Efficacy and Safety of Roflumilast Foam 0.3% in Patients With Scalp and Body Psoriasis in the Phase 3 ARRECTOR Trial

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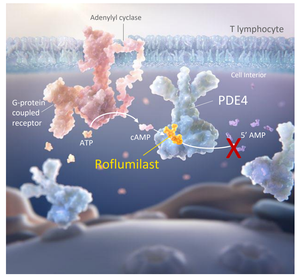
INTRODUCTION

- Plaque psoriasis is a chronic inflammatory skin condition that negatively impacts quality of life, including patients in which the disease is not extensive[1]
  - Up to 80% of patients with psoriasis experience scalp psoriasis[2-4]
- Roflumilast is a selective, nonsteroidal, potent, phosphodiesterase-4 (PDE4) inhibitor being investigated as a once-daily cream and foam formulation for long-term management of various dermatologic conditions:
  - Chronic plaque psoriasis (0.3% cream formulation approved for patients 12 years of age and up on July 29, 2022 by the US Food and Drug Administration),[5] atopic dermatitis (0.05% and 0.15% cream), and seborrheic dermatitis (0.3% foam)
- Roflumilast foam 0.3% differs from other topical foams used in the past:
  - It was adapted from the high water-content formulation of roflumilast cream 0.3%
  - Excipients include an emulsifier novel to prescription topical products, which does not extract epidermal lipids at safe skin temperatures[6]
  - Does not contain ethanol, propylene glycol, or fragrances that can irritate skin

Figure 1. Roflumilast Mechanism of Action: A Selective and Potent PDE4 Inhibitor



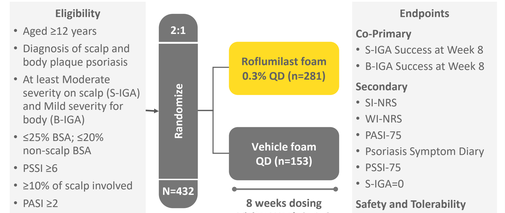
AMP: adenosine monophosphate; ATP: adenosine triphosphate; cAMP: cyclic AMP; PDE4: phosphodiesterase 4.

- Roflumilast has a greater affinity for PDE4 than apremilast and crisaborole
  - 25- to >300-fold more potent in in vitro assays[7]
- Roflumilast modulates inflammatory cytokines through inhibition of PDE4 (**Figure 1**)[7]
  - Decreases conversion of cyclic adenosine monophosphate (cAMP)[8]
  - Results in decreased expression of key pro-inflammatory cytokines[7]
    - T-helper (Th)1 (interferon-gamma [IFN-γ], tumor necrosis factor [TNF-α])
    - Th2 (interleukin [IL]-4)
    - Th17 (IL-17, IL-23)
  - Increases anti-inflammatory cytokines such as IL-10[8]

METHODS

- ARRECTOR was a randomized, parallel-group, double-blind, vehicle-controlled, multicenter phase 3 study (NCT05028582; **Figure 2**)

Figure 2. Study Design



S-IGA Success = Clear or Almost Clear with at least a 2-grade improvement from baseline

B-IGA Success = Clear or Almost Clear with at least a 2-grade improvement from baseline

B-IGA: Body-Investigator Global Assessment; BSA: body surface area; PASI: Psoriasis Area and Severity Index; PASI-75: 75% reduction in PASI; PSSI: Psoriasis Scalp Severity Index; PSSI-75: 75% reduction in PSSI; QD: once daily; S-IGA: Scalp-Investigator Global Assessment; SI-NRS: Scalp Itch-Numeric Rating Scale; WI-NRS: Worst Itch-Numeric Rating Scale.

RESULTS

- Almost 90% of patients receiving roflumilast foam completed the trial (**Table 1**)
  - Few patients discontinued due to adverse events (≤1.8% in any treatment group) or due to lack of efficacy (≤1.1% in any treatment group)
- Overall, baseline demographics and disease characteristics were well-balanced (**Table 2**)
- Roflumilast foam 0.3% provided greater efficacy than vehicle across multiple endpoints (**Figures 3–9**)
- Incidence of treatment-emergent adverse events was low and local tolerability was favorable in both treatment groups (**Table 2** and **Figure 10**)

Table 1. Patient Disposition

n (%)	Roflumilast Foam 0.3% (n=281)	Vehicle Foam (n=151)
Completed	**250 (89.0)**	**126 (83.4)**
Prematurely discontinued	**31 (11.0)**	**25 (16.6)**
Reason for discontinuation		
Lost to follow-up	11 (3.9)	9 (6.0)
Withdrawal of consent	9 (3.2)	10 (6.6)
Adverse events	5 (1.8)	2 (1.3)
Lack of efficacy	3 (1.1)	1 (0.7)
Request of PCP/Investigator	0	1 (0.7)
Death	0	0
Pregnancy	0	0
Other	3 (1.1)	2 (1.3)

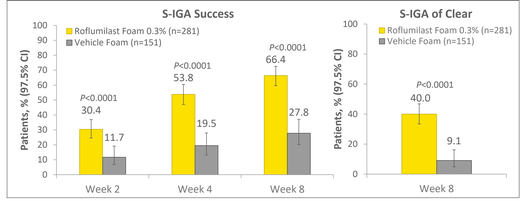
PCP: primary care physician.

Table 2. Patient Demographics and Baseline Disease Characteristics

Patients, n (%)	Roflumilast Foam 0.3% (n=281)	Vehicle Foam (n=151)
Age, years, mean (SD)	**48.6 (14.9)**	**45.0 (14.3)**
Gender		
Male	129 (45.9)	60 (39.7)
Female	152 (54.1)	91 (60.3)
Ethnicity		
Hispanic or Latino	48 (17.1)	28 (18.5)
Not Hispanic or Latino	224 (79.7)	121 (80.1)
Not reported	9 (3.2)	2 (1.3)
Race		
American-Indian or Alaskan Native	0	3 (2.0)
Asian	26 (9.3)	4 (2.6)
Black or African American	12 (4.3)	6 (4.0)
Native Hawaiian, Other Pacific Islander	3 (1.1)	1 (0.7)
White	225 (80.1)	129 (85.4)
Other	11 (3.9)	7 (4.6)
More than one race	4 (1.4)	1 (0.7)
Baseline S-IGA		
3 (moderate)	239 (85.1)	131 (86.8)
4 (severe)	42 (14.9)	20 (13.2)
Baseline B-IGA		
2 (mild)	76 (27.0)	43 (28.5)
3 (moderate)	191 (68.0)	99 (65.6)
4 (severe)	14 (5.0)	9 (6.0)
PSSI, mean (SD)	21.4 (11.1)	22.2 (11.0)
PASI, mean (SD)	6.7 (3.6)	6.0 (3.3)
PSD, total mean (SD)	73.4 (40.2)	75.2 (36.9)
BSA (%), mean (SD)	6.1 (4.3)	6.0 (4.3)
SI-NRS, mean (SD)	5.8 (2.6)	6.1 (2.3)
WI-NRS, mean (SD)	5.7 (2.6)	5.5 (2.6)

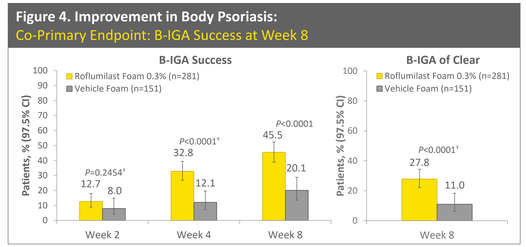
B-IGA: Body-Investigator Global Assessment; BSA: body surface area; PASI: Psoriasis Area and Severity Index; PSD: Psoriasis Symptom Diary; PSSI: Psoriasis Scalp Severity Index; SD: standard deviation; S-IGA: Scalp-Investigator Global Assessment; SI-NRS: Scalp Itch-Numeric Rating Scale; WI-NRS: Worst Itch-Numeric Rating Scale.

Figure 3. Improvement in Scalp Psoriasis: Co-Primary Endpoint: S-IGA Success at Week 8



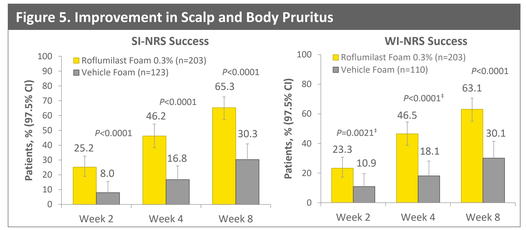
S-IGA Success = Clear or Almost Clear with at least a 2-grade improvement from baseline.
CI: confidence interval; S-IGA: Scalp-Investigator Global Assessment.

Figure 4. Improvement in Body Psoriasis: Co-Primary Endpoint: B-IGA Success at Week 8



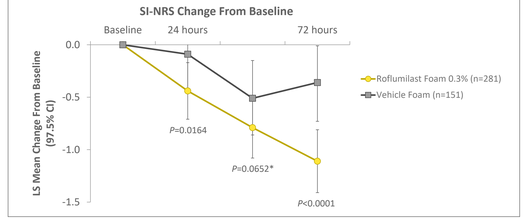
B-IGA Success = Clear or Almost Clear with at least a 2-grade improvement from baseline; †Nominal *P*-value.
B-IGA: Body-Investigator Global Assessment; CI: confidence interval.

Figure 5. Improvement in Scalp and Body Pruritus



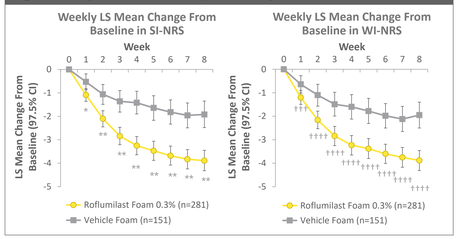
SI-NRS Success: achievement of ≥4-point improvement from baseline in patients with baseline SI-NRS ≥4; WI-NRS Success: achievement of ≥4-point improvement from baseline in patients with baseline WI-NRS ≥4; †Nominal *P*-value.
CI: confidence interval; SI-NRS: Scalp Itch-Numeric Rating Scale; WI-NRS: Worst Itch-Numeric Rating Scale.

Figure 6. Improvement in Scalp Pruritus at 24 Hours After First Application



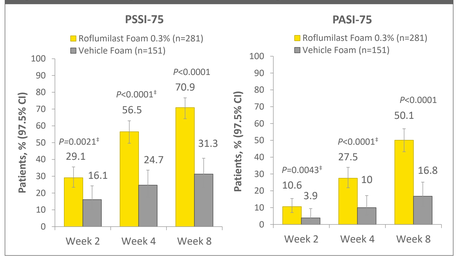
*Nominal *P*-value. Intent to treat population.
CI: confidence interval; LS: least squares; SI-NRS: Scalp Itch-Numeric Rating Scale.

Figure 7. Improvement in Scalp and Body Pruritus



*P=0.0002. **Nominal *P*<0.0001. †††Nominal *P*=0.0006. ††††Nominal *P*<0.0001. Intent-to-treat (all randomized subjects). As observed.
CI: confidence interval; LS, least squares; SI-NRS: Scalp Itch-Numeric Rating Scale; WI-NRS: Worst Itch-Numeric Rating Scale.

Figure 8. Percentage of Patients Achieving PSSI-75 and PASI-75



‡Nominal *P*-value.
CI: confidence interval; PASI: Psoriasis Area and Severity Index; PASI-75: 75% reduction in PASI; PSSI: Psoriasis Scalp Severity Index; PSSI-75: 75% reduction on PSSI.

Table 3. Safety

Patients, n (%)	Roflumilast Foam 0.3% (n=281)	Vehicle Foam (n=151)
Patients with any TEAE	75 (26.7)	25 (16.6)
Patients with any treatment-related TEAE	16 (5.7)	3 (2.0)
Patients with any treatment-emergent SAE	2 (0.7)	1 (0.7)
Patients with any treatment-related SAE	1 (0.4)	0
Patients who discontinued study drug due to AE	7 (2.5)	2 (1.3)
Patients who discontinued study due to AE	5 (1.8)	2 (1.3)
Most common TEAEs by preferred term, ≥1% in any group		
Headache	13 (4.6)	3 (2.0)
Diarrhea	9 (3.2)	4 (2.6)
COVID-19	8 (2.8)	4 (2.6)
Nausea	6 (2.1)	0
Nasopharyngitis	4 (1.4)	2 (1.3)
Hypertension	3 (1.1)	2 (1.3)
Upper respiratory tract infection	3 (1.1)	0
Urinary tract infection	2 (0.7)	2 (1.3)

SAEs include bipolar disorder (roflumilast; unrelated), gastritis (roflumilast; possibly related), joint dislocation, peripheral artery occlusion and radius fracture (vehicle; all unrelated).
AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

ACKNOWLEDGEMENTS

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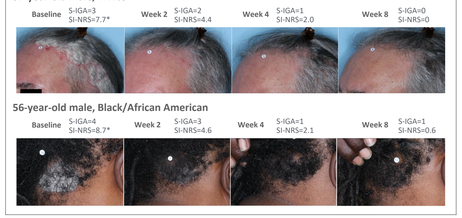
DISCLOSURES

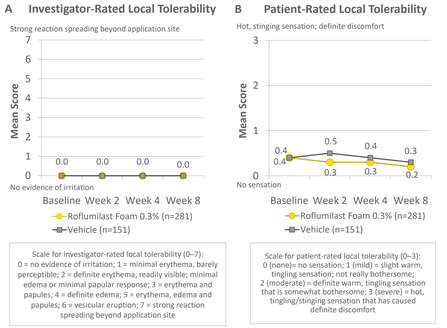
MG, JB, JD, LHK, BL, KAP, and **JS** are investigators and/or consultants for Arcutis Biotherapeutics, Inc. and received grants/research funding and/or honoraria; **DK, PB, DRB,** and **DHC** are employees of Arcutis Biotherapeutics, Inc. Additional disclosures provided on request.

Figure 9. Scalp Psoriasis Response to Roflumilast Foam 0.3%



*SI-NRS is average weekly SI-NRS score for each week.
S-IGA: Scalp-Investigator Global Assessment; SI-NRS: Scalp Itch-Numeric Rating Scale.

Figure 10. Local Tolerability Assessments: Investigator- and Patient-Rated



Scale for investigator-rated local tolerability (0–7):
0 = no evidence of irritation; 1 = minimal erythema, barely perceptible; 2 = definite erythema, readily visible; minimal edema or minimal papular response; 3 = erythema and papules; 4 = definite edema; 5 = erythema, edema and papules; 6 = vesicular eruption; 7 = strong reaction spreading beyond application site

Scale for patient-rated local tolerability (0–3):
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

CONCLUSIONS

- Foam formulations are able be applied through the hair more easily to reach lesions on the skin of the scalp and other hair-bearing areas
- Once-daily, nonsteroidal roflumilast foam 0.3% demonstrated improvement across multiple efficacy endpoints versus vehicle in patients with scalp and body psoriasis:
  - Significant improvement in both scalp and body psoriasis as early as 2 weeks after treatment initiation, the first timepoint measured
  - Significant improvement in pruritus at 24 hours following first dose
- Safety and local tolerability were favorable
  - Low rates of adverse events and discontinuations due to adverse events, similar to vehicle

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