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Phase 3 Trials of Tapinarof Cream for Plaque Psoriasis

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ABSTRACT

BACKGROUND

Tapinarof cream is a topical aryl hydrocarbon receptor–modulating agent under investigation for the treatment of psoriasis. Tapinarof modulates the expression of interleukin-17 and the skin-barrier proteins filaggrin and loricrin.

METHODS

We conducted two identical phase 3 randomized trials of tapinarof in patients with mild-to-severe plaque psoriasis. Adults with a baseline Physician's Global Assessment (PGA) score of 2 (mild) to 4 (severe) (on a scale from 0 to 4, with higher scores indicating more severe psoriasis) and a percent of total body-surface area affected of 3 to 20% were randomly assigned in a 2:1 ratio to use tapinarof 1% cream or vehicle cream once daily for 12 weeks. The primary end point, PGA response, was a PGA score of 0 (clear) or 1 (almost clear) and a decrease from baseline of at least 2 points at week 12. Secondary efficacy end points at week 12 were a reduction of at least 75% in the Psoriasis Area and Severity Index (PASI) score, a PGA score of 0 or 1, the mean change from baseline in the percent of body-surface area affected, and a reduction of at least 90% in the PASI score. Patient-reported outcomes were the mean changes from baseline to week 12 in the proportion of patients who had a decrease of at least 4 points in the Peak Pruritus Numeric Rating Scale (PP-NRS) score (range, 0 [no itch] to 10 [worst imaginable itch]), the PP-NRS total score, the Dermatology Life Quality Index total score, and the Psoriasis Symptom Diary score.

RESULTS

In trials 1 and 2, a total of 692 and 674 patients, respectively, were screened, with 510 and 515 patients being enrolled. A PGA response occurred in 35.4% of the patients in the tapinarof group and in 6.0% of those in the vehicle group in trial 1 and in 40.2% and 6.3%, respectively, in trial 2 ($P<0.001$ for both comparisons). Results for secondary end points and patient-reported outcomes were generally in the same direction as those for the primary end point. Adverse events with tapinarof cream included folliculitis, nasopharyngitis, contact dermatitis, headache, upper respiratory tract infection, and pruritus.

CONCLUSIONS

Tapinarof 1% cream once daily was superior to vehicle control in reducing the severity of plaque psoriasis over a period of 12 weeks but was associated with local adverse events and headache. Larger and longer trials are needed to evaluate the efficacy and safety of tapinarof cream as compared with existing treatments for psoriasis. (Funded by Dermavant Sciences; PSOARING 1 and 2 ClinicalTrials.gov numbers, NCT03956355 and NCT03983980, respectively.)

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Psoriasis is a chronic, immune-mediated skin disease that affects approximately 2% of persons worldwide.[1] Several targeted systemic and biologic therapies have been approved for the treatment of moderate-to-severe psoriasis in adults; however, topical therapies remain the mainstay of treatment for most patients, regardless of disease severity.[2,3] Topical therapies may be associated with poor adherence to treatment and low patient satisfaction owing to the frequency and difficulty of application, as well as to the properties of the formulation and vehicle.[4-6] Although existing topical therapies, including glucocorticoids, are efficacious, especially in short-term treatment of localized disease, some medications in this class have restrictions relating to duration and extent of use and application sites.

Tapinarof is a nonsteroidal, topical aryl hydrocarbon receptor–modulating agent[7,8] in development for the treatment of psoriasis[9-11] and atopic dermatitis.[12,13] The aryl hydrocarbon receptor is a ligand-dependent transcription factor with roles in the regulation of cytokine and skin-barrier–protein expression and antioxidant activity, which makes it a reasonable therapeutic target for the treatment of inflammatory skin diseases and potentially other immunologic diseases.[14-16] Tapinarof binds to and activates the aryl hydrocarbon receptor and has been shown in preclinical studies to modulate the expression of type 17 helper T cytokines implicated in psoriasis, including interleukin-17A and interleukin-17F,[16] the skin barrier proteins filaggrin and loricrin,[16] and the aryl hydrocarbon receptor nuclear factor erythroid 2–related factor 2 (Nrf2) transcription factor pathway[14] leading to expression of antioxidant enzyme genes, such as nicotinamide adenine dinucleotide (phosphate) quinone oxidoreductase 1 and heme oxygenase-1, that reduce oxidative stress.[7,8,16] Taken together, these findings suggest that the mechanism of action of tapinarof involves immune modulation, skin-barrier normalization, and antioxidant activity.

In a phase 2b dose-finding trial, tapinarof cream was efficacious in adults with plaque psoriasis.[9,10] Here, we present the results of PSOARING 1 and PSOARING 2, two identical phase 3 trials that were designed to assess the efficacy and safety of tapinarof 1% cream, used once daily, in patients with plaque psoriasis.

Methods

Trial Design and Oversight

In these two identical, phase 3, multicenter, randomized, double-blind, vehicle-controlled trials, we assessed the efficacy and safety of tapinarof 1% cream as treatment for mild-to-severe plaque psoriasis. PSOARING 1 (trial 1) and PSOARING 2 (trial 2) were conducted at a total of 97 sites in the United States and Canada. The trials involved patients 18 to 75 years of age. Discrepancies between the dates of formal trial registration and the inception of the trials are explained in the Supplementary Appendix, which is available with the full text of this article at NEJM.org. After a maximum 34-day screening period, eligible patients were randomly assigned in a 2:1 ratio to receive either tapinarof 1% cream or vehicle cream, with stratification according to the baseline Physician's Global Assessment (PGA) score (2, 3, or 4; range, 0 to 4, with higher scores indicating worse psoriasis). Trial visits occurred at screening, at baseline, and at weeks 2, 4, 8, and 12 during the double-blind period. After the double-blind period, patients could enroll in a separate open-label, long-term extension trial (PSOARING 3; ClinicalTrials.gov number, NCT04053387) or complete a follow-up visit 4 weeks after the end of the double-blind period (i.e., at week 16).

The trials were conducted in compliance with the guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. Approval was obtained from the local ethics committee or institutional review board at each trial center. All the patients provided written informed consent. The first draft of the manuscript was written by the first author, edited by a medical writer (paid by the sponsor, Dermavant Sciences), and reviewed by all the authors, who had access to the full data set. The investigators had contracts and confidentiality agreements with the sponsor that allowed the sponsor to have the first option to publish the data, as well as to review and edit the manuscript, but that did not allow the sponsor to prevent the submission of the data for publication by the investigators or academic authors. The sponsor designed the trials, provided the tapinarof 1% and vehicle creams, analyzed the data, and funded professional editorial and medical writing assistance.

TRIAL PARTICIPANTS

Eligible participants were adults 18 to 75 years of age with a clinical diagnosis of chronic plaque psoriasis who had had stable disease for at least 6 months before the trials; had a body-surface area involvement of 3 to 20% (not including the scalp, palms, fingernails, toenails, and soles); and had a PGA score of 2 (mild), 3 (moderate), or 4 (severe) at screening and baseline (prerandomization). Patients with mild or severe psoriasis were to be limited to approximately 10% each of the total enrolled population (such that ≥80% of the population in each trial would have moderate disease). Full inclusion and exclusion criteria are provided in the trial protocols, which are available at NEJM.org.

TRIAL TREATMENT

Tapinarof 1% or vehicle control cream was dispensed to patients during clinic visits and was administered by the patients between visits. Excipients, which were identical in the tapinarof cream and vehicle control cream, included medium-chain triglycerides, emollients, stabilizers, and purified water but did not include petrolatum. Patients were instructed to apply a thin layer of cream once daily to cover psoriasis lesions completely, including newly appearing lesions and any lesions or areas in which psoriasis abated or cleared during the trial. Patients were instructed to complete a daily diary indicating the time of each application; these data were used to estimate adherence to the regimen. Adherence was defined as application on at least 80% of the days over the entire trial duration. Patients were allowed, but not required, to treat fingernail, toenail, palm, sole, and scalp lesions with the cream; however, efficacy analyses did not include the assessment of abatement of psoriasis in these areas.

Except on the morning of trial visits, patients were permitted to use nonmedicated emollients on nonlesional skin. Skin lesions could be treated only with the trial cream. Medications that were prohibited during the trial and for a minimum period before baseline were biologic agents (for five half-lives before baseline) and other systemic treatments, including apremilast, methotrexate, and glucocorticoids for 4 weeks before baseline. A list of the permitted and prohibited medications and nondrug therapies is provided in the trial protocols.

TRIAL END POINTS

The primary efficacy end point was PGA response, defined as a PGA score of 0 (clear) or 1 (almost clear) and a decrease from baseline of at least 2 points on the 5-point PGA scale at week 12. Secondary end points were the percentage of patients who had a reduction of at least 75% in the Psoriasis Area and Severity Index (PASI) score (PASI 75); the percentage of patients with a PGA score of 0 or 1 at week 12; the mean change in the percent of total body-surface area affected from baseline to week 12; and the percentage of patients who had a reduction of at least 90% in the PASI score (PASI 90) from baseline to week 12.

PATIENT-REPORTED OUTCOMES

Patient-reported outcomes were a decrease from baseline of at least 4 points in the Peak Pruritus Numeric Rating Scale (PP-NRS) score (assessed on an 11-point scale, ranging from 0 [no itch] to 10 [worst imaginable itch]) at week 12 among patients with a baseline score of at least 4 points; the mean change in the total PP-NRS score from baseline to week 12; the mean change in the Dermatology Life Quality Index total score from baseline to week 12 (assessed on a 10-item scale on which each of the 10 items is used to rate the effect on quality of life on a 4-point scale from 0 [not at all] to 3 [very much]; total scores range from 0 to 30, with lower scores indicating better health-related quality of life); and the mean change in the Psoriasis Symptom Diary score from baseline to week 12. The Psoriasis Symptom Diary score is assessed on the basis of 16 items, each rated on an 11-point scale ranging from 0 (absent) to 10 (worst imaginable), with total scores ranging from 0 to 160.

SAFETY

The primary investigators, who were responsible for assessing adverse events, were board-certified dermatologists. All the site staff who were responsible for investigating, documenting, and reporting adverse events were unaware of the trial-group assignments. Safety assessments included the incidence and frequency of adverse events and serious adverse events, the evaluation of local (application site) side effects (by patients and investigators), laboratory values, vital signs, electrocardiograms, and physical examinations. The severity of adverse events was based on the

Common Terminology Criteria for Adverse Events, version 5.0, in which grade 1 corresponds to mild, grade 2 to moderate, grade 3 to severe, grade 4 to life-threatening, and grade 5 to fatal. On the basis of previous clinical trials,[10-12] adverse events of special interest were folliculitis, contact dermatitis, and headache.

STATISTICAL ANALYSIS

Trial power was calculated with the use of a Fisher's exact sample-size calculation. We estimated that the enrollment of 500 patients in each trial would provide the trial with more than 99% power to detect a significant difference at a two-sided P value of less than 0.05, assuming that 40% of the patients in the tapinarof groups and 15% of those in the vehicle groups would meet the primary end point. The trial power was calculated to be more than 94% if 35% of the patients in the tapinarof groups and 20% of those in the vehicle groups met the primary end point. The power calculations assumed that up to 25% of patients would be lost to follow-up by week 12.

The primary efficacy end point and the dichotomous secondary end points (PASI 75, PGA score of 0 or 1, and PASI 90) were analyzed by a Cochran–Mantel–Haenszel test with stratification according to PGA score at baseline (2, 3, or 4) and were presented as relative rates. The mean change in the percent of total body-surface area affected by psoriasis was analyzed with the use of analysis of covariance (ANCOVA), with body-surface area and PGA score at baseline as covariates.

Efficacy end points were based on the intention-to-treat population, with the use of multiple imputation to handle missing data with 100 imputations generated with the use of the PROC MI procedure (fully conditional specification model with the use of the regression method, with the response at previous postbaseline visits, baseline PGA score, baseline value of the corresponding end point, and trial group as covariates) in SAS/STAT software, version 9.4 (SAS Institute). Randomization was not stratified according to trial center or country but was stratified according to the baseline PGA score. The type I error for multiple comparisons of the secondary efficacy end points was controlled by a fixed-sequence method in which the end points were tested sequentially in the prespecified order of PASI 75, PGA score of 0 or 1, the mean change in the percent of total body-surface area affected, and PASI 90 until nonsignificance (defined as a two-sided P value of ≥0.05) was observed.

Patient-reported outcomes were based on the intention-to-treat population, with the use of multiple imputation to handle missing data with 100 imputations (post hoc analyses). Exploratory efficacy end points (PASI 75 at each visit and changes in the PASI score at each visit) were also analyzed with multiple imputation with the Cochran–Mantel–Haenszel analysis or ANCOVA. A prespecified pooled analysis of PGA response according to baseline PGA score was conducted with the use of a Cochran–Mantel–Haenszel analysis stratified according to baseline PGA score. Because there was no plan to adjust the 95% confidence intervals for multiple comparisons, no conclusions can be drawn from the patient-reported or exploratory outcomes.

RESULTS

PATIENTS

Trial 1 was conducted from April 25, 2019, to May 26, 2020, and trial 2 from May 30, 2019, to May 13, 2020. Of the 674 patients who underwent screening in trial 1 and the 692 patients who underwent screening in trial 2, a total of 510 and 515 patients, respectively, underwent randomization. In trial 1, a total of 340 patients were assigned to receive tapinarof 1% cream and 170 to receive vehicle cream; in trial 2, a total of 343 patients were assigned to receive tapinarof 1% cream and 172 to receive vehicle cream (Figs. S1 and S2 in the Supplementary Appendix).

At baseline, in the populations of trials 1 and 2, a total of 79.2% and 83.9% of the patients, respectively, had a PGA score of 3 (moderate), the mean PASI score was 8.9 and 9.1, and the mean body-surface area affected by psoriasis was 7.9% and 7.6%; the between-group distributions were similar in each trial. The characteristics of the patients at baseline were generally similar in the two groups in each trial except that in trial 2, a total of 22.4% of the patients in the tapinarof group had a duration of disease less than 5 years, as compared with 16.3% of those in the vehicle group (Table 1).

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	PSOARING 1		PSOARING 2	
	Tapinarof 1% Cream (N=340)	Vehicle Cream (N=170)	Tapinarof 1% Cream (N=343)	Vehicle Cream (N=172)
Age — yr	49.8±13.7	49.1±13.3	50.0±13.1	50.0±13.7
Male sex — no. (%)	213 (62.6)	86 (50.6)	188 (54.8)	102 (59.3)
Weight — kg	91.7±24.6	92.8±22.7	92.9±24.3	89.6±19.9
Body-mass index	31.4±7.8	32.5±7.6	31.8±7.7	30.7±6.3
Race or ethnic group — no. (%)†				
White	286 (84.1)	146 (85.9)	300 (87.5)	138 (80.2)
Black	18 (5.3)	11 (6.5)	12 (3.5)	6 (3.5)
Asian	21 (6.2)	4 (2.4)	25 (7.3)	21 (12.2)
American Indian or Alaska Native	0	0	2 (0.6)	2 (1.2)
Native Hawaiian or other Pacific Islander	1 (0.3)	0	0	1 (0.6)
Other	10 (2.9)	7 (4.1)	3 (0.9)	3 (1.7)
Not reported	4 (1.2)	2 (1.2)	1 (0.3)	1 (0.6)
Duration of psoriasis — no. (%)				
<5 yr	77 (22.6)	45 (26.5)	77 (22.4)	28 (16.3)
5–10 yr	67 (19.7)	40 (23.5)	61 (17.8)	49 (28.5)
>10 yr	196 (57.6)	85 (50.0)	205 (59.8)	95 (55.2)
PGA score — no. (%)‡				
2: Mild	39 (11.5)	21 (12.4)	28 (8.2)	15 (8.7)
3: Moderate	271 (79.7)	133 (78.2)	288 (84.0)	144 (83.7)
4: Severe	30 (8.8)	16 (9.4)	27 (7.9)	13 (7.6)
PASI score§	8.7±4.0	9.2±4.4	9.1±3.7	9.3±4.0
Percent of body-surface area affected by psoriasis	7.8±4.6	8.2±5.1	7.8±4.4	7.3±4.1
PP-NRS score¶	5.7±2.9	6.1±2.8	5.9±2.7	6.1±2.8
Dermatology Life Quality Index total score‖	8.2±5.8	8.7±5.9	8.5±5.9	8.6±5.9
Psoriasis Symptom Diary total score**	73.1±41.2	74.9±43.0	74.0±38.4	76.0±41.2

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. Data on weight and body-mass index (the weight in kilograms divided by the square of the height in meters) were missing for one patient in the tapinarof group in PSOARING 2.

† Race and ethnic group were reported by the patient.

‡ The Physician's Global Assessment (PGA) score is assessed on a scale from 0 to 4, with higher scores indicating more severe psoriasis.

§ 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 Peak Pruritus Numeric Rating Scale (PP-NRS) score is assessed on an 11-point scale, ranging from 0 (no itch) to 10 (worst imaginable itch). Data were missing for one patient in the tapinarof group in both PSOARING 1 and 2.

‖ The Dermatology Life Quality Index total score is assessed on a 10-item scale on which each of the 10 items is used to rate the effect on quality of life on a 4-point scale from 0 (not at all) to 3 (very much); total scores range from 0 to 30, with lower scores indicating better health-related quality of life. Data were missing for two patients in the tapinarof group in PSOARING 1 and for one in the tapinarof group in PSOARING 2.

** 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; total scores range from 0 to 160. Data were missing for two patients in the tapinarof group and one in the vehicle group in PSOARING 1 and for one in the tapinarof group in PSOARING 2.

In trial 1, a total of 20.9% of the patients in the tapinarof group and 23.5% of those in the vehicle group discontinued the trial; in trial 2, the corresponding values were 17.8% and 17.4%. Nonadherence to the trial regimen (defined as adherence to cream use of <80%) was observed in trial 1 in 7.9% of the patients in the tapinarof group and in 7.6% of those in the vehicle group; the corresponding values in trial 2 were 9.3% and 5.8%. Protocol deviations relating to restrictions because of the coronavirus disease 2019 (Covid-19) pandemic at week 12 (when the primary end point was assessed) resulted in two missed visits and 5.6% of the patients having remote (video chat or telephone) or modified clinic visits in trial 1 and in two missed visits and 1.4% of the patients having remote or modified clinic visits in trial 2. Discontinuations that were due to ostensibly Covid-19–related reasons (e.g., trial-site closure, travel restrictions, and fear of infection) occurred in 0.6% of the patients in the tapinarof group and in 1.2% of those in the vehicle group in trial 1 and in 0.9% and 0.6%, respectively, in trial 2.

The percentages of patients with missing data for various end points were as follows: for the PGA score, 19.1% in the tapinarof group and 22.4% in the vehicle group in trial 1 and 15.7% and 16.3%, respectively, in trial 2; for the PASI score, 19.7% and 22.4% in trial 1 and 16.0% and 16.9% in trial 2; for the percent of total body-surface area affected by psoriasis, 19.4% and 22.4% in trial 1 and 15.7% and 16.9% in trial 2; for the PP-NRS score, 19.4% and 22.9% in trial 1 and 16.9% and 16.9% in trial 2; for the evaluation of a decrease of at least 4 points in the PP-NRS score, 20.4% and 23.9% in trial 1 and 18.2% and 18.2% in trial 2; for the Dermatology Life Quality Index total score, 20.0% and 21.8% in trial 1 and 16.6% and 16.9% in trial 2; and for the Psoriasis Symptom Diary score, 20.6% and 22.4% in trial 1 and 16.3% and 18.0% in trial 2. Because of the prespecified use of multiple imputation, the main results are presented as percentages rather than as raw numbers.

PRIMARY EFFICACY END POINT

The primary end point (PGA response) was observed in 35.4% of the patients in the tapinarof group, as compared with 6.0% of those in the vehicle group, in trial 1 (adjusted difference, 29.4 percentage points; relative rate, 5.8; 95% confidence interval [CI], 2.9 to 11.6; P<0.001); in trial 2, the corresponding values were 40.2% and 6.3% (adjusted difference, 33.9 percentage points; relative rate, 6.1; 95% CI, 3.3 to 11.4; P<0.001) (Table 2 and Fig. S3A). The PGA responses at weeks 2, 4, 8 and 12 are shown in Figure 1.

SECONDARY EFFICACY END POINTS

At week 12, a PASI 75 response was observed in 36.1% of the patients in the tapinarof group, as compared with 10.2% of those in the vehicle group, in trial 1 (difference, 25.9 percentage points; relative rate, 2.8; 95% CI, 1.7 to 4.5; P<0.001); the corresponding values in trial 2 were 47.6% and 6.9% (difference, 40.7 percentage points; relative rate, 6.5; 95% CI, 3.7 to 11.5; P<0.001) (Table 2 and Fig. S3B). The percentage of patients with a PGA score of 0 or 1 at week 12 was 37.8% in the tapinarof group, as compared with 9.9% in the vehicle group, in trial 1 (difference, 27.9 percentage points; relative rate, 2.7; 95% CI, 1.6 to 4.4; P<0.001); the corresponding values in trial 2 were 43.6% and 8.1% (difference, 35.5 percentage points; relative rate, 4.6; 95% CI, 2.7 to 7.6; P<0.001) (Fig. S3C).

The mean change from baseline to week 12 in the percentage of total body-surface area affected by psoriasis was −3.5 percentage points in the tapinarof group, as compared with −0.2 percentage points in the vehicle group, in trial 1 (difference, −3.3 percentage points; 95% CI, −4.4 to −2.1; P<0.001); the corresponding values in trial 2 were −4.2 percentage points and 0.1 percentage points (difference, −4.3 percentage points; 95% CI, −5.2 to −3.5; P<0.001) (Fig. S3D). At week 12, a PASI 90 response was observed in 18.8% of the patients in the tapinarof group, as compared with 1.6% of those in the vehicle group, in trial 1 (difference, 17.2 percentage points; relative rate, 8.5; 95% CI, 2.6 to 28.4; P<0.001); the corresponding values in trial 2 were 20.9% and 2.5% (difference, 18.4 percentage points; relative rate, 7.2; 95% CI, 2.9 to 18.4; P<0.001) (Fig. S3E).

PATIENT-REPORTED OUTCOMES

The mean change from baseline to week 12 in the total PP-NRS score was −3.6 in the tapinarof group and −2.7 in the vehicle group in trial 1 and −3.0 and −1.4, respectively, in trial 2 (Table 2).

Among patients who had a baseline PP-NRS score of at least 4 points, a decrease in the score of at least 4 points at week 12 was observed in 60.7% of the patients in the tapinarof group and in 43.2% of those in the vehicle group in trial 1; the corresponding values in trial 2 were 56.9% and 29.6%.

The mean change from baseline to week 12 in the Dermatology Life Quality Index total score was −4.6 in the tapinarof group and −2.8 in the vehicle group in trial 1 and −4.4 and −1.1, respectively, in trial 2. The changes in the Psoriasis Symptom Diary score at week 12 were −48.5 in the tapinarof group and −34.0 in the vehicle group in trial 1 and −42.9 and −18.8, respectively, in trial 2. Because there was no prespecified plan for adjustment of confidence intervals or imputation of missing data of these end points, no conclusions can be drawn from these data.

EXPLORATORY OUTCOMES

The changes in the percentage of patients with a PASI 75 response and in the PASI score at each visit are shown in Figure S4, and a pooled analysis of PGA response is provided in Figure S5. Because of the absence of a prespecified plan for adjustment of the width of confidence intervals for multiple comparisons, no conclusions can be drawn from these results.

SAFETY

There were no relevant differences between the tapinarof groups and the vehicle groups with regard to laboratory values, vital signs, electrocardiograms, or physical (nondermatologic) examinations. Adverse events during the trial were reported in 50.3% of the patients receiving tapinarof and in 22.4% of those receiving vehicle in trial 1 and in 54.5% and 26.2%, respectively, in trial 2 (Table 3). There were no serious adverse events that were considered by the investigators to be related to tapinarof or vehicle cream in either trial (Tables 3 and S1).

Folliculitis was reported in 23.5% of the patients receiving tapinarof and in 1.2% of those receiving vehicle in trial 1 and in 17.8% and 0.6%, respectively, in trial 2; one severe (grade 3) adverse event of folliculitis occurred in the tapinarof group in trial 1. Contact dermatitis was reported in 5.0% of the patients receiving tapinarof and in 0.6% of those receiving vehicle in trial 1 and in 5.8% of the patients receiving tapinarof and in no patients receiving vehicle in trial 2; one severe adverse event of contact dermatitis occurred in the tapinarof group in trial 2. Headache was reported in 3.8% of the patients receiving tapinarof and in 2.4% of those receiving vehicle in trial 1 and in 3.8% and 0.6%, respectively, in trial 2; one severe adverse event of headache occurred 30 days after the completion of tapinarof therapy in trial 2.

Patient-reported burning or stinging and itching, as graded on a 5-point scale (with a score of 0 indicating none, 1 slight, 2 mild, 3 moderate, and 4 strong or severe), across application sites was rated as low (numerically lower with tapinarof than with vehicle at all visits) in the two trials. There were minimal differences between trial groups and across visits, with mean scores in each trial ranging from 1.1 to 2.0 in the two trial groups (Fig. S6). The mean investigator-assessed overall application-site irritation scores ranged from 0.1 to 0.2 (on a scale from 0 to 4, with a score of 0 indicating no irritation and a score of 1 mild irritation) in the two trial groups at all time points in each trial, including when the cream was applied to sensitive skin areas (Figs. S7 and S8).

DISCUSSION

Topical tapinarof 1% cream administered once daily was superior to a vehicle control cream in reducing the severity of plaque psoriasis over a period of 12 weeks in our two trials. The findings of these 12-week phase 3 trials are similar to the results in phase 2 trials.[9-11] Use of topical tapinarof cream was associated with folliculitis, contact dermatitis, and headache. Folliculitis has been noted more often in patients receiving tapinarof than in those receiving vehicle control in previous trials.[9,17] Across the two present trials, one adverse event of folliculitis was severe, and folliculitis led to trial discontinuation in 1.8% of the patients receiving tapinarof in trial 1 and in 0.9% of those in trial 2. One severe adverse event of contact dermatitis occurred across the two trials, and contact dermatitis led to trial discontinuation in 1.5% and 2.0% of the patients receiving tapinarof in trials 1 and 2, respectively. Headache was more frequent in the tapinarof

Table 2. Primary and Secondary Efficacy End Points and Patient-Reported Outcomes at Week 12.*

End Point	PSOARING 1		PSOARING 2	
	Tapinarof 1% Cream (N=340)	Vehicle Cream (N=170)	Tapinarof 1% Cream (N=343)	Vehicle Cream (N=172)
Primary end point: PGA response				
Percent of patients with end point	35.4±2.8	6.0±2.1	40.2±2.8	6.3±2.0
Relative rate vs. vehicle (95% CI)	5.8 (2.9 to 11.6)		6.1 (3.3 to 11.4)	
P value vs. vehicle	<0.001		<0.001	
Secondary end points in order of hierarchical testing				
PASI 75†				
Percent of patients with end point	36.1±2.7	10.2±2.4	47.6±2.8	6.9±2.0
Relative rate vs. vehicle (95% CI)	2.8 (1.7 to 4.5)		6.5 (3.7 to 11.5)	
P value vs. vehicle	<0.001		<0.001	
PGA score of 0 (clear) or 1 (almost clear)				
Percent of patients with end point	37.8±2.8	9.9±2.5	43.6±2.8	8.1±2.2
Relative rate vs. vehicle (95% CI)	2.7 (1.6 to 4.4)		4.6 (2.7 to 7.6)	
P value vs. vehicle	<0.001		<0.001	
Change in percent of body-surface area affected by psoriasis				
Mean change — percentage points	−3.5±0.5	−0.2±0.6	−4.2±0.4	0.1±0.4
Difference vs. vehicle (95% CI) — percentage points	−3.3 (−4.4 to −2.1)		−4.3 (−5.2 to −3.5)	
P value vs. vehicle	<0.001		<0.001	
PASI 90‡				
Percent of patients with end point	18.8±2.2	1.6±1.0	20.9±2.3	2.5±1.2
Relative rate vs. vehicle (95% CI)	8.5 (2.6 to 28.4)		7.2 (2.9 to 18.4)	
P value vs. vehicle	<0.001		<0.001	
Patient-reported outcomes§				
PP-NRS score				
Change in score	−3.6±0.2	−2.7±0.2	−3.0±0.2	−1.4±0.3
Least-squares mean difference vs. vehicle (95% CI)	−0.8 (−1.3 to −0.4)		−1.6 (−2.1 to −1.1)	
≥4-point decrease in PP-NRS score¶				
No. of patients with data	255	134	264	137
Percent of patients with end point	60.7±3.3	43.2±4.6	56.9±3.2	29.6±4.1
Relative rate vs. vehicle (95% CI)	1.4 (1.1 to 1.7)		1.8 (1.4 to 2.4)	
Dermatology Life Quality Index total score				
Change in score	−4.6±0.3	−2.8±0.4	−4.4±0.4	−1.1±0.5
Least-squares mean difference vs. vehicle (95% CI)	−1.8 (−2.6 to −1.0)		−3.3 (−4.2 to −2.4)	
Psoriasis Symptom Diary score				
Change in score	−48.5±2.4	−34.0±2.9	−42.9±2.9	−18.8±3.5
Least-squares mean difference vs. vehicle (95% CI)	−14.4 (−20.3 to −8.5)		−24.1 (−30.7 to −17.6)	

Table 2. (Continued.)

* All end points represent means of proportions (±SE) on the basis of 100 imputed data sets and cannot be presented as a numerator and denominator. Multiple imputation reflects variation both within and across imputations. A PGA response was defined as a PGA score of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points from baseline at week 12. At week 12, the percentages of patients with data imputed were as follows: for the PGA score, 19.1% in the tapinarof group and 22.4% in the vehicle group in PSOARING 1 (trial 1) and 15.7% and 16.3%, respectively, in PSOARING 2 (trial 2); for the PASI score, 19.7% and 22.4% in trial 1 and 16.0% and 16.9% in trial 2; for the percent of total body-surface area affected by psoriasis, 19.4% and 22.4% in trial 1 and 15.7% and 16.9% in trial 2; for the PP-NRS score, 19.4% and 22.9% in trial 1 and 16.9% and 16.9% in trial 2; for the decrease of at least 4 points in the PP-NRS score, 20.4% and 23.9% in trial 1 and 18.2% and 18.2% in trial 2; for the Dermatology Life Quality Index total score, 20.0% and 21.8% in trial 1 and 16.6% and 16.9% in trial 2; and for the Psoriasis Symptom Diary score, 20.6% and 22.4% in trial 1 and 16.3% and 18.0% in trial 2.
† PASI 75 indicates that the patient had a reduction from baseline of at least 75% in the PASI score.
‡ PASI 90 indicates that the patient had a reduction from baseline of at least 90% in the PASI score.
§ Because of the absence of a prespecified plan for adjustment of the size of confidence intervals for multiple outcomes, no conclusions can be drawn from these data.
¶ This analysis involved only patients who had a baseline PP-NRS score of 4 or higher.

groups than in the vehicle groups. The mean patient- and investigator-rated local irritation scores were no worse than "mild" with tapinarof cream, including when it was applied to sensitive skin, such as the face and intertriginous areas.

Approximately 15 to 20% of end-point data were missing, and multiple imputation was used to adjust for missing data as prespecified in the statistical analysis plan in providing estimates of many of the trial end points. The tapinarof and control creams contained the same vehicle and had identical consistencies and appearances, but local adverse events may have unmasked the active treatment in the trials. These trials enrolled adults with plaque psoriasis in the United States and Canada, so the results may not be generalizable to other populations or to all forms of psoriasis. Furthermore, approximately 80% of the patients in these trials had a baseline PGA score of 3 (indicating moderate disease), and patients with very limited (<3%) or very extensive (>20%) body-surface areas affected by psoriasis were excluded from the trials, which limits the generalizability of the conclusions to the full spectrum of severity of plaque psoriasis.

In these 12-week trials, the topical aryl hydrocarbon receptor–modulating agent tapinarof was superior to vehicle in reducing the manifestations

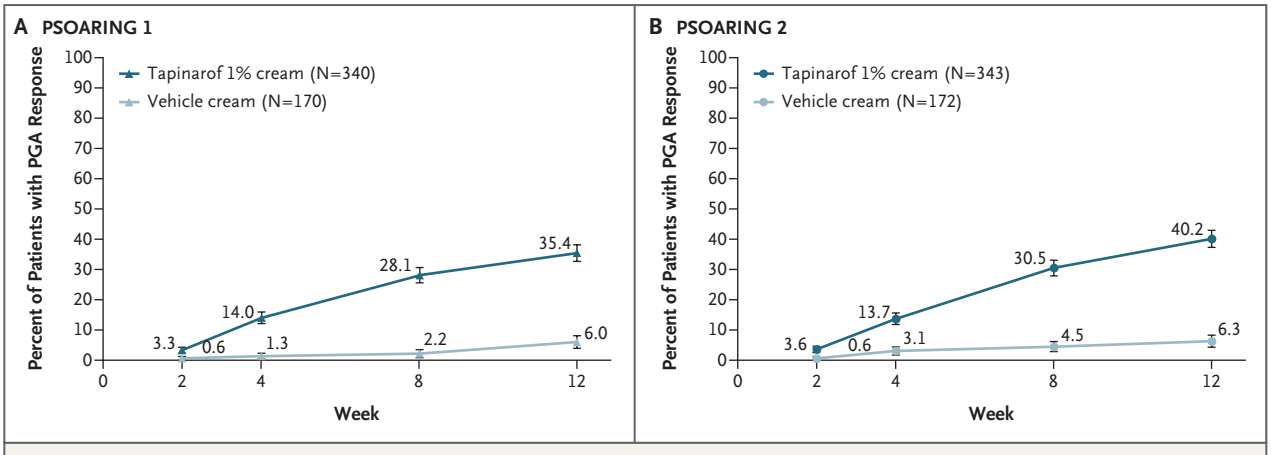

Figure 1. PGA Response at Each Visit (Intention-to-Treat Population).

A Physician's Global Assessment (PGA) response was defined as a PGA score of 0 (clear) or 1 (almost clear) and a decrease from baseline of at least 2 points at week 12 (range, 0 to 4, with higher scores indicating more severe psoriasis). Data represent the mean percentage of patients with a PGA response on the basis of 100 imputed data sets. I bars indicate the standard error. The multiple-imputation standard error reflects variation both within and across imputations. At weeks 2, 4, 8, and 12, respectively, the percentages of patients who had data imputed for the PGA response were 4.1%, 6.8%, 13.5%, and 19.1% in the tapinarof group and 5.9%, 11.2%, 15.3%, and 22.4% in the vehicle group in the PSOARING 1 trial (Panel A) and 2.9%, 6.4%, 11.7%, and 15.7% in the tapinarof group and 2.3%, 4.1%, 12.2%, and 16.3% in the vehicle group in the PSOARING 2 trial (Panel B).

Table 3. Adverse Events (Safety Population).*

Event	PSOARING 1		PSOARING 2	
	Tapinarof 1% Cream (N=340)	Vehicle Cream (N=170)	Tapinarof 1% Cream (N=343)	Vehicle Cream (N=172)
	number of patients (percent)			
Any adverse event	171 (50.3)	38 (22.4)	187 (54.5)	45 (26.2)
Grade 4 adverse event†	2 (0.6)	0	1 (0.3)	0
Adverse event leading to trial discontinuation	19 (5.6)	0	20 (5.8)	1 (0.6)
Most frequent adverse events‡				
Folliculitis§	80 (23.5)	2 (1.2)	61 (17.8)	1 (0.6)
Grade 3	1 (0.3)	0	0	0
Led to trial discontinuation	6 (1.8)	0	3 (0.9)	0
Nasopharyngitis	25 (7.4)	10 (5.9)	14 (4.1)	5 (2.9)
Contact dermatitis§	17 (5.0)	1 (0.6)	20 (5.8)	0
Grade 3	0	0	1 (0.3)	0
Led to trial discontinuation	5 (1.5)	0	7 (2.0)	0
Headache§	13 (3.8)	4 (2.4)	13 (3.8)	1 (0.6)
Grade 3	0	0	1 (0.3)	0
Led to trial discontinuation	1 (0.3)	0	2 (0.6)	0
Upper respiratory tract infection	5 (1.5)	4 (2.4)	12 (3.5)	8 (4.7)
Pruritus	8 (2.4)	0	7 (2.0)	2 (1.2)
Viral upper respiratory tract infection	7 (2.1)	2 (1.2)	3 (0.9)	0

* Shown are adverse events that started on or after the date of the first dose of tapinarof 1% cream or vehicle cream. Each patient with an adverse event was counted only once for each *Medical Dictionary for Regulatory Activities* (MedDRA), version 22.0, preferred term. Severity was not based on morphologic grading but according to the Common Terminology Criteria for Adverse Events, version 5.0, on which grade 1 (mild) indicates asymptomatic or mild symptoms or clinical or diagnostic observations only, with intervention not indicated; grade 2 (moderate), minimal, local, or noninvasive intervention indicated, causing limitations on age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, and managing money); grade 3 (severe or medically significant but not immediately life-threatening), hospitalization or prolongation of hospitalization indicated, a disabling event, causing limitations on self-care–related activities of daily living (bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications; but not bedridden); grade 4 (life-threatening consequences), urgent intervention indicated; and grade 5 (death related to adverse event).
† No life-threatening (grade 4) adverse events were considered by the investigators to be related to tapinarof 1% cream.
‡ The most frequent adverse events were defined as those that occurred in at least 2% of the patients in any group.
§ No prespecified adverse events of special interest (investigator-grouped MedDRA preferred terms) were considered by the investigators to be life-threatening or related to death (grade 4 or 5).

of psoriasis but was associated with local adverse events and headache. Larger and longer trials are needed to evaluate the efficacy and safety of tapinarof cream as compared with existing treatments for psoriasis.

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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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