Investigator- and Patient-Rated Local Tolerability in Phase 3 Trials of Topical Roflumilast in Patients With Psoriasis, Seborrheic Dermatitis, and Atopic Dermatitis

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INTRODUCTION

- The formulation of a topical product and the occurrence of local skin reactions are both important factors contributing to patient treatment adherence and satisfaction[1]
- Excipients such as propylene glycol, polyethylene glycol, and ethanol are in almost all topical prescriptions and are the most utilized penetration enhancers to overcome barrier properties of the skin[2,3]
  - These excipients may irritate the skin, causing local tolerability reactions such as burning and stinging, which can reduce patient adherence[2]
- Topical roflumilast, is a highly potent (Kd~0.7 nM) phosphodiesterase 4 inhibitor, formulated as a water-based foam and a cream with no sensitizers, penetration enhancers, or fragrances[4]
  - Vehicle excipients in topical roflumilast include ceteareth-10 phosphate, cetearyl phosphate, cetostearyl alcohol, diethylene glycol monoethyl ether, hexylene glycol, isopropyl palmitate, methylparaben, propylparaben, purified water, sodium hydroxide, and white petrolatum[5]
- Investigator- and patient-rated local tolerability was assessed prospectively in Phase 3 clinical trials in patients with psoriasis (DERMIS-1, DERMIS-2, ARRECTOR), seborrheic dermatitis (STRATUM), and atopic dermatitis (INTEGUMENT-1, INTEGUMENT-2)
  - Investigator- and patient-reported local tolerability report different aspects of irritation, with only patient-reported local tolerability assessing sensation (stinging and burning) of a topically applied treatment

METHODS

- These were randomized, parallel-group, double-blind, vehicle-controlled, multicenter Phase 3 studies (Table 1)
- Investigators assessed local tolerability on an 8-point scale in the clinic before investigational product (IP) application (Table 2)
- Patients reported local tolerability on a 4-point scale in the clinic 10–15 minutes after IP application (Table 2)
- Tolerability was also assessed by reviewing documented adverse events

Table 1. Study Designs

Trial	Treatment Groups	Inclusion Criteria	Tolerability Assessments
DERMIS-1/-2[6] (psoriasis)	Roflumilast cream 0.3% (N=576) Vehicle (N=305)	≥2 years of age BSA: 2–20% IGA ≥2 (Mild) PASI ≥2	Baseline, Weeks 4, 8
ARRECTOR (scalp and body psoriasis)	Roflumilast foam 0.3% (N=281) Vehicle (N=151)	≥12 years of age BSA: ≤25% (≤20% non-scalp, ≥10% scalp) S-IGA: ≥3 (Moderate) B-IGA: ≥2 (Mild) PSSI: ≥6 PASI: ≥2	Baseline, Weeks 2, 4, 8
STRATUM (seborrheic dermatitis)	Roflumilast foam 0.3% (N=304) Vehicle (N=153)	≥9 years of age BSA: ≤20% IGA: ≥3 (Moderate)	Baseline, Weeks 4, 8
INTEGUMENT-1/-2 (atopic dermatitis)	Roflumilast cream 0.15% (N=884) Vehicle (N=453)	≥6 years of age BSA: ≥3% vIGA-AD: 2 (Mild) to 3 (Moderate) EASI: ≥5	Baseline, Weeks 1, 2, 4

B-IGA: Body-Investigator Global Assessment; BSA: body surface area; EASI: Eczema Area and Severity Index; IGA: Investigator Global Assessment; PASI: Psoriasis Area and Severity Index; PSSI: Psoriasis Scalp Severity Index; S-IGA: Scalp-Investigator Global Assessment; vIGA-AD: Validated Global Assessment for Atopic Dermatitis.

Table 2. Local Tolerability Scales

Investigator-Rated Local Tolerability Conducted by the investigator PRIOR to application in the clinic		Patient-Rated Local Tolerability Reported by the patient 10–15 minutes AFTER application in clinic*	
Grade	Dermal response	Grade	Sensation Following Drug Application
0	No evidence of irritation	0	No sensation
1	Minimal erythema, barely perceptible	1	Slight warm, tingling sensation; not really bothersome
2	Definite erythema, readily visible; minimal edema or minimal papular response	2	Definite warm, tingling sensation that is somewhat bothersome
3	Erythema and papules	3	Hot, tingling/stinging sensation that has caused definite discomfort
4	Definite edema		
5	Erythema, edema, and papules		
6	Vesicular eruption		
7	Strong reaction spreading beyond application site		

*At some timepoints, patient-reported local tolerability was based on the recall of the experience post application on the day prior to the clinic visit: INTEGUMENT (Week 4), STRATUM (Weeks 4, 8), ARRECTOR (Week 8).

Baseline Demographic and Disease Characteristics

- Baseline demographics and disease characteristics were similar across trials and groups
- Facial and genital involvement at baseline in each trial is shown in Table 3

Table 3. Facial and Genital Involvement at Baseline

Trial	Face, n (%)	Genitalia, n (%)
Pooled DERMIS (N=881)	234 (26.6)	137 (15.6)
ARRECTOR (N=432)	157 (36.3)	75 (17.4)
STRATUM (N=457)	284 (62.1)	Data not collected
Pooled INTEGUMENT (N=1337)	567 (42.4)	Data not collected

Investigator-Rated Local Tolerability

- Most patients in the roflumilast-treated groups had no evidence of irritation as assessed by investigators across trials and timepoints (Table 4)
- Most patients reported mild to no sensation across all trials, improving with treatment (DERMIS: Figure 1; ARRECTOR: Figure 2; STRATUM: Figure 3; INTEGUMENT: Figure 4)

Table 4. Investigator-Rated Local Tolerability

		% of patients with no evidence (score=0) of irritation per investigator			
Trial	Disease	Treatment	Baseline	Week 4	Week 8
DERMIS-1/-2	Psoriasis	Roflumilast cream 0.3% (N=576)	99.8	98.8	98.6
		Vehicle (N=305)	100	97.7	98.4
ARRECTOR	Scalp and body psoriasis	Roflumilast foam 0.3% (N=281)	100	99.6	100
		Vehicle (N=151)	100	98.5	100
STRATUM	Seborrheic dermatitis	Roflumilast foam 0.3% (N=304)	100	98.9	100
		Vehicle (N=153)	100	100	100
INTEGUMENT-1/-2	Atopic dermatitis	Roflumilast cream 0.15% (N=885)	100	97.3	NA
		Vehicle (N=451)	100	97.4	NA

NA: not applicable.

Figure 1. Patient-Rated Local Tolerability: Psoriasis

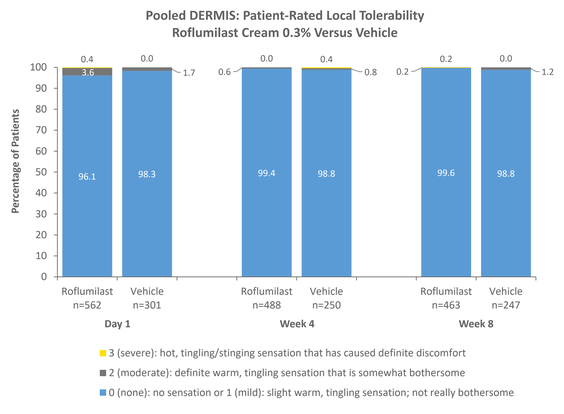


Figure 2. Patient-Rated Local Tolerability: Scalp and Body Psoriasis

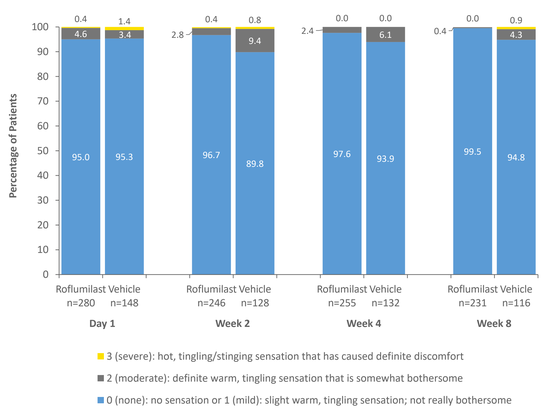


Figure 3. Patient-Rated Local Tolerability: Seborrheic Dermatitis

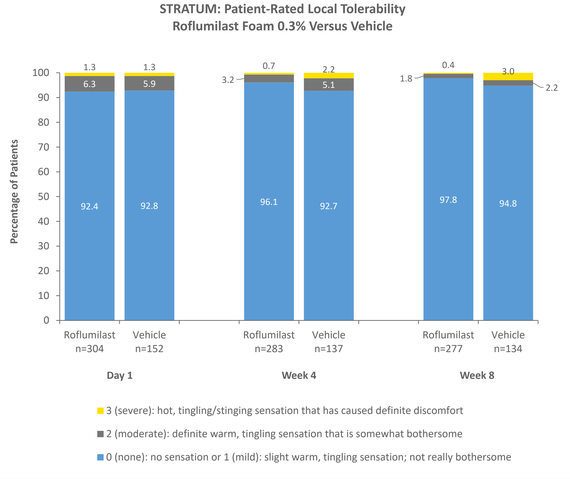
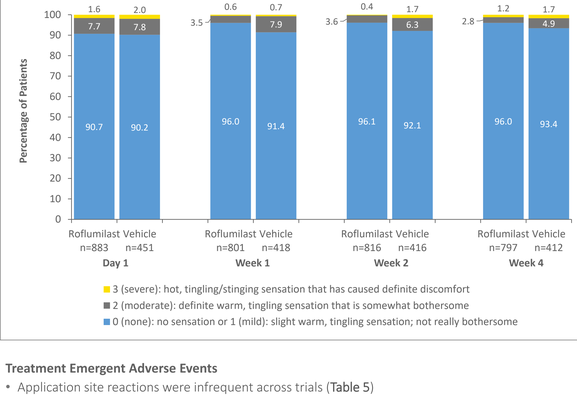


Figure 4. Patient-Rated Local Tolerability: Atopic Dermatitis



Treatment Emergent Adverse Events

- Application site reactions were infrequent across trials (Table 5)

Table 5. Treatment-Emergent Adverse Events Reported at the Site of Application, by Preferred Term, in ≥1% in the Roflumilast-treated Patients in Any Trial

TEAE, n (%)	Pooled DERMIS Psoriasis		ARRECTOR Scalp and Body Psoriasis		STRATUM Seborrheic Dermatitis		Pooled INTEGUMENT Atopic Dermatitis	
	Roflumilast Cream 0.3% (N=576)	Vehicle (N=305)	Roflumilast Foam 0.3% (N=281)	Vehicle (N=151)	Roflumilast Foam 0.3% (N=304)	Vehicle (N=153)	Roflumilast Cream 0.15% (N=885)	Vehicle (N=451)
Application site pain	6 (1.0)	1 (0.3)	1 (0.4)	0	1 (0.3)	3 (2.0)	13 (1.5)	3 (0.7)
Application site pruritis	3 (0.5)	1 (0.3)	0	0	3 (1.0)	0	2 (0.2)	0

TEAE: treatment-emergent adverse event.

CONCLUSIONS

- Local tolerability was favorable across timepoints and improved with treatment, regardless of indication, cream or foam formulation, or roflumilast concentration
- Rates of application site AEs were low and consistent with vehicle across trials
- Roflumilast cream and foam formulations demonstrated favorable local tolerability based on investigator- and patient-rated assessments in patients with psoriasis, seborrheic dermatitis, and atopic dermatitis, including in patients with involvement in sensitive areas such as the face, genital, and intertriginous areas

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DISCLOSURES

CGB, NB, JDR, ZDD, LFE, LHK, MGL, MG, LJG, AAH, RBV, MZ, ELS, and LSG are investigators and/or consultants for Arcutis Biotherapeutics, Inc. and received grants/research funding and/or honoraria; MS, SS, DWO, PB, RCH, DHC, and DRB are employees of Arcutis Biotherapeutics, Inc. Additional disclosures provided on request.

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