Safety and Efficacy of Once-Daily Roflumilast Cream 0.3%, a Potent Phosphodiesterase-4 Inhibitor for the Treatment of Psoriasis in the DERMIS-1 and DERMIS-2 Phase 3 Trials

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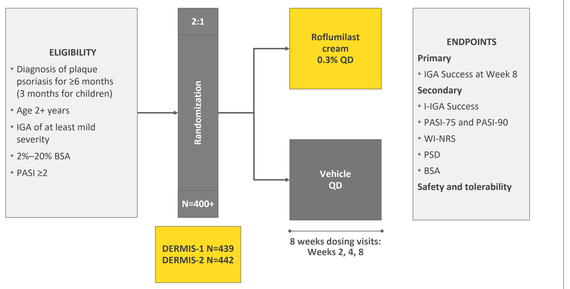
INTRODUCTION

- No nonsteroidal topical therapies with novel mechanism of action for psoriasis have been approved in more than 20 years
  - Available topical treatments are less than ideal, necessitating a trade-off between efficacy and tolerability[1]
- Roflumilast is a selective and highly potent phosphodiesterase-4 inhibitor being investigated as a once-daily, nonsteroidal, topical treatment for various inflammatory dermatologic conditions
  - In a phase 2b, randomized, double-blind, vehicle-controlled trial, roflumilast cream provided
    - Significant and rapid improvement of psoriasis
    - Demonstrated efficacy for intertriginous plaques
    - Reduction of itch[2]
- This poster presents efficacy and safety results from DERMIS-1 (ClinicalTrials.gov Identifier: NCT04211363) and DERMIS-2 (ClinicalTrials.gov Identifier: NCT04211389)
  - These were 2 identical phase 3, randomized, double-blind, vehicle-controlled studies of once-daily roflumilast cream 0.3% in patients with psoriasis (Figure 1)

Figure 1. Study Design



BSA: body surface area; IGA: Investigator Global Assessment; I-IGA: intertriginous-Investigator Global Assessment; PASI: Psoriasis Area and Severity Index; PASI-75: 75% reduction from baseline in PASI; PASI-90: 90% reduction from baseline in PASI; PSD: Psoriasis Symptom Diary; QD: once daily; WI-NRS: Worst Itch-Numeric Rating Scale.

METHODS

- The primary endpoint was analyzed using a Cochran-Mantel-Haenszel test stratified by site, baseline Investigator Global Assessment (IGA), and baseline intertriginous involvement
  - Statistical significance was concluded at the 5% significance level (2-sided)
  - Missing IGA scores were imputed using multiple imputation
- To control for multiple comparisons among the secondary endpoints, a multiplicity procedure was used
  - Upon successful testing of the primary endpoint, the α was partitioned to test secondary endpoints

RESULTS

- 439 patients were enrolled in DERMIS-1 and 442 patients were enrolled in DERMIS-2
- Most patients (86.2% to 91.0%) completed the studies (Table 1)
- Baseline disease characteristics were balanced across treatment groups and similar between the 2 studies (Table 2)

Table 1. Patient Disposition

	DERMIS-1		DERMIS-2	
Patients, n (%)	Roflumilast Cream 0.3% (n=286)	Vehicle Cream (n=153)	Roflumilast Cream 0.3% (n=290)	Vehicle Cream (n=152)
Completed	255 (89.2)	133 (86.9)	264 (91.0)	131 (86.2)
Prematurely discontinued	31 (10.8)	20 (13.1)	26 (9.0)	21 (13.8)
Reason for discontinuation				
Withdrawal by patient	11 (3.8)	11 (7.2)	10 (3.4)	11 (7.2)
Physician decision	0	1 (0.7)	0	0
Noncompliance	0	0	0	1 (0.7)
Protocol violation	1 (0.3)	0	0	0
Lost to follow-up	12 (4.2)	4 (2.6)	15 (5.2)	7 (4.6)
Adverse event	5 (1.7)	2 (1.3)	1 (0.3)	2 (1.3)
Pregnancy	1 (0.3)	0	0	0
Other	1 (0.3)	2 (1.3)	0	0

Table 2. Baseline Disease Characteristics (ITT Population)

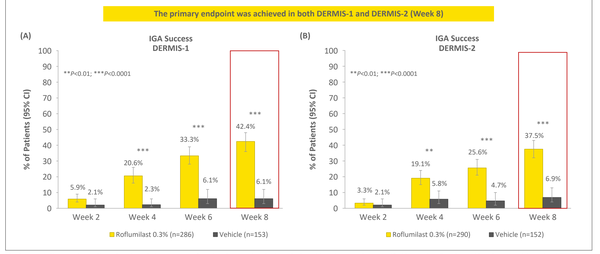
	DERMIS-1		DERMIS-2	
	Roflumilast Cream 0.3% (n=286)	Vehicle (n=153)	Roflumilast Cream 0.3% (n=290)	Vehicle (n=152)
Psoriasis-affected BSA, mean % (SD)	6.3 (4.38)	7.4 (4.76)	7.1 (4.84)	7.7 (5.05)
PASI, mean score (SD)	6.3 (3.15)	6.8 (3.70)	6.5 (3.22)	7.0 (3.52)
WI-NRS, mean score (SD)	5.7 (2.75)	5.7 (2.84)	5.8 (2.61)	6.1 (2.75)
WI-NRS score ≥4, n (%)	218 (76.2)	115 (75.2)	229 (79.0)	116 (76.3)
PSD, mean total score (SD)	72.1 (42.75)	73.4 (41.29)	69.3 (40.66)	77.4 (41.24)
IGA score, n (%)				
2 (mild)	51 (17.8)	20 (13.1)	50 (17.2)	24 (15.8)
3 (moderate)	206 (72.0)	122 (79.7)	220 (75.9)	118 (77.6)
4 (severe)	29 (10.1)	11 (7.2)	20 (6.9)	10 (6.6)
I-IGA score, n (%)	n=63	n=32	n=53	n=31
2 (mild)	33 (52.4)	16 (50.0)	25 (47.2)	13 (41.9)
3 (moderate)	27 (42.9)	16 (50.0)	27 (50.9)	17 (54.8)
4 (severe)	3 (4.8)	0	1 (1.9)	1 (3.2)

BSA: body surface area; IGA: Investigator Global Assessment; I-IGA: Intertriginous-Investigator Global Assessment; ITT: intent-to-treat; PASI: Psoriasis Area and Severity Index; PSD: Psoriasis Symptom Diary; SD: standard deviation; WI-NRS: Worst Itch-Numeric Rating Scale.

Efficacy

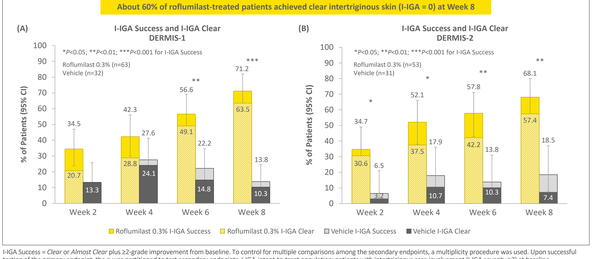
- Both phase 3 studies met the primary endpoint of IGA Success at Week 8 (Figure 2)
  - Significantly greater percentages of roflumilast-treated patients achieved IGA Success versus vehicle (Figure 2)
- Roflumilast significantly increased the percentage of patients achieving Intertriginous-Investigator Global Assessment (I-IGA) Success and an I-IGA status of *Clear* (Figure 3)

Figure 2. Percentages of Patients With IGA Success in DERMIS-1 and DERMIS-2



IGA Success = *Clear* or *Almost Clear* plus ≥2-grade improvement from baseline. Analyzed using a Cochran-Mantel-Haenszel test stratified by site, baseline IGA, and baseline intertriginous involvement; missing scores imputed using multiple imputations. Intent-to-treat population. CI: confidence interval; IGA: Investigator Global Assessment.

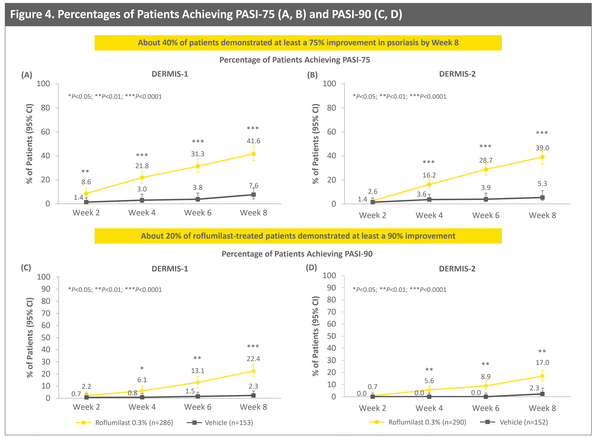
Figure 3. Percentages of Patients Achieving I-IGA Success and I-IGA Status of *Clear* in DERMIS-1 and DERMIS-2



I-IGA Success = *Clear* or *Almost Clear* plus ≥2-grade improvement from baseline. To control for multiple comparisons among the secondary endpoints, a multiplicity procedure was used. Upon successful testing of the primary endpoint, the α was partitioned to test secondary endpoints. I-IGA-intent-to-treat population: patients with intertriginous area involvement (I-IGA severity ≥2) at baseline. Observed data. CI: confidence interval; I-IGA: Intertriginous-Investigator Global Assessment.

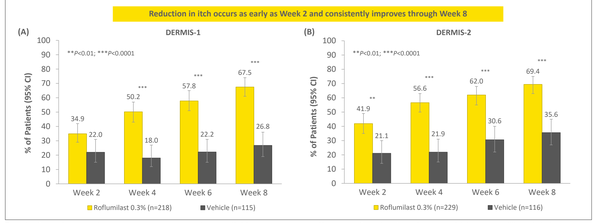
- Roflumilast provided statistically superior reduction of psoriasis as indicated by percentages of patients achieving Psoriasis Area and Severity Index (PASI)-75 and PASI-90 (Figure 4)
- Roflumilast provided significant reduction in itch as indicated by the Worst Itch-Numeric Rating Scale (WI-NRS; Figure 5)
- Roflumilast treatment significantly reduced body surface area affected by psoriasis (Figure 6)

Figure 4. Percentages of Patients Achieving PASI-75 (A, B) and PASI-90 (C, D)



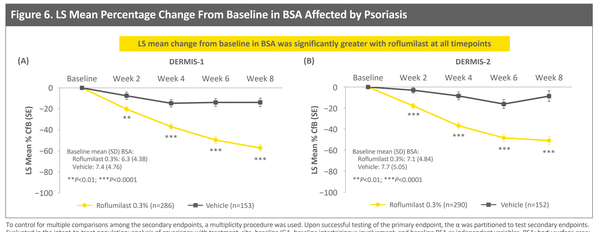
To control for multiple comparisons among the secondary endpoints, a multiplicity procedure was used. Upon successful testing of the primary endpoint, the α was partitioned to test secondary endpoints; missing scores imputed using multiple imputations. Intent-to-treat population. Observed data. CI: confidence interval; PASI: Psoriasis Area Severity Index; PASI-75: 75% reduction in PASI total score from baseline; PASI-90: 90% reduction in PASI total score from baseline.

Figure 5. Percentages of Patients With WI-NRS Success (≥4-Point Improvement in WI-NRS From Baseline Score of ≥4)



To control for multiple comparisons among the secondary endpoints, a multiplicity procedure was used. Upon successful testing of the primary endpoint, the α was partitioned to test secondary endpoints; missing scores imputed using multiple imputations. Evaluated in a subset of the intent-to-treat population of patients with WI-NRS pruritus score ≥4 at baseline. Observed data. CI: confidence interval; WI-NRS: Worst Itch-Numeric Rating Scale.

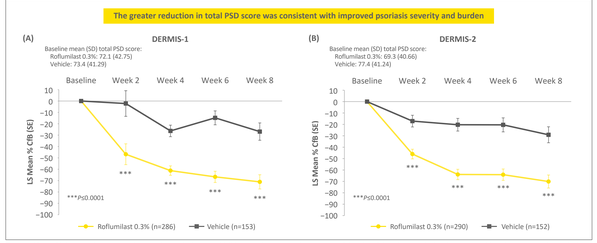
Figure 6. LS Mean Percentage Change From Baseline in BSA Affected by Psoriasis



To control for multiple comparisons among the secondary endpoints, a multiplicity procedure was used. Upon successful testing of the primary endpoint, the α was partitioned to test secondary endpoints. Evaluated in the intent-to-treat population; analysis of covariance with treatment, site, baseline IGA, baseline intertriginous involvement, and baseline BSA as independent variables. BSA: body surface area; CfB: change from baseline; LS: least squares; PASI: Psoriasis Area Severity Index; PASI-75: 75% reduction in PASI total score from baseline; PASI-90: 90% reduction in PASI total score from baseline; SE: standard error.

- Roflumilast improves disease severity and burden as indicated by significant reductions in the Psoriasis Symptom Diary total score (Figure 7)

Figure 7. LS Mean Percentage Change From Baseline in Total PSD Score



To control for multiple comparisons among the secondary endpoints, a multiplicity procedure was used. Upon successful testing of the primary endpoint, the α was partitioned to test secondary endpoints. Evaluated in the intent-to-treat population; analysis of covariance with treatment, site, baseline IGA, baseline intertriginous involvement, and baseline PSD score as independent variables. Observed data. CfB: change from baseline; IGA: Investigator Global Assessment; LS: least squares; PSD: Psoriasis Symptom Diary; SE: standard error.

Safety

- Roflumilast cream demonstrated low rates of application-site adverse events (AEs), treatment-related AEs, and discontinuations due to AEs, comparable with that of vehicle (Table 3)
- There were no treatment-related serious AEs
- Few patients discontinued due to AEs
- Application-site reactions were low
- Over 96% of patients in each group had no evidence of irritation at Weeks 4 or 8 as assessed by the investigators

Table 3. Adverse Events

	DERMIS-1		DERMIS-2	
n (%)	Roflumilast Cream 0.3% (n=286)	Vehicle Cream (n=153)	Roflumilast Cream 0.3% (n=290)	Vehicle Cream (n=152)
Patients with any TEAE	72 (25.2)	36 (23.5)	75 (25.9)	28 (18.4)
Patients with any treatment-related TEAE	7 (2.4)	3 (2.0)	16 (5.5)	8 (5.3)
Patients with any serious AE	2 (0.7)	1 (0.7)	0	1 (0.7)
Patients who discontinued study due to AE	5 (1.7)	2 (1.3)	1 (0.3)	2 (1.3)
Most common TEAE (>2% in any group), preferred term				
Hypertension[a]	5 (1.7)	6 (3.9)	4 (1.4)	0
Headache	3 (1.0)	2 (1.3)	11 (3.8)	1 (0.7)
Diarrhea	10 (3.5)	0	8 (2.8)	0
Psoriasis	0	3 (2.0)	1 (0.3)	0
Nasopharyngitis	5 (1.7)	3 (2.0)	1 (0.3)	1 (0.7)

[a]Hypertension includes synonymous terms (eg, blood pressure increased). Data are presented for safety population. AE: adverse event; TEAE: treatment-emergent adverse event.

CONCLUSIONS

Once-daily roflumilast cream 0.3% demonstrated:

- Significant improvements in psoriasis disease severity were observed based on IGA success at the primary endpoint of 8 weeks
  - Results were reproducible across both phase 3 studies
- Significant improvements in intertriginous areas were observed as measured by I-IGA Success and I-IGA *clear*
- Superior improvement across multiple other efficacy endpoints versus vehicle cream
  - Onset of efficacy occurred as early as 2 weeks, the post-baseline timepoint
- In patients with psoriasis, roflumilast cream was well tolerated with low rates of application-site AEs, treatment-related AEs, and discontinuations due to AEs, comparable with that of vehicle

These 2 phase 3 studies suggest **roflumilast cream**, an investigational once-daily, nonsteroidal topical phosphodiesterase-4 inhibitor, has the potential to address many shortcomings of existing topical treatments for plaque psoriasis

REFERENCES

1. Elmets CA, et al. *J Am Acad Dermatol* 2021;84:432-470.
2. Lebwohl MG, et al. *N Engl J Med* 2020;383:229-239.

ACKNOWLEDGEMENTS

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DISCLOSURES

ML, LHK, AYM, LSG, JDR, ZDD, MJG, LJG, AAH, KAP, JB, NB, LKF, TJ, SEK, DMP, PSY, and MZ are investigators and/or consultants for Arcutis Biotherapeutics, Inc. and received grants/research funding and/or honoraria; **AF, PB, RCH,** and **DRB** are employees of Arcutis Biotherapeutics, Inc. Additional disclosures provided on request.