Roflumilast Cream (ARQ-151) Improved Itch Severity and Itch-Related Sleep Loss in Adults With Chronic Plaque Psoriasis in a Phase 2b Study

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INTRODUCTION

- Roflumilast cream (ARQ-151), a potent phosphodiesterase-4 (PDE-4) inhibitor, is under investigation as a once-daily topical treatment for plaque psoriasis[1,2]
- In a randomized, double-blind, phase 2b trial of 331 adults with chronic plaque psoriasis, roflumilast cream administered once daily was superior to vehicle cream[2]
  - Primary endpoint of achievement of "clear" or "almost clear" skin based on Investigator Global Assessment (IGA) at Week 6 was met
    - Roflumilast 0.3%: 28.0% (*P*<0.001 vs vehicle)
    - Roflumilast 0.15%: 22.8% (*P*=0.004 vs vehicle)
    - Vehicle: 8.3%
  - Treatment-related adverse events (AEs), including application site pain, were uncommon and the frequency was similar in all groups
- Here we report the effect of roflumilast cream on itch, a highly prevalent and frequently bothersome symptom of chronic plaque psoriasis that negatively impacts quality of life,[3] assessed using patient-reported outcome (PRO) measures in this study

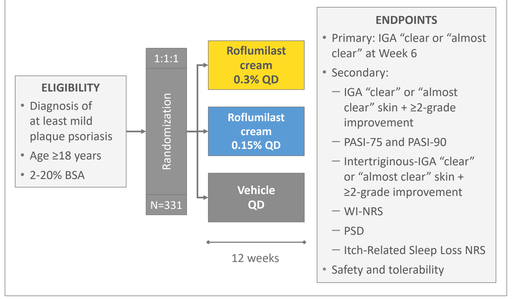
OBJECTIVE

- To assess the effect of roflumilast cream on various PROs related to itch

METHODS

- Design: parallel-group, randomized, double-blind, vehicle-controlled phase 2b study (ClinicalTrials.gov NCT03638258; **Figure 1**)[2]
- Location: 30 sites in the United States and Canada

Figure 1. Study Design



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

- Itch was assessed at baseline and Weeks 2, 4, 6, 8, and 12 using PRO measures:
  - Worst Itch Numeric Rating Scale (WI-NRS)[3] assessed the worst itch
  - Psoriasis Symptom Diary (PSD) Items 1 and 2[4-6] assessed burden and severity of itch
  - Itch-Related Sleep Loss NRS assessed intensity of sleep loss
  - All PRO measures assessed itch over the previous 24 hours and were rated on a scale from 0 (no impact) to 10 (as bad as it can be)

RESULTS

- In total, 331 patients were randomized to roflumilast 0.3% (n=109), roflumilast 0.15% (n=113), or vehicle (n=109)[2]
- Baseline characteristics are presented in **Table 1**

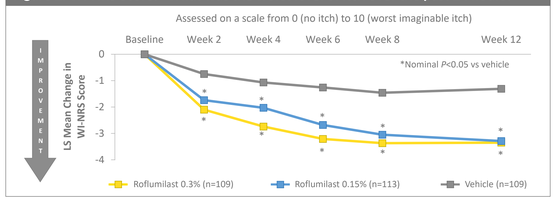
Table 1. Baseline Characteristics

	Roflumilast 0.3% (n=109)	Roflumilast 0.15% (n=113)	Vehicle (n=109)
Age, mean (SD), years	51.7 (14.1)	54.4 (14.2)	55.5 (13.5)
Sex, male, n (%)	56 (51.4)	62 (54.9)	67 (61.5)
Race, n (%)			
White	82 (75.2)	95 (84.1)	92 (84.4)
Black	12 (11.0)	10 (8.8)	7 (6.4)
Multiple/other	15 (13.8)	8 (7.1)	10 (9.2)
Psoriasis-affected BSA, mean (SD), %	6.3 (4.0)	6.4 (3.9)	6.4 (3.6)
IGA score			
2 (mild), %	15.6	15.9	10.1
3 (moderate), %	77.1	73.5	81.7
4 (severe), %	7.3	10.6	8.3
PASI, mean score (SD)	7.7 (3.6)	8.0 (3.9)	7.6 (3.1)
WI-NRS score ≥6, n (%)	71 (65.1)	62 (54.9)	64 (58.7)
WI-NRS, mean score* (SD)	6.1 (2.7)	5.6 (3.1)	5.9 (2.9)
PSD Item 1, Itch Severity,* mean score (SD)	5.5 (2.8)	5.3 (3.1)	5.5 (3.0)
PSD Item 2, Itch Burden,* mean score (SD)	5.2 (3.0)	5.2 (3.3)	5.5 (3.2)
Itch-Related Sleep Loss NRS,* mean score (SD)	2.9 (3.2)	3.0 (3.2)	3.4 (3.2)

Data are presented for intent-to-treat population. *Scale of 0 (none) to 10 (worst). BSA: body surface area; IGA: Investigator Global Assessment; NRS: numeric rating scale; PASI: Psoriasis Area and Severity Index; PSD: Psoriasis Symptom Diary; SD: standard deviation; WI-NRS: Worst Itch Numeric Rating Scale.

- Both roflumilast doses showed similar improvements in WI-NRS score and mean change from baseline in WI-NRS score was significantly superior to vehicle throughout the trial (*P*≤0.002; **Figure 2**)

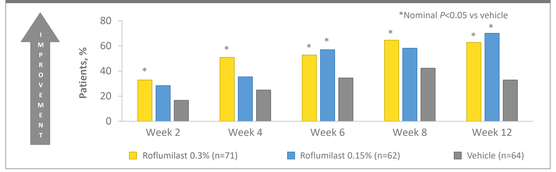
Figure 2. WI-NRS Score: "What was the worst level of itch over the past 24 hours?"



Data are presented for intent-to-treat population. Missing data imputed using linear interpolation and last observation carried forward where linear interpolation was not computationally possible. LS: least squares; WI-NRS: Worst Itch Numeric Rating Scale.

- Previous studies have shown that a 4-point change is optimal for demonstrating a clinically meaningful itch response in patients with moderate to severe plaque psoriasis[7]
- Among patients with a WI-NRS score ≥6 at baseline (n=197/331), rates of achievement of a ≥4-point reduction from baseline in WI-NRS score were significantly greater with roflumilast 0.3% vs vehicle at all timepoints (*P*≤0.034), and significantly greater with roflumilast 0.15% vs vehicle at Weeks 6 and 12 (*P*≤0.012; **Figure 3**)

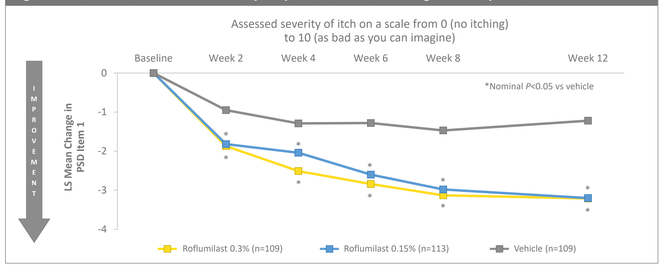
Figure 3. Proportion of Patients With a WI-NRS Score ≥6 at Baseline Who Achieved a ≥4-Point Reduction From Baseline in WI-NRS Score



WI-NRS assessed the worst itch over the past 24 hours on a scale ranging from 0 (no itch) to 10 (worst imaginable itch). Data are presented for intent-to-treat population. Missing data imputed using linear interpolation and last observation carried forward where linear interpolation was not computationally possible. WI-NRS: Worst Itch Numeric Rating Scale.

- Robust improvements in severity of itch based on Item 1 of the PSD were observed for both roflumilast 0.3% and 0.15% at Weeks 2 through 12 (*P*≤0.012 vs vehicle; **Figure 4**)

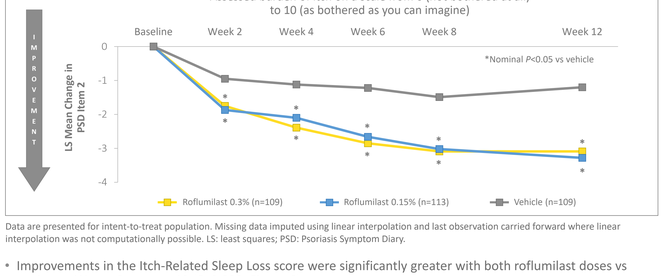
Figure 4. PSD Item 1: "How severe was your psoriasis-related itching over the past 24 hours?"



Data are presented for intent-to-treat population. Missing data imputed using linear interpolation and last observation carried forward where linear interpolation was not computationally possible. LS: least squares; PSD: Psoriasis Symptom Diary.

- Robust improvements in burden of itch based on Item 2 of the PSD were observed for both roflumilast 0.3% and 0.15% at Weeks 2 through 12 (*P*≤0.012 vs vehicle; **Figure 5**)

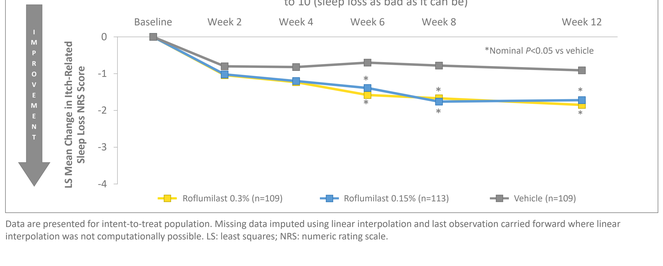
Figure 5. PSD Item 2: "How bothered were you by your psoriasis-related itching over the past 24 hours?"



Data are presented for intent-to-treat population. Missing data imputed using linear interpolation and last observation carried forward where linear interpolation was not computationally possible. LS: least squares; PSD: Psoriasis Symptom Diary.

- Improvements in the Itch-Related Sleep Loss score were significantly greater with both roflumilast doses vs vehicle at Weeks 6 through 12 (*P*≤0.022; **Figure 6**)

Figure 6. Itch-Related Sleep Loss NRS Score: "How intense was your itch-related sleep loss over the past 24 hours?"



Data are presented for intent-to-treat population. Missing data imputed using linear interpolation and last observation carried forward where linear interpolation was not computationally possible. LS: least squares; NRS: numeric rating scale.

- Treatment-emergent AEs were uncommon in this study and were similar across treatment groups (**Table 2**)[2]
- More patients discontinued the study due to an AE in the vehicle group than in the roflumilast groups
- Rates of application site pain were low and similar to vehicle
- 97% of AEs were rated mild or moderate

Table 2. Summary of AEs

TEAE, n (%)	Roflumilast 0.3% (n=109)	Roflumilast 0.15% (n=110)	Vehicle (n=107)
Patients with any TEAE	42 (38.5)	30 (27.3)	32 (29.9)
Patients with any treatment-related TEAE	7 (6.4)	3 (2.7)	7 (6.5)
Patients with any SAE[a]	1 (0.9)	1 (0.9)	2 (1.9)
Patients who discontinued study due to AE[b]	1 (0.9)	0	2 (1.9)
Most common TEAE (>2% of patients in any group)			
Upper respiratory tract infection (including viral)	9 (8.3)	8 (7.3)	4 (3.7)
Nasopharyngitis	4 (3.7)	3 (2.7)	4 (3.7)
Application site pain	2 (1.8)	1 (0.9)	3 (2.8)
Sinusitis	3 (2.8)	0	0
Urinary tract infection	0	3 (2.7)	1 (0.9)

[a]Roflumilast 0.3%: worsening of chest pain in a patient with history of myocardial infarction; roflumilast 0.15%: melanoma (not in treatment area); vehicle group: acute infarction of left basal ganglia, spontaneous miscarriage. [b]Roflumilast 0.3%: onset of worsening psoriasis; vehicle: mood swings, contact dermatitis. Data are presented for safety population. AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

CONCLUSIONS

- Once-daily roflumilast cream demonstrated significant improvement in reducing itch in patients with psoriasis compared with vehicle cream
  - Patients reported a rapid and clinically significant reduction in the severity and burden of itch
  - Significant itch reduction occurred by Week 2 and continued with further reductions through Week 12
  - In a subgroup of patients with greater severity of itch at baseline (WI-NRS ≥6), more than half of the patients had a substantial (≥4-point) reduction in itch by Week 6, and the response rate continued to increase through Week 12
  - Reduction in itch resulted in significant improvement in sleep loss by Week 6
- Roflumilast cream was well-tolerated and application site pain was uncommon and similar to vehicle

In a phase 2b study, **roflumilast cream**, an investigational once-daily, nonsteroidal topical PDE-4 inhibitor, was effective in achieving "clear" or "almost clear" skin and improving itch and itch-related sleep loss in patients with chronic plaque psoriasis

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DISCLOSURES

LSG, MGL, KAP, MJG, LHK, ZDD, SEK, DMP, JA-L, and **DPT:** Investigator, consultant, and/or advisory board member for Arcutis Biotherapeutics, Inc. **ZDD** has received grant support from Arcutis Biotherapeutics, Inc. **KS, RCH, LN,** and **DRB:** Employees of Arcutis Biotherapeutics, Inc. **HW** has a patent application relevant to this work.

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