Antifungal Effects on *Malassezia* Species in an Open-Label, Phase 1, Maximal Use Study of Roflumilast Foam 0.3% in Patients With Seborrheic Dermatitis

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INTRODUCTION

- Seborrheic dermatitis (SD) is an inflammatory skin disease characterized by immune dysregulation, skin barrier disruption, and chronic inflammation[1-4]
  - Distinct but overlapping signaling pathways compared with atopic dermatitis and psoriasis
  - A lack of Th2 dysregulation in adults
  - Unique polarization to Th17/Th22 supports host immune response to commensal *Malassezia* in areas affected by SD
  - Inflammation results in increased cell turnover in the epidermis and scaling and is exacerbated by *Malassezia* metabolites
- Distribution of *Malassezia* species dependent on regional, skin, and environmental differences
  - *M. globosa* and *M. restrica* among most prevalent species isolated in SD[5]
- Historically, topical treatment options for SD include corticosteroids, antifungals, and calcineurin inhibitors
- Roflumilast is a highly potent phosphodiesterase 4 inhibitor approved as a once-daily 0.3% foam formulation for the treatment of SD

METHODS

- Here we present the results from a 2-week, Phase 1, open-label, maximal use pharmacokinetic (PK) and safety trial of once-daily roflumilast foam 0.3% conducted in children (9 to ≤16 years old; n=10) and adults (≥18 years old; n=12) with SD
- Plasma pre-dose samples for PK analysis were taken from all patients at Week 2 (Day 15)
  - Plasma post-dose samples were taken from adult patients at 1, 2, 4, 8, and 24 hours after dosing at Week 2 (Day 15)
  - Additional samples were collected in adults at 1, 2, and 3 weeks after the last dose administered (ie, at Weeks 3, 4, and 5)
- Exploratory efficacy assessments included Investigator Global Assessment (IGA), overall assessment of erythema, overall assessment of scaling, Worst Itch-Numerical Rating Scale (WI-NRS), Scalpdex patient-reported outcomes, and body surface area (BSA)
- The exploratory analysis aimed to identify and quantify gene copy counts of *Malassezia furfur*, *Malassezia globosa*, *Malassezia restricta* and total gene copy counts of all *Malassezia* species on the skin, as well as monitor any changes occurring after 2 weeks of once-daily treatment with roflumilast foam 0.3% (n=20)
  - Four skin swabs (duplicate swabs for each area) were collected from treated and untreated areas at two time points (Day 1/baseline prior to roflumilast foam 0.3% application and Day 15/Week 2; n=20)
    - Treated areas were areas affected by SD and treated with roflumilast foam 0.3%
    - Untreated areas were areas not affected by SD and not treated with roflumilast foam 0.3%
  - Gene copy counts were quantified using quantitative polymerase chain reaction (qPCR)
    - Descriptive statistics for raw gene copy counts and for $\log_{10}$ gene copy counts at baseline and Week 2, for samples from treated and untreated areas, respectively
    - Least-square (LS) mean change from baseline to Week 2 and associated/corresponding 95% confidence intervals (CIs) and *P*-values were obtained from a repeated measurements analysis of variance (ANOVA) of $\log_{10}$ (gene copy counts) with time point (baseline or Week 2) as a factor, for treated and untreated, respectively

RESULTS

- At baseline, all patients in the safety population (n=22) had 5%–20% BSA involvement and IGA score ≥3 (**Table 1**)
- The mean ± standard deviation (SD) pre-dose serum concentrations at Day 15 were (**Table 2**):
  - Roflumilast: 0.943±1.23 ng/mL in children and 1.95±1.66 ng/mL in adults
  - Roflumilast N-oxide (the less potent, active metabolite): 10.5±16.8 ng/mL in children and 12.7±9.32 ng/mL in adults
- The mean (SD) elimination half-lives at Day 15 in adults were:
  - 3.6 (2.19) days for roflumilast and 4.4 (1.65) days for roflumilast N-oxide

Table 1. Baseline Demographics

Characteristic	Pediatric Patients (n=10)	Adult Patients (n=12)
Age, years, mean (SD)	13.9 (2.13)	45.7 (19.9)
Median (min, max)	14.0 (11, 16)	37.5 (22, 81)
Sex, n (%)		
Male	6 (60.0)	6 (50.0)
Female	4 (40.0)	6 (50.0)
Race, n (%)		
Asian	1 (10.0)	0
White	8 (80.0)	12 (100.0)
>1 race	1 (10.0)	0
Ethnicity, n (%)		
Hispanic or Latino	6 (60.0)	7 (58.3)
Not Hispanic or Latino	4 (40.0)	5 (41.7)
Fitzpatrick skin type, n (%)		
I–III	4 (40.0)	9 (75.0)
IV–VI	6 (60.0)	3 (25.0)
IGA score, n (%)		
3 (moderate)	7 (70.0)	8 (66.6)
4 (severe)	3 (30.0)	4 (33.3)
BSA, mean (SD)	5.5 (1.3)	6.3 (1.1)
Median (min, max)	5.0 (5.0, 9.0)	6.0 (5.0, 9.0)
WI-NRS, mean (SD)	5.2 (2.7)	5.3 (2.7)
Median (min, max)	5.0 (1, 9)	5.0 (1, 10)

The WI-NRS was determined by asking the patient's assessment of worst itch over the past 24 hours using a scale from 0 (no itch) to 10 (worst imaginable itch).
BSA: body surface area; IGA: Investigator Global Assessment; SD: standard deviation; WI-NRS: Worst Itch Numerical Rating Scale.

Table 2. Day 15 Pre-dose Concentrations Following Daily Topical Administration of Roflumilast Foam 0.3%

	BSA, % (SD)	Target Dose, mg (SD)	Roflumilast		Roflumilast N-Oxide	
			Conc., ng/mL (SD)	Extrapolated $AUC_{0\text{-}24}$, h·ng/mL (SD)	Conc., ng/mL (SD)	Extrapolated $AUC_{0\text{-}24}$, h·ng/mL (SD)
Pediatric patients (n=10)	5.50 (1.27)	7.82 (1.80)	0.943 (1.23)	25.1 (30.2)	10.5 (16.8)	253 (404)
Adult patients (n=10)	6.50 (1.08)	10.0 (1.66)	1.95 (1.66)	51.9 (38.4)	12.7 (9.32)	305 (224)

$AUC_{0\text{-}24}$: area under the plasma concentration by time curve from time = 0 to 24 hours post dose administration; conc.: concentration.

- Statistically significant reductions from baseline in *Malassezia* mean gene copy counts were found at Week 2 in samples from treated areas in all targets tested (**Table 3**, **Figure 1**)
  - Proportional decreases show ≥82% reduction in geometric mean gene copy counts
- Samples from untreated areas did not show the same magnitude of reduction (**Table 4**, **Figure 1**)
  - *Malassezia* gene count numbers were notably lower in the untreated areas as compared with the treated areas at baseline (**Figure 1**)
  - The proportional reductions in geometric mean gene copy counts in samples from untreated areas ranged between 40% and 56%

Table 3. Reduction From Baseline in *Malassezia* Species Gene Count at Week 2 in Treated Areas

Change From Baseline in $\log_{10}$ at Week 2 in Areas Treated With Roflumilast Foam 0.3%

Species	LS Mean	95% CI	*P*-value	Ratio of Geometric Means (Week 2 Over Baseline)	Proportional Decrease
Malassezia globosa	-0.7468	(-1.12, -0.37)	0.0005	0.1792	82.1%
Malassezia restricta	-0.7618	(-1.18, -0.34)	0.0012	0.1731	82.7%
Malassezia species	-0.9600	(-1.47, -0.45)	0.0009	0.1097	89.0%

M. furfur was detected in only 2 patients, so the results are not presented. M. furfur gene counts decreased to undetectable levels at Week 2 in both of these patients
Repeated-measure ANOVA.

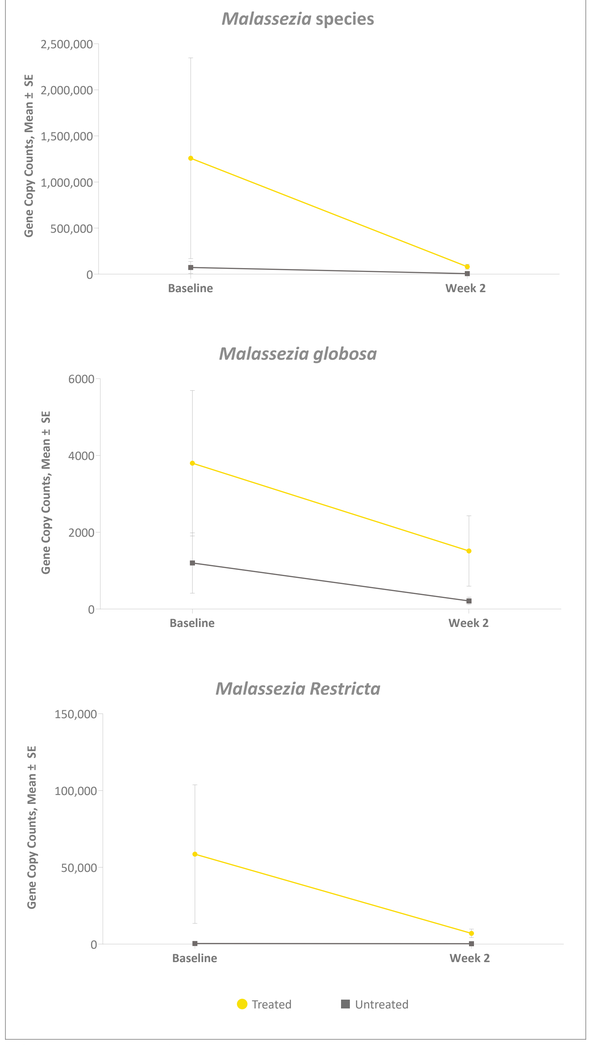
Table 4. Reduction From Baseline in *Malassezia* Species Gene Count at Week 2 in Untreated Areas

Change From Baseline in $\log_{10}$ at Week 2 in Areas **Not** Treated With Roflumilast Foam 0.3%

Species	LS Mean	95% CI	*P*-value	Ratio of Geometric Means (Week 2 Over Baseline)	Proportional Decrease
Malassezia globosa	-0.3598	(-0.60, -0.12)	0.0058	0.4367	56.3%
Malassezia restricta	-0.2559	(-0.59, 0.08)	0.1255	0.5547	44.5%
Malassezia species	-0.2221	(-0.54, 0.09)	0.1544	0.5996	40.0%

M. furfur was detected in only one patient, so the results are not presented. M. furfur gene counts were undetectable at Week 2 in that patient.
Repeated-measure ANOVA.

Figure 1. Mean Change in *Malassezia* Gene Copy Counts



M. furfur was not present in quantifiable amounts in either treated or untreated areas.
SE: standard error.

- For the exploratory efficacy evaluations at Week 2:
  - 60% of patients achieved IGA of clear/almost clear, half of whom were completely clear
  - 45% of patients achieved WI-NRS 0/1
  - 40% of patients had no evidence of erythema
  - 35% of patients had no evidence of scaling
  - Total Scalpdex score improved, with a mean (SD) percentage reduction from baseline of 36.3% (27.5%)
  - Reduction of affected BSA was observed, with a mean (SD) percentage change from baseline of -62.2% (35.1%)
- The rates of adverse events (AEs) were low, with no serious treatment-emergent AEs (TEAEs) and no treatment-emergent AEs leading to discontinuation (**Table 5**)
  - Investigators reported 'No evidence of irritation' in all patients, as measured by the Investigator Local Tolerability Assessment

Table 5. Adverse Events

Patients, n (%)	Pediatric Patients (n=10)	Adult Patients (n=12)
Patients with ≥1 TEAE	1 (10.0)	4 (33.3)
Mild	1 (10.0)	2 (16.7)
Moderate	0	2 (16.7)
Treatment-related	1 (10.0)	1 (8.3)
Patients with ≥1 treatment-emergent SAE	0	0
Patients with ≥1 TEAE leading to discontinuation of either treatment or study	0	0
Most common TEAEs by preferred term		
Headache	0	2 (16.7)
Eczema[a]	1 (10.0)	0
Herpes zoster	0	1 (8.3)
Nausea[b]	0	1 (8.3)
Otitis externa	0	1 (8.3)
Palpitations	0	1 (8.3)

[a]Eczema was not in the treatment area; [b]Mild, unrelated per investigator.
AE: adverse event; SAE: serious adverse event; TEAE: treatment emergent adverse event.

CONCLUSION

- Treatment with roflumilast suggests a direct or indirect effect on *Malassezia* in patients with SD
  - The Week 2 reduction in mean gene copy counts in the treated area was significant for *Malassezia* species (*P*=0.0007), *Malassezia globosa* (*P*=0.0003), and *Malassezia restricta* (*P*=0.009)
- Roflumilast foam 0.3% was well tolerated, with no serious AEs (SAEs) and few TEAEs, all of which were of mild or moderate in severity
  - No discontinuation of roflumilast due to AEs was reported for any patient
  - Following daily topical administration, PK results of this maximal use study in patients with SD treated with roflumilast foam 0.3% were consistent with those of the maximal use study performed with roflumilast cream 0.3% in patients with plaque psoriasis[6]

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DISCLOSURES

MZ, RC, JD, EG, VL, ML, AM, JR, and GZ, are investigators and/or consultants for Arcutis Biotherapeutics, Inc. and received grants/research funding and/or honoraria; MSS, XM, PB, DHC, DB, and SK are employees of Arcutis Biotherapeutics, Inc. Additional disclosures provided on request.

ACKNOWLEDGMENTS

Thank you to the investigators and their staff for their participation in the trials. We are grateful to the study participants and their families for their time and commitment. Writing support was provided by Lauren Ramsey, PharmD, Alligent Biopharm Consulting LLC, and funded by Arcutis Biotherapeutics, Inc.