Roflumilast Cream 0.3% Improved the Severity and Impact of Itch in Patients With Chronic Plaque Psoriasis in the Phase 3 DERMIS-1 and DERMIS-2 Studies

Melinda J. Gooderham,[1] Javier Alonso-Llamazares,[2] Jerry Bagel,[3] John C. Browning,[4] Zoe D. Draelos,[5] Kimberly K. Grande,[6] Adelaide A. Hebert,[7] H. Chih-ho Hong,[8] Mark Lebwohl,[9] Wei Jing Loo,[10] Walter K. Nahm,[11] Kim A. Papp, [12] David M. Pariser,[13] Jennifer Soung,[14] Linda Stein Gold,[15] Irina Turchin,[16] Amy Feng,[17] Patrick Burnett,[17] Robert C. Higham,[17] David R. Berk[17]

[1]Skin Centre for Dermatology, Probity Medical Research and Queen's University, Peterborough, ON, Canada; [2]Driven Research LLC, Coral Gables, FL, USA; [3]Psoriasis Treatment Center of Central New Jersey, Windsor, NJ, USA; [4]Texas Dermatology and Laser Specialists, San Antonio, TX, USA; [5]Dermatology Consulting Services, High Point, NC, USA; [6]The Skin Wellness Center, P.C., Knoxville, TN, USA; [7]UT Health McGovern Medical School, Houston, TX, USA; [8]Probity Medical Research and Department of Dermatology and Skin Science, University of British Columbia, Surrey, BC, Canada; [9]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [10]DermEffects and Probity Medical Research, London, ON, Canada; [11]University of California, San Diego, School of Medicine, La Jolla, CA, USA; [12]Probity Medical Research and K Papp Clinical Research, Waterloo, ON, Canada; [13]Eastern Virginia Medical School and Virginia Clinical Research, Inc., Norfolk, VA, USA; [14]Southern California Dermatology, Santa Ana, CA, USA; [15]Henry Ford Medical Center, Detroit, MI, USA; [16]Brunswick Dermatology Center, Fredericton, NB, Canada and Probity Medical Research; [17]Arcutis Biotherapeutics, Inc., Westlake Village, CA, USA

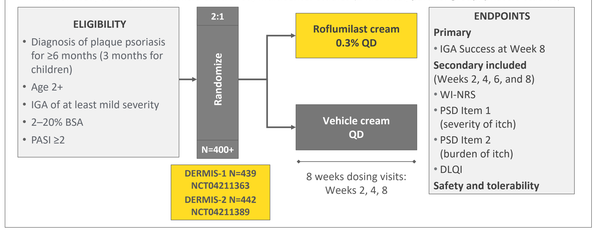
INTRODUCTION

- Itch is the most burdensome and frequently reported symptom of psoriasis[1,2]
- Roflumilast is a selective and highly potent phosphodiesterase-4 inhibitor being investigated as a once-daily, nonsteroidal, topical treatment for various dermatologic conditions
  - Roflumilast cream provided significant and rapid improvement of patients with psoriasis, including improving intertriginous plaques and reducing itch, in a phase 2b and 2 randomized phase 3, double-blind, vehicle-controlled trials[3,4]
- Here we report the results of patient-reported outcomes, including itch, from the DERMIS-1 and DERMIS-2 phase 3 trials

METHODS

- DERMIS-1 and DERMIS-2 were identical randomized, multicenter, parallel-group, double-blind, vehicle-controlled studies (Figure 1)
- Patients eligible for inclusion in the DERMIS-1 and DERMIS-2 studies were ≥2 years old with psoriasis on the face, extremities, trunk, and/or intertriginous areas involving 2% to 20% of body surface area (BSA), not including the scalp, palms, or soles; Investigator Global Assessment (IGA) score of at least mild at baseline; and a baseline Psoriasis Area and Severity Index (PASI) score ≥2
- Patients were randomized 2:1 to receive once-daily (QD) roflumilast cream 0.3% or vehicle cream
- The primary efficacy endpoint for both studies was IGA Success (defined as achievement of clear or almost clear status plus a ≥2-grade improvement from baseline) at Week 8
  - Secondary efficacy endpoints included ≥4-point reduction on the Worst Itch-Numeric Rating Scale (WI-NRS Success; determined in patients ≥12 years with WI-NRS score ≥4 at baseline), change in Psoriasis Symptom Diary Item 1 (severity of itch), change in Psoriasis Symptom Diary Item 2 (burden of itch), and change in Dermatology Life Quality Index (DLQI)
- The primary endpoint was analyzed using a Cochran-Mantel-Haenszel test stratified by site, baseline 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

Figure 1. Study Design



BSA: body surface area; DLQI: Dermatology Life Quality Index; IGA: Investigator Global Assessment; PASI: Psoriasis Area and Severity Index; PSD: Psoriasis Symptom Diary; QD: once daily; WI-NRS: Worst Itch-Numeric Rating Scale.

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)
  - Few patients discontinued due to adverse events (AEs)
- 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 (n=153)	Roflumilast Cream 0.3% (n=290)	Vehicle (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)

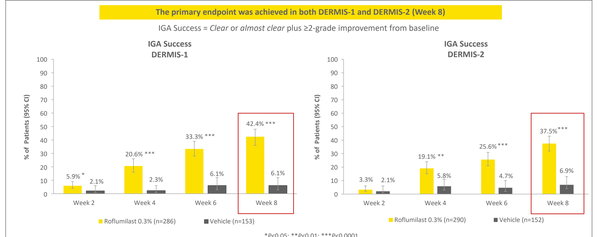
	DERMIS-1		DERMIS-2	
	Roflumilast Cream 0.3% (n=286)	Vehicle (n=153)	Roflumilast Cream 0.3% (n=290)	Vehicle (n=152)
Psoriasis-affected BSA, mean % (SD)	6.3 (4.38)	7.4 (4.76)	7.1 (4.84)	7.7 (5.05)
IGA score, n (%)				
2 (mild)	51 (17.8)	20 (13.1)	50 (17.2)	24 (15.8)
3 (moderate)	206 (72.0)	122 (79.7)	220 (75.9)	118 (77.6)
4 (severe)	29 (10.1)	11 (7.2)	20 (6.9)	10 (6.6)
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 total score, mean (SD)	72.1 (42.75)	73.4 (41.29)	69.3 (40.66)	77.4 (41.24)
PSD Item 1: severity of itch, mean (SD)	5.5 (2.89)	5.6 (2.88)	5.6 (2.74)	6.0 (2.88)
PSD Item 2: burden of itch, mean (SD)	5.4 (2.97)	5.3 (2.98)	5.4 (2.89)	6.0 (3.02)
DLQI, mean score (SD)	7.4 (5.69)	7.0 (5.04)	6.9 (5.51)	7.8 (5.74)

BSA: body surface area; DLQI: Dermatology Life Quality Index; IGA: Investigator Global Assessment; ITT: intent-to-treat; PASI: Psoriasis Area Severity Index; PSD: Psoriasis Symptoms Diary; SD: standard deviation; WI-NRS: Worst Itch-Numeric Rating Scale.

Efficacy

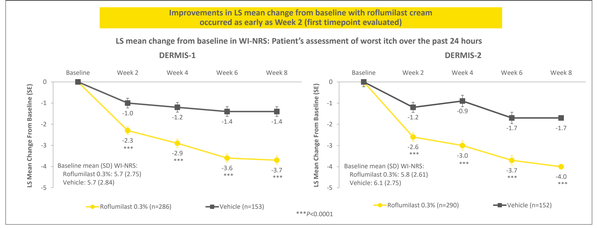
- Both phase 3 studies met the primary endpoint of IGA Success at Week 8 (Figure 2)
  - Significantly greater percentages of roflumilast-treated patients achieved IGA Success with roflumilast than with vehicle (Figure 2)
- Least squares (LS) mean change from baseline in WI-NRS was significantly greater with roflumilast cream (Figure 3)
- Significantly greater percentages of roflumilast-treated patients achieved ≥4-point reduction in WI-NRS at Week 8 (Figure 4)
- Roflumilast cream reduced the patient-reported severity of itch (Figure 5)
- Roflumilast cream significantly reduced patient-reported burden of itch at all timepoints (Figure 6)
- Roflumilast cream improved patient quality of life as indicated by changes in DLQI (Figure 7)

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



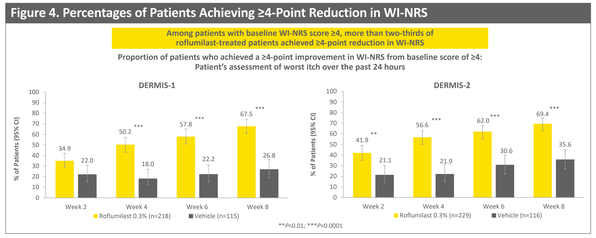
Analyzed using a Cochran-Mantel-Haenszel test stratified by site, baseline IGA, and baseline intertriginous involvement; 95% CI obtained using the Wilson method; missing scores imputed using multiple imputations. Intent-to-treat population. CI: confidence interval; IGA: Investigator Global Assessment.

Figure 3. LS Mean Change From Baseline in WI-NRS in DERMIS-1 and DERMIS-2



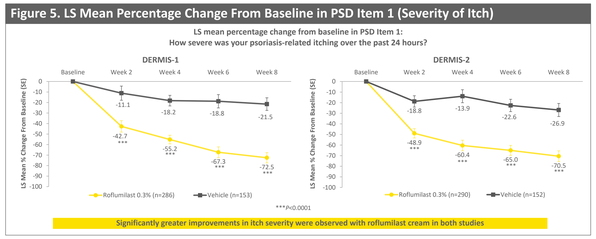
WI-NRS scale: 0 (no itch) to 10 (worst imaginable itch). Evaluated in the intent-to-treat population of patients; analysis of covariance with treatment, site, baseline IGA, baseline intertriginous involvement, and baseline WI-NRS score as independent variables. IGA: Investigator Global Assessment; LS: least squares; SE: standard error; WI-NRS: Worst Itch-Numeric Rating Scale.

Figure 4. Percentages of Patients Achieving ≥4-Point Reduction in WI-NRS



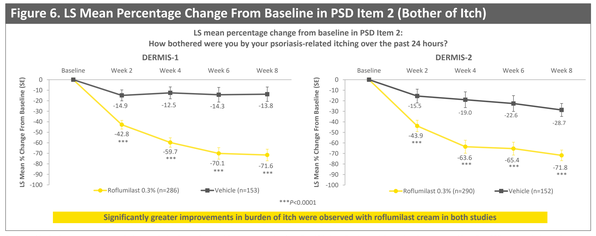
WI-NRS scale: 0 (no itch) to 10 (worst imaginable itch). Evaluated in a subset of the intent-to-treat population of patients with WI-NRS pruritus score ≥4 at baseline using a Cochran-Mantel-Haenszel test stratified by site, baseline IGA, and baseline intertriginous involvement; missing scores imputed using multiple imputations; 95% CI obtained using the Wilson method. CI: confidence interval; WI-NRS: Worst Itch-Numeric Rating Scale.

Figure 5. LS Mean Percentage Change From Baseline in PSD Item 1 (Severity of Itch)



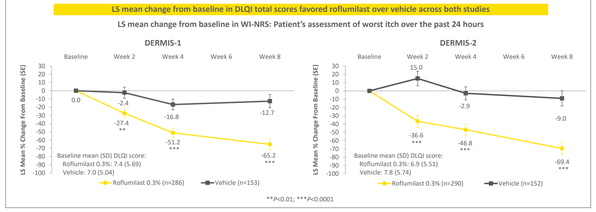
Evaluated in the intent-to-treat population; analysis of covariance with treatment, site, baseline IGA, baseline intertriginous involvement, and baseline PSD score as independent variables. IGA: Investigator Global Assessment; LS: least squares; PSD: Psoriasis Symptom Diary; SE: standard error; WI-NRS: Worst Itch-Numeric Rating Scale.

Figure 6. LS Mean Percentage Change From Baseline in PSD Item 2 (Bother of Itch)



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. IGA: Investigator Global Assessment; LS: least squares; PSD: Psoriasis Symptom Diary; SE: standard error; WI-NRS: Worst Itch-Numeric Rating Scale.

Figure 7. LS Mean Percentage Change From Baseline in DLQI



Evaluated in the intent-to-treat population; analysis of covariance with treatment, site, baseline IGA, baseline intertriginous involvement, and baseline DLQI score as independent variables. DLQI: Dermatology Life Quality Index; IGA: Investigator Global Assessment; LS: least squares; SD: standard deviation; SE: standard error; WI-NRS: Worst Itch-Numeric Rating Scale.

Safety

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

Table 3. Adverse Events

	DERMIS-1		DERMIS-2	
n (%)	Roflumilast Cream 0.3% (n=286)	Vehicle (n=153)	Roflumilast Cream 0.3% (n=290)	Vehicle (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 treatment with roflumilast cream 0.3% provided significant, consistent, and sustained improvements in the severity and burden of itch and quality of life in patients with chronic plaque psoriasis
  - Onset of action of patient-reported improvements were observed as early as the first timepoint measured (2 weeks) and improvement continued through Week 8
  - Results were reproducible across both phase 3 studies
- Roflumilast cream was associated with low rates of application-site AEs, treatment-related AEs, and discontinuations due to AEs
- DERMIS-1 and DERMIS-2 support the potential use of investigational roflumilast cream as an effective and well-tolerated nonsteroidal topical therapy in patients with chronic plaque psoriasis

These two phase 3 studies demonstrate roflumilast cream, an investigational once-daily, nonsteroidal topical phosphodiesterase-4 inhibitor, was effective in reducing itch, which decreased disease burden and improved quality of life in patients with chronic plaque psoriasis

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DISCLOSURES

MJG, **JA-L**, **JB**, **JCB**, **ZDD**, **KKG**, **AAH**, **HCH**, **ML**, **WJL**, **WKN**, **KAP**, **DMP**, **JS**, **LSG**, and **IT** 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.