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Mark G. Lebwohl

Kim A. Papp

Linda F. Stein Gold
Henry Ford Health, lstein1@hfhs.org

Melinda J. Gooderham

Leon H. Kircik

See next page for additional authors

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Authors

Mark G. Lebwohl, Kim A. Papp, Linda F. Stein Gold, Melinda J. Gooderham, Leon H. Kircik, Zoe D. Draelos, Steven E. Kempers, Mathew Zirwas, Kathleen Smith, David W. Osborne, Marie-Louise Trotman, Lynn Navale, Charlotte Merritt, David R. Berk, and Howard Welgus

ORIGINAL ARTICLE

Trial of Roflumilast Cream for Chronic Plaque Psoriasis

Mark G. Lebwohl, M.D., Kim A. Papp, M.D., Ph.D., Linda Stein Gold, M.D., Melinda J. Gooderham, M.D., Leon H. Kircik, M.D., Zoe D. Draelos, M.D., Steven E. Kempers, M.D., Mathew Zirwas, M.D., Kathleen Smith, M.B.A., David W. Osborne, Ph.D., Marie-Louise Trotman, M.S., Lynn Navale, M.S., Charlotte Merritt, M.B.A., David R. Berk, M.D., and Howard Welgus, M.D., for the ARQ-151 201 Study Investigators*

ABSTRACT

BACKGROUND

Systemic oral phosphodiesterase type 4 (PDE-4) inhibitors have been effective in the treatment of psoriasis. Roflumilast cream contains a PDE-4 inhibitor that is being investigated for the topical treatment of psoriasis.

METHODS

In this phase 2b, double-blind trial, we randomly assigned adults with plaque psoriasis in a 1:1:1 ratio to use roflumilast 0.3% cream, roflumilast 0.15% cream, or vehicle (placebo) cream once daily for 12 weeks. The primary efficacy outcome was the investigator's global assessment (IGA) of a status of clear or almost clear at week 6 (assessed on a 5-point scale of plaque thickening, scaling, and erythema; a score of 0 indicates clear, 1 almost clear, and 4 severe). Secondary outcomes included an IGA score indicating clear or almost clear plus a 2-grade improvement in the IGA score for the intertriginous area and the change in the Psoriasis Area and Severity Index (PASI) score (range, 0 to 72, with higher scores indicating worse disease). Safety was also assessed.

RESULTS

Among 331 patients who underwent randomization, 109 were assigned to roflumilast 0.3% cream, 113 to roflumilast 0.15% cream, and 109 to vehicle cream. An IGA score indicating clear or almost clear at week 6 was observed in 28% of the patients in the roflumilast 0.3% group, in 23% in the roflumilast 0.15% group, and in 8% in the vehicle group ($P<0.001$ and $P=0.004$ vs. vehicle for roflumilast 0.3% and 0.15%, respectively). Among the approximately 15% of patients overall who had baseline intertriginous psoriasis of at least mild severity, an IGA score at week 6 indicating clear or almost clear plus a 2-grade improvement in the intertriginous-area IGA score occurred in 73% of the patients in the roflumilast 0.3% group, 44% of those in the roflumilast 0.15% group, and 29% of those in the vehicle group. The mean baseline PASI scores were 7.7 in the roflumilast 0.3% group, 8.0 in the roflumilast 0.15% group, and 7.6 in the vehicle group; the mean change from baseline at week 6 was −50.0%, −49.0%, and −17.8%, respectively. Application-site reactions occurred with similar frequency in the roflumilast groups and the vehicle group.

CONCLUSIONS

Roflumilast cream administered once daily to affected areas of psoriasis was superior to vehicle cream in leading to a state of clear or almost clear at 6 weeks. Longer and larger trials are needed to determine the durability and safety of roflumilast in psoriasis. (Funded by Arcutis Biotherapeutics; ARQ-151 201 ClinicalTrials.gov number, NCT03638258.)

From the Icahn School of Medicine at Mount Sinai, New York (M.G.L., L.H.K.); Probity Medical Research and K. Papp Clinical Research, Waterloo (K.A.P.), and the SkiN Centre for Dermatology, Probity Medical Research and Queen's University, Peterborough (M.J.G.) — both in Ontario, Canada; Henry Ford Medical Center, Detroit (L.S.G.); Indiana Medical Center, Indianapolis (L.H.K.); Physicians Skin Care and DermResearch, Louisville, KY (L.H.K.); Dermatology Consulting Services, High Point, NC (Z.D.D.); Minnesota Clinical Study Center, Fridley (S.E.K.); Dermatologists of the Central States, Probity Medical Research, and Ohio University, Bexley (M.Z.); and Arcutis Biotherapeutics, Westlake Village (K.S., D.W.O., L.N., C.M., D.R.B., H.W.), and ML Trotman Consulting, Newbury Park (M.-L.T.) — both in California. Address reprint requests to Dr. Lebwohl at the Icahn School of Medicine at Mount Sinai, 5 E. 98th St., 5th Fl., New York, NY 10029, or at mark.lebwohl@mssm.edu.

*A complete list of the ARQ-151 201 Study Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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High-potency topical glucocorticoids and vitamin D derivatives are the main treatments for psoriasis. Topical glucocorticoids are effective in the treatment of psoriasis, but their use is usually limited to no more than 2 to 8 weeks, and they may be associated with adverse events that resolve slowly, such as skin atrophy, or that are irreversible with long-term use, such as striae.[1,2] Vitamin D derivatives are less efficacious than topical glucocorticoids and can cause local irritation.[3] Topical calcineurin inhibitors are not approved for the treatment of psoriasis but have been used off-label to treat facial and intertriginous psoriasis.[4] The frequency of their use decreased when black-box warnings were added regarding a risk of cancer. They are not effective on nonfacial, intertriginous sites. Likewise, the retinoid prodrug topical tazarotene has been used but can be locally irritating.[5] Treatment of sensitive areas such as the face and intertriginous areas with topical agents requires special consideration because of the sensitivity of the skin in these areas as well its thinness — factors that potentially enhance systemic absorption.

Phosphodiesterase type 4 (PDE-4) is an enzyme that maintains intracellular levels of cyclic adenosine monophosphate (cAMP)[6] and mediates biologic responses to extracellular stimuli in numerous cell types, including immune cells.[7] PDE-4 activity is greater in psoriatic skin than in healthy skin,[8] and inhibition of PDE-4 results in down-regulation of immune modulators, including tumor necrosis factor α, interferon-γ, interleukin-17, and interleukin-23.[9] The oral PDE-4 inhibitor apremilast has been approved for the treatment of moderate-to-severe plaque psoriasis,[10] and crisaborole ointment has been approved for the treatment of atopic dermatitis[11]; however, topical PDE-4 inhibitors are currently not approved for the treatment of psoriasis.

The topical PDE-4 inhibitor roflumilast, a once-daily cream consisting of roflumilast in a high-water-content moisturizing cream base vehicle containing the cosmetic solvent ethoxydiglycol (Transcutol), is being investigated for the treatment of plaque psoriasis. A previous 1-month, phase 2a trial involving 89 patients showed reductions in severity and size of up to three target psoriatic plaques and showed that roflumilast had a safety profile similar to that of the vehicle (placebo) cream.[12] In this phase 2b trial, we evaluated the efficacy and safety of two dose levels of roflumilast cream, administered daily over a period of 12 weeks, for the treatment of plaque psoriasis.

Methods

Trial Design and Oversight

We conducted this parallel-group, double-blind, placebo vehicle–controlled trial at 30 sites in the United States and Canada. The trial enrolled adults with mild, moderate, or severe chronic plaque psoriasis affecting 2 to 20% of the body-surface area, excluding the scalp, palms, and soles. Patients were randomly assigned in a 1:1:1 ratio to receive roflumilast 0.3% cream, roflumilast 0.15% cream, or vehicle (placebo) cream, applied once daily to affected skin areas for 12 weeks.

At week 12, patients could enter an open-label extension study for up to 12 months. Patients who did not enter the open-label study had a final follow-up visit at week 16. Roflumilast cream or the vehicle cream was applied once daily to all psoriasis lesions, including those on the face and in intertriginous areas but not including any areas on the scalp. The palms and the soles of the feet were treated but were not counted toward any measurements of efficacy.

The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation. The protocol, available with the full text of this article at NEJM.org, was approved by the Aspire Institutional Review Board for U.S. sites, by the Western Institutional Review Board for sites in Canada, and by local institutional review boards for sites not covered by these central institutional review boards. All the patients provided written informed consent before the initiation of trial-specific procedures.

The first and last authors designed the trial, with input from the other authors. The sponsor, Arcutis Biotherapeutics, provided the roflumilast cream and placebo vehicle cream, compiled the data, and paid for editorial writing assistance. Data analysis was performed by the sponsor and overseen by the authors. The investigators collected the data and had full editorial control, including the decision to submit the manuscript for publication. There were confidentiality agreements in place between the authors and the sponsor. All the authors vouch for the adherence of the trial

to the protocol, for the accuracy of the data, and for the complete reporting of adverse events.

Kits of the active-treatment creams and vehicle cream were labeled with unique, random numbers and dispensed to the patients. Patients and assessors of outcomes were unaware of the trial-group assignments. Randomization was performed according to a computer-generated randomization list.

PATIENTS

Eligible patients were 18 years of age or older and, at the time of their initial trial visit, had had plaque psoriasis for at least 6 months. Patients had to have a score indicating a psoriasis status of at least mild severity (score, ≥2) on a 5-point investigator's global assessment (IGA; a 5-point scale assessing plaque thickening, scaling, and erythema, ranging from 0 [clear] and 1 [almost clear] to 4 [severe]). Patients with an IGA score indicating mild psoriasis (score of 2) were limited to 20% of the total enrollment, patients with an IGA score indicating severe psoriasis (score of 4) were limited to 15% of the total enrollment, and all the enrolled patients must have had at least 2% and no more than 20% involvement of the body-surface area with plaque psoriasis.

In addition to having an IGA score indicating a status of at least mild severity (≥2), patients had to have a score of at least 2 on the modified Psoriasis Area and Severity Index (PASI; a measurement that combines severity of lesions and the area affected in one score that ranges from 0 [no disease] to 72 [maximal disease]) at screening. Key exclusion criteria were above-normal exposure to sunlight or tanning beds; diagnosis of guttate psoriasis (small individual spots of psoriasis), palmoplantar involvement only, or pustular psoriasis; an inability to discontinue treatment with cytochrome P450 inducers or inhibitors; and the receipt of oral roflumilast or other PDE-4 inhibitors such as apremilast within the previous 4 weeks.

TRIAL OUTCOMES

The primary efficacy outcome was an IGA status of clear or almost clear (score of 0 or 1)[13] at week 6. For patients with psoriasis of at least mild severity (IGA score ≥2) in the intertriginous area only at baseline, a separate assessment as a secondary outcome was conducted with the use of an analogous IGA scale but with evaluation only of intertriginous areas (intertriginous-area IGA).

Other secondary outcomes were the change in the PASI score[14] and the percent of the body-surface area affected by psoriasis. Secondary outcomes that were patient-reported assessments included the Worst Itch Numeric Rating Scale (WI-NRS) score, which was assessed on a scale of 0 (no itch) to 10 (worst itch imaginable) for the preceding 24 hours[15]; the Psoriasis Symptom Diary score, which assessed variables such as itching, stinging, burning, pain, skin cracking, scaling, and discoloration (this 16-item scale evaluates the effect of psoriasis symptoms on the patient's life, with each variable scored on a scale from 0 to 10, with higher scores indicating greater effect); and the Dermatology Life Quality Index.[16-18] The original protocol included as a secondary outcome a modified version of the PASI that we had developed to more precisely reflect the status of limited disease, in which involvement of anatomical areas of 1 to 9% of the body-surface area is recorded as a fraction instead of being recorded as a "1" (e.g., 0.5 for 5% involvement of the anatomical area). This measure includes all the elements of the conventional PASI and allows derivation of the PASI score, which is reported here. Efficacy assessments were conducted at screening, at baseline, and at weeks 2, 4, 6, 8, and 12 and were considered to be independent outcomes.

Safety was monitored during in-person visits by means of application-site assessments including investigator-rated skin irritation on a scale of 0 (no evidence of irritation) to 7 (strong reaction spreading beyond the application site) and patient-rated local symptoms of burning and stinging on a scale of 0 (none) to 3 (severe). Other safety assessments were laboratory variables, 12-lead electrocardiograms, vital signs, the Patient Health Questionnaire depression scale (PHQ-8), and the Columbia Suicide Severity Rating Scale (C-SSRS).

STATISTICAL ANALYSIS

Since previous efficacy data regarding the primary outcome in our trial were limited, we did not determine the sample size on the basis of the statistical power to calculate significance for the primary outcome. Efficacy data from the phase 1–2a study[12] was considered to broadly support and justify the conduct of this phase 2b trial, and

investigators selected the sample size on the basis of the desired precision of the resulting estimates. Efficacy analyses were conducted in the intention-to-treat population (i.e., all the patients who had undergone randomization).

The primary efficacy outcome of an IGA status of clear or almost clear (score, 0 or 1) at week 6 was analyzed by logistic regression with trial group as a factor. The percentage of patients with an IGA status and intertriginous-area IGA status of clear or almost clear plus a 2-grade improvement from baseline was determined for each trial group. Analyses of response included the percentage of patients with an improvement of at least 50%, 75%, or 90% in the PASI score (called PASI 50, PASI 75, and PASI 90, respectively) and an improvement of at least 4 points in the WI-NRS score. The Psoriasis Symptom Diary total score and the change from baseline in the total score at weeks 4, 6, 8, and 12 were analyzed. Dichotomized analyses of IGA and PASI scores were analyzed by logistic regression, and the remaining secondary efficacy outcomes were analyzed with the use of analysis of covariance. The results of the modified PASI, from which the PASI score was derived, were similar to those for PASI and are presented in Table S2.

There was no plan for adjustment for multiplicity of secondary outcomes, and these outcomes are reported as point estimates with multiplicity-unadjusted 95% confidence intervals, without P values, from which no clinical inferences can be made. Missing efficacy data were imputed with the use of a mixture of linear interpolation (when patients had observed values before and after the missing assessment) and the last-observation-carried-forward approach (when the missing assessment was not followed by a nonmissing value). Analyses were performed primarily with the use of SAS software, version 9.4 (SAS Institute).

Safety analyses were conducted in the safety population (i.e., all the patients who received at least one dose of roflumilast cream or vehicle cream and had at least one safety assessment). Adverse events during the intervention period were coded according to the *Medical Dictionary for Regulatory Activities*, version 20.1, with severity assessed as grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (life-threatening consequences), or grade 5 (death related to adverse event), according to the Common Terminology Criteria for Adverse Events. The statistical analysis plan is available with the protocol at NEJM.org.

RESULTS

PATIENTS

Between September 21, 2018, and May 29, 2019, a total of 331 patients (intention-to-treat population) were randomly assigned to receive roflumilast 0.3% cream (109 patients), roflumilast 0.15% cream (113 patients), or vehicle cream (109 patients) (Fig. 1). (One patient was not included in the intention-to-treat population because this person underwent randomization in error and did not receive roflumilast or placebo.) At baseline, the mean percentage of the body-surface area that was affected by psoriasis was approximately 6.4%, and the mean PASI scores ranged from 7.6 to 8.0 (Table 1). Overall, 39 patients (12%) discontinued the trial; more patients completed the trial in the roflumilast 0.3% group (94%) and the roflumilast 0.15% group (92%) than in the vehicle group (79%). The safety population comprised 109 patients in the roflumilast 0.3% group, 110 in the roflumilast 0.15% group, and 107 in the vehicle group.

EFFICACY

The primary efficacy outcome of an IGA score indicating a status of clear or almost clear (score, 0 or 1) at week 6 was observed in 28% of the patients in the roflumilast 0.3% group, in 23% of those in the roflumilast 0.15% group, and in 8% of those in the vehicle group ($P<0.001$ and $P=0.004$ vs. vehicle for roflumilast 0.3% and 0.15%, respectively). An IGA status indicating clear or almost clear was observed at both weeks 8 and 12 in 38% of the patients in the roflumilast 0.3% group; at these respective time points in 31% and 32% of the patients in the roflumilast 0.15% group; and at these respective time points in 12% and 16% of the patients in the vehicle group. Results regarding the secondary outcomes, presented with 95% confidence intervals that were not adjusted for multiplicity, are shown in Table 2 and Table S1 in the Supplementary Appendix; no clinical conclusions can be drawn from these data because of a lack of plan for multiple comparisons of secondary outcomes. The percentage of patients with a status of clear or almost clear plus a 2-grade improve-

ment from baseline at week 12 was 31% in the roflumilast 0.3% group, 27% in the roflumilast 0.15% group, and 14% in the vehicle group. Among the approximately 15% of patients overall who had baseline intertriginous psoriasis of at least mild severity, an IGA score indicating clear or almost clear plus a 2-grade improvement in the intertriginous-area IGA score occurred at week 6 in 73% of the patients in the roflumilast 0.3% group, in 44% of those in the roflumilast 0.15% group, and in 29% of those in the vehicle group. By week 12, a total of 14 of 15 patients (93%) treated with roflumilast 0.3% had an intertriginous-area IGA score of 0 (clear), as compared with 3 of 17 patients (18%) in the vehicle group.

Reductions in the PASI score in the roflumilast groups as compared with the vehicle group were in the same direction as the primary outcome from week 2 through week 12; the mean change from baseline in the PASI score at week 6 was −50.0% in the roflumilast 0.3% group, −49.0% in the roflumilast 0.15% group, and −17.8% in the vehicle group. For the PASI 75 response, results with roflumilast 0.3% and 0.15% as compared with those with vehicle were generally in the same direction as the primary outcome at week 6 through week 12. A total of 31% of the patients in the roflumilast 3.0% group, as compared with 13% of those in the vehicle group, met the criterion for the PASI 75 response at week 8, and 34% as compared with 16% met the criterion for the PASI 75 response at week 12. Results for the PASI 90 response and other secondary outcomes at weeks 4, 6, 8, and 12 are shown in Table 2 and Table S1. The results of the modified PASI, from which the PASI score was derived, were similar to those for PASI and are presented in Table S2.

Results were generally in the same direction with regard to the primary outcome among pa-

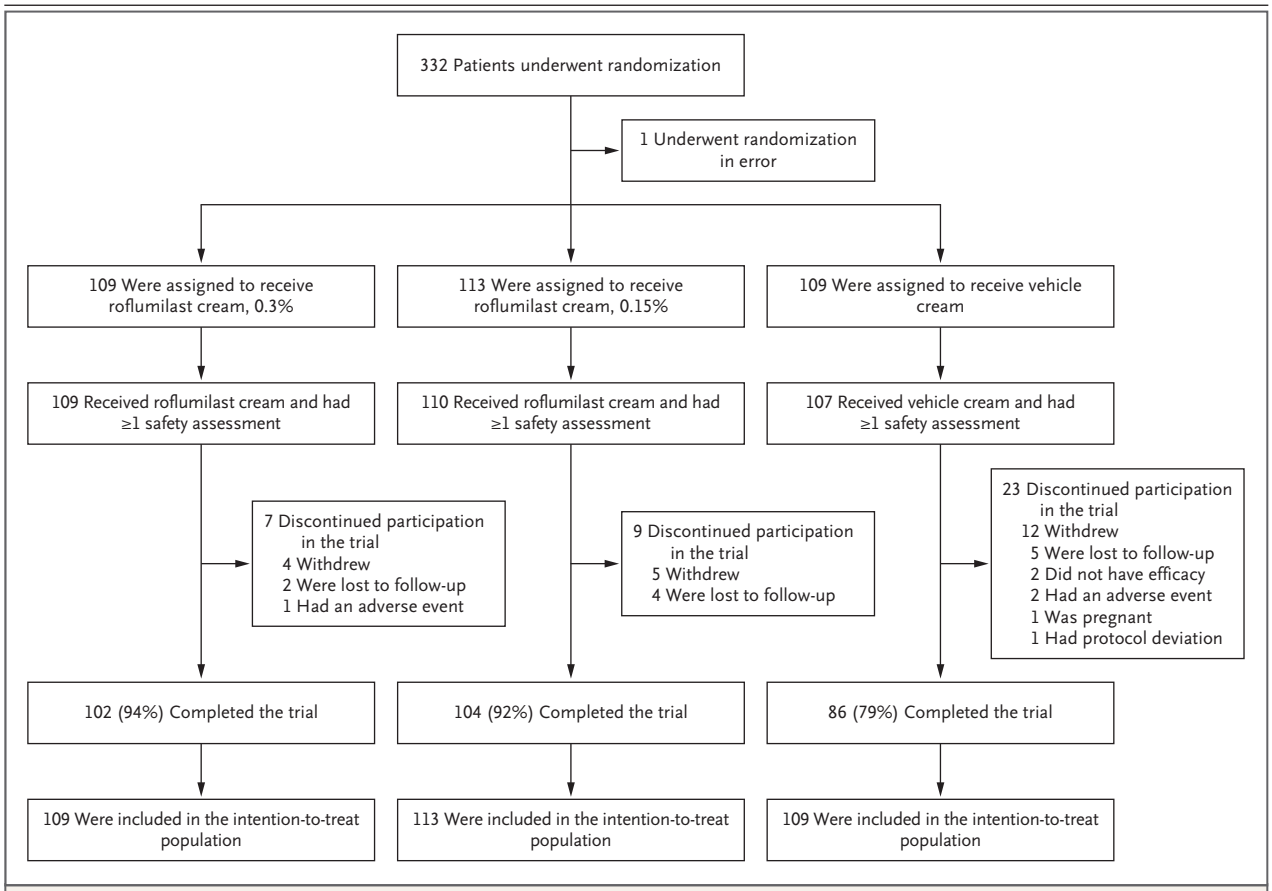

Figure 1. Randomization and Follow-up of the Patients.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Roflumilast Cream, 0.3% (N=109)	Roflumilast Cream, 0.15% (N=113)	Vehicle Cream (N=109)
Age — yr	51.7±14.1	54.4±14.2	55.5±13.5
Male sex — no. (%)	56 (51)	62 (55)	67 (61)
Race — no. (%)†			
White	82 (75)	95 (84)	92 (84)
Black	12 (11)	10 (9)	7 (6)
Asian	8 (7)	7 (6)	5 (5)
American Indian or Alaska Native	0	0	1 (1)
Multiple or other	7 (6)	1 (1)	4 (4)
Percent of body-surface area affected by psoriasis	6.3±4.0	6.4±3.9	6.4±3.6
IGA score — no. (%)‡			
2: Mild	17 (16)	18 (16)	11 (10)
3: Moderate	84 (77)	83 (73)	89 (82)
4: Severe	8 (7)	12 (11)	9 (8)
Intertriginous area involvement — no. (%)	16 (15)	18 (16)	17 (16)
Intertriginous-area IGA score — no./total no. (%)‡			
1: Almost clear	1/16 (6)	2/18 (11)	0/17
2: Mild	6/16 (38)	12/18 (67)	7/17 (41)
3: Moderate	8/16 (50)	3/18 (17)	8/17 (47)
4: Severe	1/16 (6)	1/18 (6)	2/17 (12)
PASI score§	7.7±3.6	8.0±3.9	7.6±3.1
WI-NRS score¶			
Mean	6.1±2.7	5.6±3.1	5.9±2.9
Score ≥6 — no. (%)	71 (65)	62 (55)	64 (59)
Psoriasis Symptom Diary total score‖	68.9±41.2	69.6±46.2	75.1±42.6

* Plus–minus values are ±SD. The intention-to-treat population included all the patients who had undergone randomization. Percentages may not total 100 because of rounding.
† Race was reported by the patient.
‡ The Investigator Global Assessment (IGA) is a 5-point scale for assessing plaque thickening, scaling, and erythema; scores range from 0 (clear) and 1 (almost clear) to 4 (severe). Patients in this trial were required to have a score of 2 (mild) or higher.
§ The Psoriasis Area and Severity Index (PASI) is a measurement that combines severity of lesions and the area affected into one score; scores range from 0 (no disease) to 72 (maximal disease).
¶ The Worst Itch Numeric Rating Scale (WI-NRS) score is a patient-reported assessment of itch in the preceding 24 hours; scores range from 0 (no itch) to 10 (worst itch imaginable).
‖ The Psoriasis Symptom Diary was used to assess variables such as itching, stinging, burning, pain, skin cracking, scaling, and discoloration. This 16-item scale evaluates the effect of psoriasis symptoms on the patient's life, with each variable scored on a scale from 0 to 10, with higher scores indicating greater effect. Overall, the scale of the total score ranges from 0 to 160.

tients who had a reduction of at least 4 points in the WI-NRS score (a change that was considered to indicate a response). This was also the case with regard to the Psoriasis Symptom Diary total score and item scores.

SAFETY

Adverse events were reported in 39% of the patients receiving roflumilast 0.3%, in 27% of those receiving roflumilast 0.15%, and in 30% of those receiving vehicle (Table 3); 97% of the adverse events were rated as being mild or moderate in severity. Four serious adverse events were reported: worsening of chest pain in a patient with history of myocardial infarction (in the roflumilast 0.3% group), melanoma (not in the area where roflumilast cream was applied; in the roflumilast 0.15% group), acute infarction of the

Table 2. Efficacy Outcomes (Intention-to-Treat Population).*

Outcome	Roflumilast Cream, 0.3% (N = 109)	Roflumilast Cream, 0.15% (N = 113)	Vehicle Cream (N = 109)
Primary outcome			
IGA score of 0 or 1 at wk 6 — % of patients (95% CI)	28 (20 to 37)†	23 (16 to 31)‡	8 (4 to 15)
Secondary outcomes§			
IGA score of 0 or 1 plus 2-grade improvement at wk 12 — % of patients (95% CI)	31 (23 to 41)	27 (20 to 36)	14 (8 to 21)
IGA score of 0 or 1 at wk 12 — % of patients (95% CI)	38 (29 to 47)	32 (24 to 41)	16 (10 to 24)
IGA score of 0 or 1 plus 2-grade improvement at wk 12 among patients with baseline intertriginous-area IGA score ≥2 — % of patients (95% CI)¶	94 (67 to 99)	32 (14 to 60)	24 (9 to 50)
IGA score of 0 or 1 at wk 12 among patients with baseline intertriginous-area IGA score ≥2 — % of patients (95% CI)¶	95 (69 to 99)	49 (24 to 74)	24 (9 to 50)
Least-squares mean change in PASI score at wk 12 — % (95% CI)	−53.2 (−61.1 to −45.2)	−55.0 (−62.8 to −47.2)	−17.0 (−25.0 to −9.1)
PASI response at wk 12 — % of patients (95% CI)‖			
PASI 50	62 (53 to 71)	64 (55 to 73)	24 (17 to 33)
PASI 75	34 (26 to 43)	31 (23 to 40)	16 (10 to 24)
PASI 90	20 (14 to 29)	13 (8 to 21)	7 (4 to 14)
WI-NRS response at wk 12 among patients with baseline WI-NRS score ≥6 — % of patients (95% CI)**	63 (51 to 73)	70 (58 to 80)	33 (22 to 45)
Least-squares mean change in PSD score at wk 12 (95% CI)	−42.0 (−48.5 to −35.6)	−44.2 (−50.5 to −37.9)	−20.9 (−27.3 to −14.5)

* All changes and improvements were assessed against baseline values. Missing data were imputed with the use of linear interpolation and the last-observation-carried-forward method in cases in which linear interpolation was not computationally possible. Unadjusted 95% confidence intervals (CIs) of the point estimates are presented. PSD denotes Psoriasis Symptom Diary.

† $P<0.001$ as compared with vehicle cream.

‡ $P=0.004$ as compared with vehicle cream.

§ Secondary outcomes at weeks 2, 4, 6, and 8 are provided in Table S1.

¶ The outcome was assessed in patients with intertriginous-area involvement at baseline (15 patients in the roflumilast 0.3% group, 16 in the roflumilast 0.15% group, and 17 in the vehicle group).

‖ PASI 50 indicates a reduction from baseline in the PASI score of at least 50%, PASI 75 a reduction of at least 75%, and PASI 90 a reduction of at least 90%. Results of the modified PASI, from which the PASI score was derived, are shown in Table S2.

** A WI-NRS response was defined as a reduction of at least 4 points from baseline.

Table 3. Summary of Adverse Events (Safety Population).*

Event	Roflumilast Cream, 0.3% (N=109)	Roflumilast Cream, 0.15% (N=110)	Vehicle Cream (N=107)
	no. of patients with event (%)		
Any adverse event	42 (39)	30 (27)	32 (30)
Serious adverse event	1 (1)	1 (1)	2 (2)
Adverse event leading to discontinuation of trial regimen	1 (1)	0	3 (3)
Adverse events in >1% of patients in any group			
Upper respiratory tract infection	8 (7)	7 (6)	0
Nasopharyngitis	4 (4)	3 (3)	4 (4)
Sinusitis	3 (3)	0	0
Application-site pain	2 (2)	1 (1)	3 (3)
Limb abscess	2 (2)	0	0
Weight increased	2 (2)	0	0
Pain in arm or leg	2 (2)	0	0
Insomnia	2 (2)	1 (1)	0
Cough	2 (2)	0	0
Hypertension	2 (2)	2 (2)	1 (1)
Viral upper respiratory tract infection	1 (1)	1 (1)	4 (4)
Bronchitis	1 (1)	2 (2)	0
Arthralgia	1 (1)	2 (2)	1 (1)
Influenza-like illness	1 (1)	0	2 (2)
Headache	1 (1)	2 (2)	0
Upper abdominal pain	0	0	2 (2)
Urinary tract infection	0	3 (3)	1 (1)
Contact dermatitis	0	0	2 (2)
Adverse event considered to be related to the trial regimen	7 (6)	3 (3)	7 (7)
Adverse event considered to be related to the trial regimen and reported in >1% of the patients in any group			
Application-site pain	2 (2)	0	3 (3)
Insomnia	2 (2)	0	0

* The safety population included all the patients who received at least one dose of roflumilast cream or vehicle cream and had at least one safety assessment.

left basal ganglia (in the vehicle group), and spontaneous miscarriage (in the vehicle group). The most common adverse events (those occurring in >3% of the patients in any trial group) were upper respiratory tract infection, nasopharyngitis, and viral upper respiratory tract infection.

Adverse events that were considered by the investigators to be related to the intervention were reported in 6% of the patients receiving roflumilast 0.3%, in 3% of those receiving roflumilast 0.15%, and in 7% of those receiving vehicle. The incidence of application-site reactions (in four patients receiving roflumilast 0.3%, in one receiving roflumilast 0.15%, and in five receiving vehicle), gastrointestinal adverse events such as nausea and diarrhea (in three, two, and three, respectively), and psychiatric adverse events (in three, two, and three, respectively) was similar in the roflumilast groups and the vehicle group. Three patients in the vehicle group discontinued the intervention because of an adverse event, as compared with one patient who received roflu-

milast 0.3%, who had worsening psoriasis and discontinued on day 18; no patient who received roflumilast 0.15% discontinued.

No clinically meaningful differences across groups were reported for any laboratory variables, electrocardiographs, or vital signs (data not shown). The incidence of weight loss of more than 5% of the baseline body weight was 3% among patients receiving roflumilast 0.3% cream, 4% among those receiving roflumilast 0.15% cream, and 3% among those receiving vehicle cream. The incidence of weight gain of more than 5% of the baseline body weight was similar to the incidence of weight loss (Table S3).

No roflumilast-treated patients reported suicidal ideation or behavior, according to the C-SSRS assessments of suicide risk. Most patients across the trial groups had no or minimal depression according to PHQ-8 scores at the start of the trial (71%) and at the end of the trial (87%), and there were no differences between the roflumilast groups and the vehicle group.

DISCUSSION

In this 12-week, randomized, double-blind, placebo vehicle–controlled trial, with the primary outcome assessed at 6 weeks, we found that roflumilast cream was efficacious in reducing the severity of psoriasis according to an investigator assessment of a state of clear or almost clear of plaque psoriasis (IGA score of 0 or 1, respectively). Secondary efficacy assessments, including those reported by the investigators, were generally in the same direction as that for the primary outcome but, owing to the lack of a plan for adjustment for multiple comparisons, no definite conclusions can be drawn from these data. Improvement was seen by week 2 for both roflumilast dose levels, as compared with the vehicle cream, on several scales and with regard to the Psoriasis Symptom Diary item scores. Outcomes with the higher concentration of roflumilast cream (0.3%) were numerically better than those with the lower dose (0.15%), but no formal comparisons were made between dose levels. At week 8, roflumilast 0.3% resulted in a percentage of patients with improvement on the IGA scale similar to that reported for topical glucocorticoids on the basis of historical comparisons, but no conclusions can be drawn because of differences in trial design.[19-21] Clinical improvement was also observed in intertriginous areas.

Given limitations regarding the use of topical glucocorticoids for the treatment of psoriasis on the face and intertriginous areas, because of thinner skin in these locations and a chance of systemic absorption, we used an intertriginous-area IGA scale to assess the population of patients with this condition separately from patients who had lesions only on nonintertriginous sites. Among patients with at least mild intertriginous psoriasis at baseline who were treated with roflumilast 0.3%, treatment success (score of 0 or 1 plus a 2-grade improvement) was observed in nearly half the patients by week 4, in nearly three quarters of the patients by week 6, and in almost 90% of the patients by week 8, with nearly all the patients having an intertriginous-area IGA score of 0 (indicating a clear status).[22]

The oral PDE-4 inhibitor apremilast has been used for the treatment of moderate-to-severe plaque psoriasis.[10] In previous trials, approximately 30% of the patients with moderate-to-severe plaque psoriasis (body-surface area involvement of ≥10% and PASI score of ≥12) who were taking apremilast met the criterion for PASI 75 at week 16.[10,23] In the current phase 2b trial, in which approximately 85% of the enrolled patients had moderate-to-severe disease, a generally similar percentage of patients in the roflumilast 0.3% group (31%) met the criterion for the PASI 75 response at week 8, but differences in trial design do not allow direct comparisons to be made. Apremilast has been associated with gastrointestinal adverse events of diarrhea and nausea, whereas topical administration of roflumilast cream was associated with an incidence of less than 1% of each of these events in the present trial, possibly as a result of bypassing the gastrointestinal tract with topical administration. Another PDE-4 inhibitor, crisaborole, has been approved in an ointment formulation for the treatment of atopic dermatitis and has also been used to treat psoriasis. Local irritation is the main reported adverse event. In our trial of roflumilast cream, application-site reactions were similar in the active-treatment groups and in the vehicle group.

Limitations of the trial include the short duration of 12 weeks, the duration of only 6 weeks for assessing the primary outcome in patients

with this chronic disease, and the small sample of patients with intertriginous psoriasis (approximately 15% of the patients). We were also unable to draw clinical conclusions regarding the large number of secondary outcomes as a result of the lack of a plan for adjustment of the 95% confidence intervals for multiple comparisons.

This phase 2b trial of roflumilast cream showed greater reductions in psoriasis signs and symptoms than placebo vehicle cream at 6 weeks. Longer and larger trials are necessary to determine the effectiveness and safety of roflumilast.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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