%)		52.2% (30.4%, 74.0%)	
Odds Ratio (95% CI)[4]	17.9 (2.3, 138.2)		11.7 (2.4, 56.6)	
P-Value[4]	<0.001		<0.001	

Source: Applicant's Analysis; ADEFF.xpt
[1] Missing data were imputed using multiple imputation; the rates displayed are the averages over the imputed datasets.
[2] I-IGA-ITT population, defined as randomized subjects with intertriginous area involvement of at least 'mild' (I-IGA ≥2) at baseline
[3] Treatment success is defined as an Intertriginous area IGA (I-IGA) score of 0 (clear) or 1 (almost clear) with at least a two-grade reduction from baseline
[4] Estimate, 95% CI, and p-value are based on CMH test stratified by site and IGA at baseline (based on IVRS); p-value for odds ratio obtained using the Wilson Hilferty transformation.
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; I-IGA, Intertriginous-Investigator's Global Assessment; IVRS, interactive voice response system; MI, multiple imputation

Table 47. Response Rates for ≥4-Point Improvement From Baseline on Worst Itch NRS Based on Applicant's Analysis – Trials ARQ-151-301/302 (PRU4-ITT; MI[1])

	Trial ARQ-151-301		Trial ARQ-151-302	
Week	Roflumilast Cream, 0.3% (N=218)	Vehicle Cream (N=153)	Roflumilast Cream, 0.3% (N=290)	Vehicle Cream (N=152)
Week 8				
Treatment Success[2]	66.7%	25.7%	68.6%	33.3%
Difference (95% CI)[3]	42.6% (31.3%, 53.8%)		30.9% (18.9%, 43.0%)	
Odds Ratio (95% CI)[3]	7.8 (3.9, 15.9)		3.6 (2.1, 6.2)	
P-Value[3]	<0.001		<0.001	
Week 4				
Treatment Success[2]	49.4%	18.7%	55.8%	21.2%
Difference (95% CI)[3]	30.7% (19.6%, 41.7%)		33.7% (22.9%, 44.5%)	
Odds Ratio (95% CI)[3]	4.4 (2.3, 8.3)		4.9 (2.6, 9.2)	
P-Value[3]	<0.001		<0.001	
Week 2				
Treatment Success[2]	34.9%	22.7%	41.5%	21.9%
Difference (95% CI)[3]	10.8% (<1%, 21.5%)		20.0% (9.3%, 30.7%)	
Odds Ratio (95% CI)[3]	1.8 (1.0, 3.2)		2.6 (1.4, 4.6)	
P-Value[3]	0.1197		0.0026	

Source: Statistical Reviewer's Analysis; ADEFF.xpt
[1] Pruritus ITT Population (PRU4-ITT): randomized subjects with WI-NRS pruritus score ≥4 at baseline; the rates displayed are the averages over the imputed datasets.
[2] Treatment success is defined as ≥4-point Improvement from baseline on worst itch NRS score
[3] Estimate, 95% CI, and p-value are based on CMH test stratified by site, baseline IGA (based on IVRS), and baseline intertriginous involvement (based on IVRS); p-value for odds ratio obtained using the Wilson Hilferty transformation.
Note: Results based on the PRU4-mITT population (not presented here) are similar to those based on the PRU4-ITT population.
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; IGA, Investigator's Global Assessment; IVRS, interactive voice response system; MI, multiple imputation; NRS, numeric rating scale

Additional Clinical Outcome Assessment Analyses

Not applicable.

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07/27/2022 08:44:39 PM

NINA NI
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