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CASE SERIES

Tapinarof Cream 1% Once Daily for the Treatment of Plaque Psoriasis: Case Photography of Clinical Outcomes from Three Phase 3 Trials

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ABSTRACT

Tapinarof cream 1% (VTAMA®; Dermavant Sciences, Inc.) is a non-steroidal, topical, aryl hydrocarbon receptor agonist approved by the US Food and Drug Administration (FDA) to treat plaque psoriasis in adults and under investigation for the treatment of psoriasis in children down to 2 years of age, and for atopic dermatitis in adults and children down to 2 years of age. The PSOARING phase 3 clinical trial program evaluated tapinarof cream 1% once daily (QD) in adults with mild to severe plaque psoriasis for up to 52 weeks (NCT03956355, NCT03983980, NCT04053387). Here we present case photography documenting outcomes in the PSOARING trials. Cases illustrate various outcomes across different body areas, including responses meeting the formal FDA-mandated regulatory endpoint of a Physician Global Assessment (PGA) score of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points from baseline at

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week 12, meaningful clinical improvement not meeting this formal endpoint, patient-reported outcomes, and pre-specified adverse events of special interest (AESIs). Tapinarof cream 1% QD demonstrated rapid and highly statistically significant efficacy, with improvements in disease activity and quality of life. In addition, a high rate (40.9%; $n = 312/763$) of complete disease clearance (PGA = 0) was achieved, and improvements exceeding National Psoriasis Foundation treatment goals were demonstrated. After first achieving complete disease clearance (PGA = 0), patients treated with tapinarof experienced an approximately 4-month remittive effect off therapy. Incidence and severity of folliculitis and contact dermatitis AESIs were generally mild or moderate, localized to the site of application, and associated with low discontinuation rates. Medical images are of importance in trials of dermatologic therapies to inform clinical decision-making and enhance patient assessment. Tapinarof cream 1% QD is efficacious and well tolerated in patients with mild to severe plaque psoriasis, with clinically relevant improvements seen early in the course of treatment.
Clinicaltrials.gov numbers: NCT03956355, NCT03983980, NCT04053387.

Keywords: Tapinarof cream 1% once daily; Aryl hydrocarbon receptor agonist; Plaque psoriasis; Phase 3 randomized controlled trials; PSOARING; Topical therapy; Case photography

Key Summary Points

Tapinarof cream 1% once daily was evaluated in adults with mild to severe plaque psoriasis in two 12-week pivotal phase 3 trials, PSOARING 1 and 2, and a long-term extension.

Images of clinical outcomes are important in trials of dermatologic therapies to inform clinical decision-making and enhance patient assessment.

Here we present patient cases illustrating treatment outcomes including responses meeting the regulatory endpoint of a Physician Global Assessment score of 0 (clear) or 1 (almost clear) and a decrease of at least 2 points from baseline at week 12, as well as patient-reported outcomes, and pre-specified adverse events of special interest (AESIs).

Tapinarof-treated patients achieving regulatory endpoints also experienced rapid, clinically meaningful improvements, while many patients who did not achieve regulatory endpoints still experienced visible and meaningful improvements in disease activity and quality of life.

Incidence and severity of AESIs, folliculitis and contact dermatitis, were generally mild or moderate, localized to application sites, and associated with low trial discontinuation rates.

INTRODUCTION

Psoriasis is a chronic, immune-mediated skin disease that affects approximately 8 million

people in the USA and 125 million people globally [1, 2]. Conventional topical treatments, including corticosteroids, and vitamin A and vitamin D analogues, are used by many patients with psoriasis [3]. Although efficacious for some patients, these topical therapies are commonly associated with restrictions on duration, extent of use, and sites of application [3, 4], and thus have limitations for managing chronic plaque psoriasis. In addition, efficacy may not be sustained after withdrawal of treatment, and rebound may be seen with some therapies, particularly corticosteroids [4, 5].

Tapinarof cream 1% (VTAMA®; Dermavant Sciences, Inc., USA) is a first-in-class, non-steroidal, topical aryl hydrocarbon receptor (AhR) agonist approved by the US Food and Drug Administration (FDA) for the treatment of plaque psoriasis in adults [6], and is under investigation for the treatment of psoriasis in children down to 2 years of age and for atopic dermatitis (AD) in adults and children down to 2 years of age. The PSOARING phase 3 clinical trial program comprised two identically designed, randomized vehicle-controlled trials, PSOARING 1 and PSOARING 2 (NCT03956355, NCT03983980), which evaluated tapinarof cream 1% once daily (QD) in adults with mild to severe plaque psoriasis [7], and a long-term extension trial, PSOARING 3 (NCT04053387), in which patients could receive an additional 40 weeks of continuous or intermittent tapinarof treatment [8]. Building on evidence from previous trials [9–12], the PSOARING program demonstrated positive, statistically significant, rapid, and durable outcomes, including high rates of complete disease clearance (40.9% [n = 312/763] achieved a Physician Global Assessment [PGA] = 0), no tachyphylaxis on therapy, and a remittive effect off therapy of approximately 4 months, defined as maintenance of a PGA score of 0 (clear) or 1 (almost clear) after first achieving a PGA score of 0 [7, 8]. The FDA approved tapinarof in May 2022 for the treatment of mild to severe plaque psoriasis in adults, without restrictions on duration, extent, or locations of use, and no label contraindications, drug interactions, warnings, or precautions [6].

Here we present case photography documenting response to therapy, including outcomes achieving and not achieving the formal regulatory trial endpoints, as well as cases of folliculitis and contact dermatitis, which were predefined adverse events of special interest (AESIs).

PSOARING PHASE 3 TRIAL PROGRAM: DESIGN

As previously reported [7, 8], all trials in the PSOARING program were conducted in accordance with Good Clinical Practice and the Helsinki Declaration. Approval was obtained from the local ethics committee or institutional review board for each trial center. All patients provided written informed consent. In PSOARING 1 and 2, patients with mild to severe plaque psoriasis were randomized to tapinarof cream 1% QD or vehicle QD for 12 weeks [7]. At baseline, patients were aged 18–75 years with stable chronic plaque psoriasis; had a body surface area (BSA) affected of 3–20%; and a PGA score of 2 (mild), 3 (moderate), or 4 (severe) [7]. The primary endpoint 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 at week 12. Secondary efficacy endpoints included achieving a reduction of $\geq$ 75% or $\geq$ 90% in Psoriasis Area and Severity Index (PASI) score (PASI75 and PASI90, respectively), proportion of patients with a PGA score of 0 or 1, and change from baseline in %BSA affected at week 12. Patient-reported outcomes (PROs) included Peak Pruritus Numerical Rating Scale (PP-NRS), Dermatology Life Quality Index (DLQI), and Psoriasis Symptom Diary (PSD) scores [7]. An itch-free state was defined as the proportion of patients achieving a PP-NRS score of 0 or 1 in PSOARING 1 and 2.

Patients completing PSOARING 1 or PSOARING 2 could enroll in PSOARING 3 for up to 40 weeks of open-label treatment with tapinarof cream 1% QD, and 4 weeks of follow-up [8]. In PSOARING 3 (Supplementary Fig. S1), patients received intermittent or continuous tapinarof treatment based on their PGA score, where those who entered with PGA $\geq$ 1

received tapinarof until complete disease clearance was achieved (PGA = 0). Those who entered with, or achieved, a PGA score of 0 discontinued treatment and were observed for remittive effect (maintenance of PGA = 0 or 1) while off therapy; if disease worsening occurred (PGA $\geq$ 2), tapinarof cream was restarted and continued until a PGA = 0 was achieved. Efficacy endpoints included the proportion of patients achieving complete disease clearance (PGA = 0 [clear]); mean total duration of remittive effect for all patients achieving a PGA score of 0; median duration of remittive effect in patients entering the open-label extension trial with a PGA score of 0; and the proportion of patients entering with a PGA score of $\geq$ 2 (mild or worse) who achieved a response (PGA = 0 or 1) at any time during the trial [8]. PROs included DLQI scores and a Patient Satisfaction Questionnaire© (PSQ). In PSOARING 3, patients were assessed in clinic by the investigator every 4 weeks.

Safety and tolerability assessments included incidence and frequency of adverse events (AEs), including folliculitis and contact dermatitis (AESIs), and local tolerability assessed by patients and investigators [7, 8]. Investigators were specifically trained to detect and monitor these AESIs during the trials.

Clinical assessments were based on validated endpoints (PGA, PASI, and BSA) reflecting the totality of patients' psoriasis disease burden, and photographs were of representative psoriasis lesions (target lesions). Target lesions were identified for serial photography before initiation of randomized treatment. Investigators were trained to take standardized photographs at trial visits, using the same camera, background, lighting, position, and distance. All patients participating in photography provided informed consent and a photographic release. Clinical photography was not required for participation in the trials. Trial assessments reflected the totality of psoriasis across the body, not only at target lesions selected for photography.

PSOARING TRIAL PROGRAM: OUTCOMES

PSOARING 1 and 2

At PSOARING 1 and 2 baseline, 79.2% (n = 404) and 83.9% (n = 432) of patients had a PGA score of 3 (moderate), mean PASI score was 8.9 and 9.1, and mean BSA affected was 7.9% and 7.6%, respectively [7]. The primary endpoint of a PGA response was highly statistically significant in the tapinarof cream 1% QD group versus vehicle at week 12 in both PSOARING 1 and 2: 35.4% vs 6.0% and 40.2% vs 6.3% (both $P < 0.0001$), respectively [7, 13]. All secondary and additional endpoints were achieved for tapinarof cream compared with vehicle in PSOARING 1 and 2 at week 12: PASI75 response (36.1% vs 10.2% and 47.6% vs 6.9%; both $P < 0.0001$), PASI90 response (18.8% vs 1.6% [$P = 0.0005$] and 20.9% vs 2.5% [$P < 0.0001$]), mean percent change in %BSA affected ($-$ 41.6% vs $-$ 0.1% and $-$ 48.1% vs 9.5%; both $P < 0.0001$), and at least a 1-grade improvement in PGA score (74.5% vs 35.6% and 80.3% vs 30.6%, respectively) [7, 13, 14]. Furthermore, significant improvements in PROs were reported at week 12 for tapinarof cream versus vehicle in PSOARING 1 and 2: change in DLQI scores ($-$ 5.0 vs $-$ 3.0 and $-$ 4.7 vs $-$ 1.6; both $P < 0.0001$), achievement of at least a 4-point improvement in PP-NRS score (67.5% vs 46.1% [$P = 0.0004$] and 59.7% vs 31.3% [$P < 0.0001$]), and change in PSD scores ($-$ 51.9 vs $-$ 34.6 and $-$ 43.5 vs $-$ 17.1; both $P < 0.0001$) [15]. An itch-free state (PP-NRS = 0 or 1) at week 12 was achieved by a significantly higher proportion of patients treated with tapinarof compared with vehicle: 49.6% vs 32.1% in PSOARING 1 ($P = 0.0007$) and 50.3% vs 27.3% in PSOARING 2 ($P < 0.0001$) [16].

PSOARING 3

The majority of eligible patients (92%, n = 763/833) elected to enroll in PSOARING 3, the long-term extension trial. Efficacy continued to improve beyond the 12-week trials with a high rate (40.9%; n = 312/763) of complete disease

clearance (PGA = 0), an approximately 4-month remittive effect off therapy (maintenance of PGA = 0 or 1) after first achieving PGA = 0, and durability of response both on or with intermittent therapy for up to 52 weeks [8]. For the 312 patients who achieved a PGA score of 0 at any time during PSOARING 3, the mean total duration of remittive effect off therapy was approximately 4 months [8].

In addition, tapinarof demonstrated durable improvements in DLQI [17], with most patients (68.0%) achieving a DLQI score of 0 or 1, indicating no impact of psoriasis on quality of life (QoL). Patients also expressed high levels of treatment satisfaction in the PSQ; most either strongly agreed or agreed with all questions on confidence and satisfaction with the efficacy of tapinarof cream (62.9–85.8%), application ease and cosmetic elegance (79.9–96.3%), and preference for tapinarof versus prior topical and systemic psoriasis therapies (55.3–81.7%) [17].

Responses Achieving Regulatory Endpoints

Case 1: Forearm—Female Patient, Aged 56 Years

This patient had moderate disease (PGA = 3) at baseline that improved to achieve the primary and secondary efficacy endpoints at week 12 (Fig. 1). In addition, a PASI75 response and 4-point reduction in PP-NRS were achieved as early as week 4. Beyond these endpoints, complete disease clearance based on a PGA, PASI, and %BSA affected of 0 at week 12 exceeded consensus treatment goals set by the US National Psoriasis Foundation (NPF) (e.g., achieving a %BSA affected of $\leq$ 1.0% at

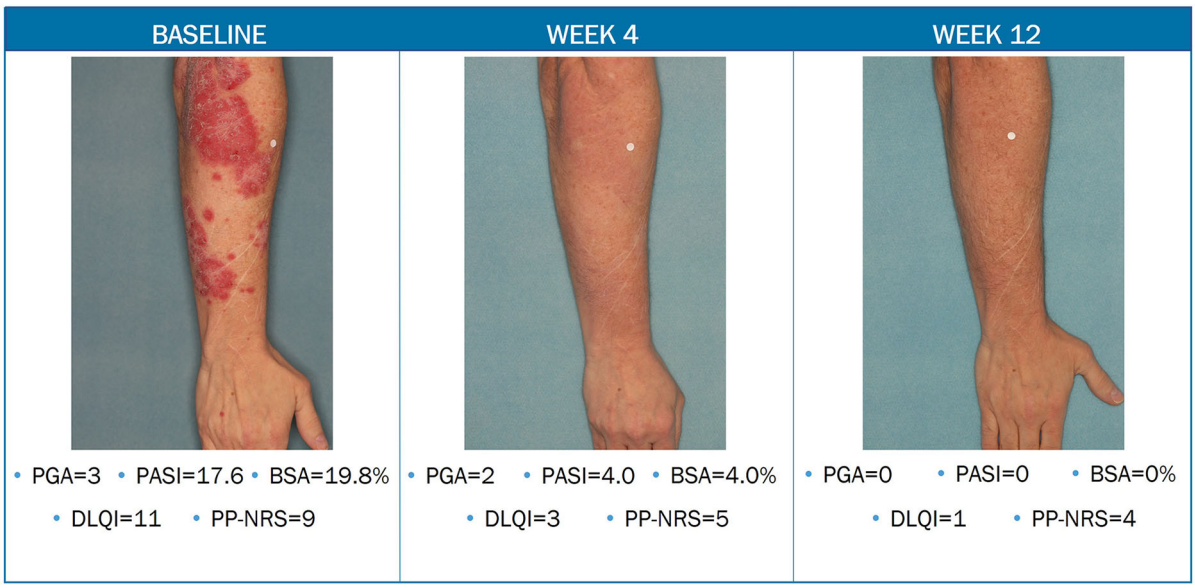

Fig. 1 Clinical response of a patient with moderate plaque psoriasis treated with tapinarof cream who achieved primary, secondary, and patient-reported endpoints in PSOARING 1. Forearm: improvement in PGA, PASI, BSA, PP-NRS, and DLQI. In addition, the secondary endpoint of a PASI75 response and the PRO of a 4-point reduction in PP-NRS were achieved as early as week 4. At baseline, well-circumscribed, erythematous plaques and patches with mild scaling are visible on the forearm. At week 4, there is complete clearing of the forearm disease, which is maintained at the 12-week endpoint. There is a notable absence of post-inflammatory hyperpigmentation at week 12 after disease resolution. Image is a representative lesion of one tapinarof-treated patient from the PSOARING 1 trial. PGA, PASI, and BSA are global efficacy assessments. Individual results may vary. *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *PASI* Psoriasis Area and Severity Index, *PASI75* a reduction of $\geq$ 75% in Psoriasis Area and Severity Index, *PGA* Physician Global Assessment, *PP-NRS* Peak Pruritus Numerical Rating Scale, *PRO* patient-reported outcome, *QD* once daily

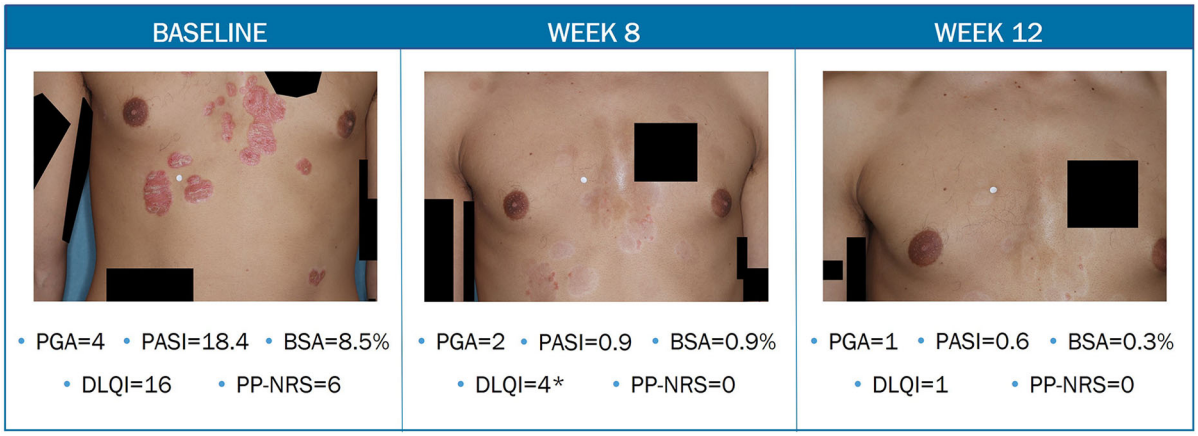

Fig. 2 Clinical response of a patient with severe plaque psoriasis treated with tapinarof cream who achieved primary, secondary, and patient-reported endpoints in PSOARING 1. Chest: improvement in PGA, PASI, BSA, PP-NRS, and DLQI. At baseline, well-circumscribed, erythematous indurated plaques with micaceous scaling are visible on the chest. At week 8, there is marked clearing with residual mild erythema that has essentially resolved at week 12. Mild post-inflammatory hyperpigmentation at sites of resolved psoriatic plaques is visible at week 12. Image is a representative lesion of one tapinarof-treated patient from the PSOARING 1 trial. PGA, PASI, and BSA are global efficacy assessments. Individual results may vary. *DLQI was assessed at baseline, week 4 (no evaluation at week 8), and week 12. *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *PASI* Psoriasis Area and Severity Index, *PGA* Physician Global Assessment, *PP-NRS* Peak Pruritus Numerical Rating Scale, *PRO* patient-reported outcome, *QD* once daily

3 months), and the European S3-Guidelines on the Systemic Treatment of Psoriasis (e.g., achieving PASI75 within 3–4 months) [18, 19]. Furthermore, the patient reported a DLQI score of 1 (no effect on QoL) and a ≥ 4-point reduction in PP-NRS score at week 12.

Case 2: Chest—Male Patient, Aged 28 Years

The response in this patient with severe disease (PGA = 4) at baseline met the primary efficacy endpoint of almost clear skin (PGA = 1) at week 12 with a 3-point improvement from baseline (Fig. 2). Secondary efficacy and PROs improved rapidly, with a PASI90 response, a PP-NRS score of 0 (itch-free state) achieved at week 8, and a DLQI score of 1 (no impact on QoL) achieved at week 12.

Case 3: Lower Leg—Male Patient, Aged 48 Years

This patient had moderate disease (PGA = 3) at baseline in PSOARING 1, which improved to achieve the primary efficacy endpoint with almost clear (PGA = 1) skin and several secondary efficacy endpoints at week 12 (Fig. 3). A DLQI score of 1 (no effect on QoL) and an 8-point reduction in PP-NRS score were reported at week 4, with further improvement to a DLQI score of 0 and a PP-NRS score of 0 (an itch-free state) at week 12.

Case 4: Thigh (Lateral View)—Female Patient, Aged 33 Years

This patient had mild disease (PGA = 2) at baseline and met the primary efficacy endpoint with a PGA score of 0 and all secondary endpoints at week 12 (Fig. 4). In addition to the regulatory endpoints, a PASI score of 0 and %BSA affected of 0 were reported at week 12. A DLQI score of 1 (no effect on QoL) and a PP-NRS score of 0 (itch-free state) were achieved at week 12.

Case 5: Torso (A), and Forearm and Elbow (B)—Female Patient, Aged 41 Years

This patient had severe disease (PGA = 4) at baseline in PSOARING 1 and improved to achieve the primary efficacy (PGA = 1), several secondary efficacy, and PRO endpoints at week 12 (Fig. 5a, b). PP-NRS scores were assessed

only during PSOARING 1. Following continuous treatment with tapinarof cream 1% QD in PSOARING 1 and an additional 3 months of treatment in PSOARING 3, the patient achieved a PGA score of 0 at week 24 (12 weeks into PSOARING 3) and discontinued therapy in accordance with the trial protocol, to be monitored for a remittive effect. The image at week 36 (week 24 of PSOARING 3) is after 3 months completely off therapy. The image at week 48 (week 36 of PSOARING 3) is after 6 months completely off therapy, with gradual return of disease (PGA = 2).

Clinical Responses Not Meeting Regulatory Endpoints

As the efficacy of treatment for plaque psoriasis continues to improve, clinical trials are required to have more stringent regulatory endpoints. Even though a patient may not achieve the FDA-mandated trial regulatory endpoint (e.g., the primary endpoint of a PGA score of 0 [clear] or 1 [almost clear], and a decrease from baseline of at least 2 points), a meaningful clinical response to treatment can still be considered a valuable outcome.

Case 6: Hand—Male Patient, Aged 26 Years

This patient had moderate disease (PGA = 3) at baseline in PSOARING 2 and reported a 1-grade improvement in PGA score at week 12, accompanied by improvements in PASI and %BSA from baseline (Fig. 6). At week 4, a DLQI score of 4 (decrease of 10 points) and a 6-point reduction in PP-NRS score (from 8 to 2) were reported, with further improvement to a DLQI score of 1 (no effect of psoriasis on QoL) and a PP-NRS score of 1 (an itch-free state) at week 12.

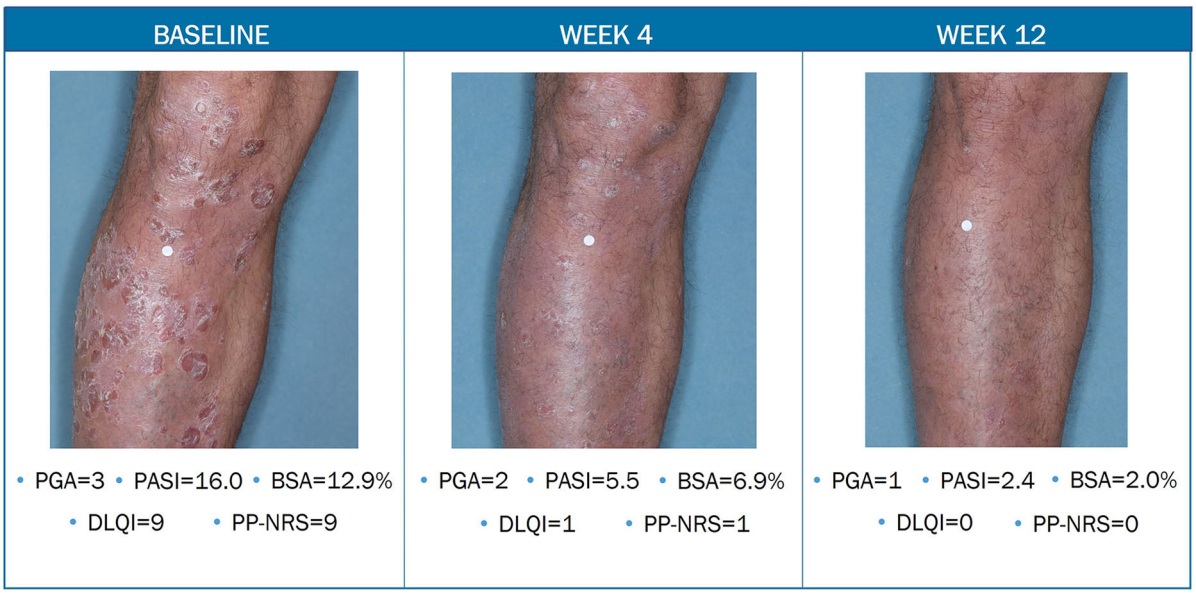

Fig. 3 Clinical response of a patient with moderate plaque psoriasis treated with tapinarof cream who achieved primary, secondary and patient-reported endpoints in PSOARING 1. Lower leg: improvement in PGA, PASI, BSA, PP-NRS, and DLQI. At baseline, well-circumscribed, erythematous nummular macules, patches, and plaques with silvery scaling are noted on the knee and shin. At week 4, there are fewer lesions and those remaining are thinner, smaller, and have less scaling. Marked improvement is noted at week 12 with only a few, barely perceptible punctate macules. Image is a representative lesion of one tapinarof-treated patient from the PSOARING 1 trial. PGA, PASI, and BSA are global efficacy assessments. Individual results may vary. *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *PASI* Psoriasis Area and Severity Index, *PGA* Physician Global Assessment, *PP-NRS* Peak Pruritus Numerical Rating Scale, *PRO* patient-reported outcomes, *QD* once daily

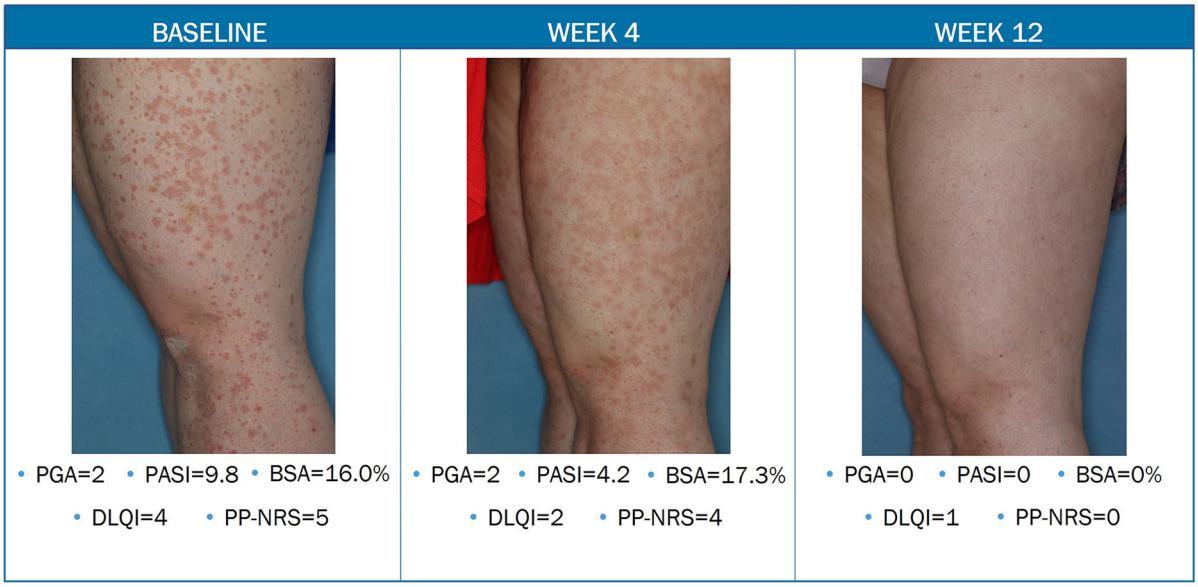

Fig. 4 Clinical response of a patient with mild plaque psoriasis including thigh lesions treated with tapinarof cream who achieved primary, secondary, and patient-reported endpoints in PSOARING 1. Thigh (lateral view): improvement in PGA, PASI, BSA, PP-NRS, and DLQI. At baseline, scattered, well-circumscribed, plaques with mild scaling are present on the thighs. At week 4, there is thinning of the plaques and diminished erythema and scaling. At week 12, complete clearing is seen with faint residual post-inflammatory hyperpigmentation. Image is a representative lesion of one tapinarof-treated patient from the PSOARING 1 trial. PGA, PASI, and BSA are global efficacy assessments. Individual results may vary. *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *PASI* Psoriasis Area and Severity Index, *PGA* Physician Global Assessment, *PP-NRS* Peak Pruritus Numerical Rating Scale, *PRO* patient-reported outcomes, *QD* once daily

Patients Randomized to Vehicle Cream in the Pivotal Trials

Case 7: Thigh (Anterior View)—Male Patient, Aged 39 Years

This patient entered the trial with severe psoriasis (PGA = 4) and was randomized to vehicle cream QD. A 1-grade improvement in PGA score was reported at week 12, from 4 (severe) to 3 (moderate) (Fig. 7). The case images show a thigh target lesion; therefore, the overall 1-grade improvement in PGA score may also reflect changes in other body regions. There was an improvement in PASI score from 21.0 to 12.8 at week 4, and to 11.2 at week 12. The patient also experienced an improvement in QoL from a "moderate effect" of psoriasis (DLQI = 8) at baseline to a "small effect" at week 4 (DLQI = 2).

Case 8: Chest and Abdomen—Male Patient, Aged 19 Years

This patient had moderate psoriasis (PGA = 3) at baseline and was randomized to vehicle cream QD. The patient did not experience any significant improvements in PGA score, extent of BSA affected, or PROs at week 12 (Fig. 8).

PSOARING TRIAL PROGRAM: SAFETY AND TOLERABILITY

Tapinarof cream 1% QD was well tolerated and had a safety profile consistent with that of previous trials [7, 8, 10, 11]. In the three phase 3 trials, treatment-emergent adverse events (TEAEs) were mostly mild or moderate and rarely led to trial discontinuation [7, 8]. In PSOARING 1 and 2, the most common TEAEs (≥ 5% in any group) were folliculitis, nasopharyngitis, and contact dermatitis [7]. In PSOARING 3, the most

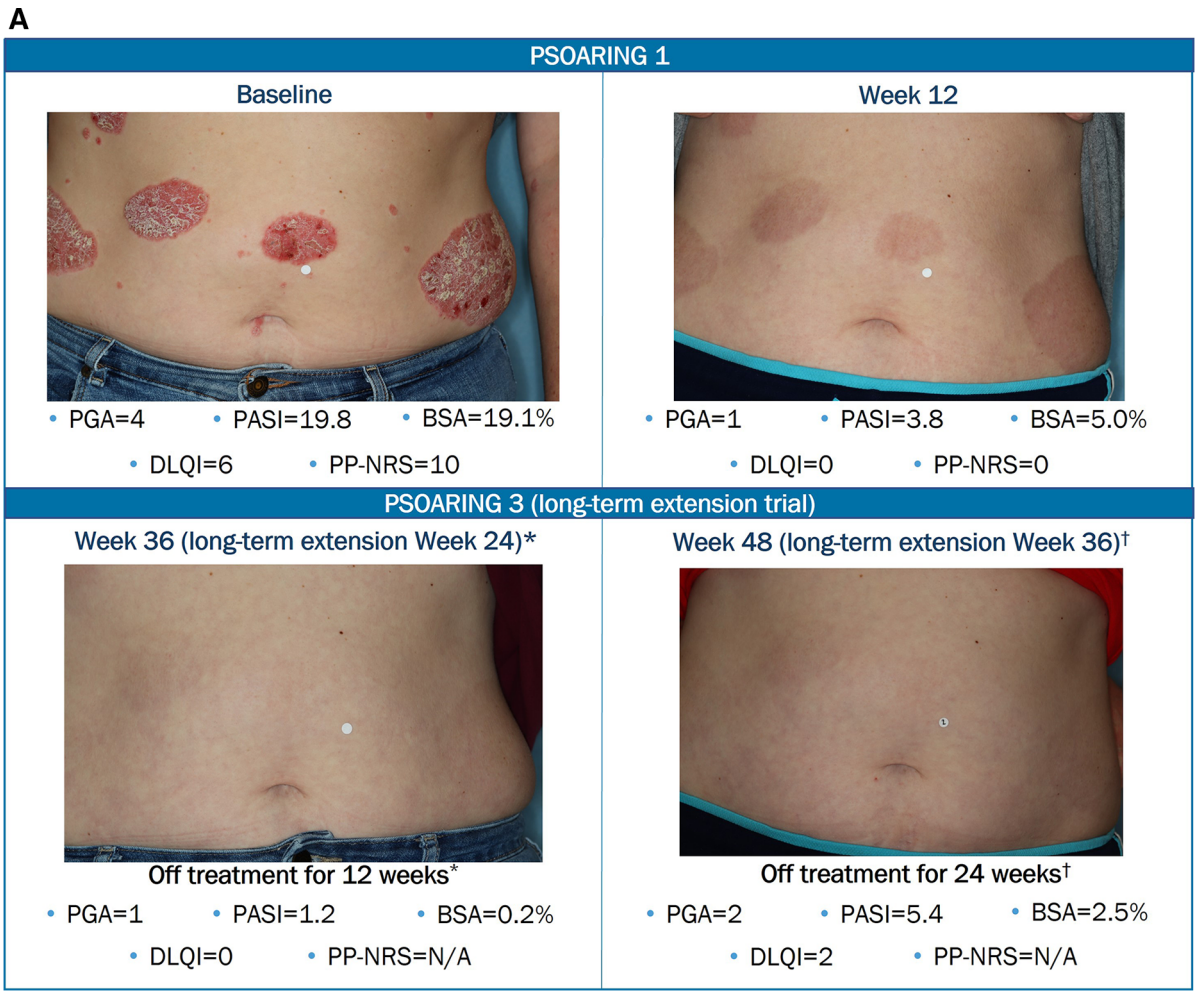

Fig. 5 Clinical response, remittive effect off therapy, and durability of response on therapy of a patient with severe plaque psoriasis treated with tapinarof cream in PSOARING 1 and PSOARING 3. (**a**) Torso: at baseline, well-circumscribed, markedly indurated, erythematous scaling plaques are present. At week 12 there is significant improvement with faint erythema and post-inflammatory hyperpigmentation. At week 36 of the long-term extension trial, a 24-week remittive effect off therapy was demonstrated after this patient achieved complete disease clearance (PGA = 0) and PASI = 0, and discontinued therapy in accordance with the trial protocol at week 12 in PSOARING 3 (after 24 weeks of tapinarof treatment). In the week 36 image, the patient has been off tapinarof treatment for 12 weeks and disease control off therapy is maintained, demonstrated by the absence of psoriatic plaques on the abdomen. The week 48 image with clear abdominal skin shows that this response is maintained for an additional 12 weeks, a total of 24 weeks off tapinarof treatment. (**b**) Forearm and elbow: at week 36 of the long-term extension trial, a 24-week remittive effect off therapy was demonstrated after this patient achieved complete disease clearance (PGA = 0) and PASI = 0, and discontinued therapy in accordance with the trial protocol at week 12 in PSOARING 3 (after 24 weeks of tapinarof treatment). Images in (**a**, **b**) are representative lesions of one tapinarof-treated patient from the PSOARING 1 and 3 trials. PGA, PASI, and BSA are global efficacy assessments. PP-NRS was not assessed in the long-term extension trial. Individual results may vary. *Long-term extension trial week 24: Off treatment for 12 weeks (after achieving PGA = 0 at long-term extension week 12). † Long-term extension trial week 36: Off treatment for 24 weeks, with re-treatment at week 36 due to disease worsening (PGA of 2 [mild]). *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *N/A* not assessed, *PASI* Psoriasis Area and Severity Index, *PGA* Physician Global Assessment, *PP-NRS* Peak Pruritus Numerical Rating Scale, *QD* once daily

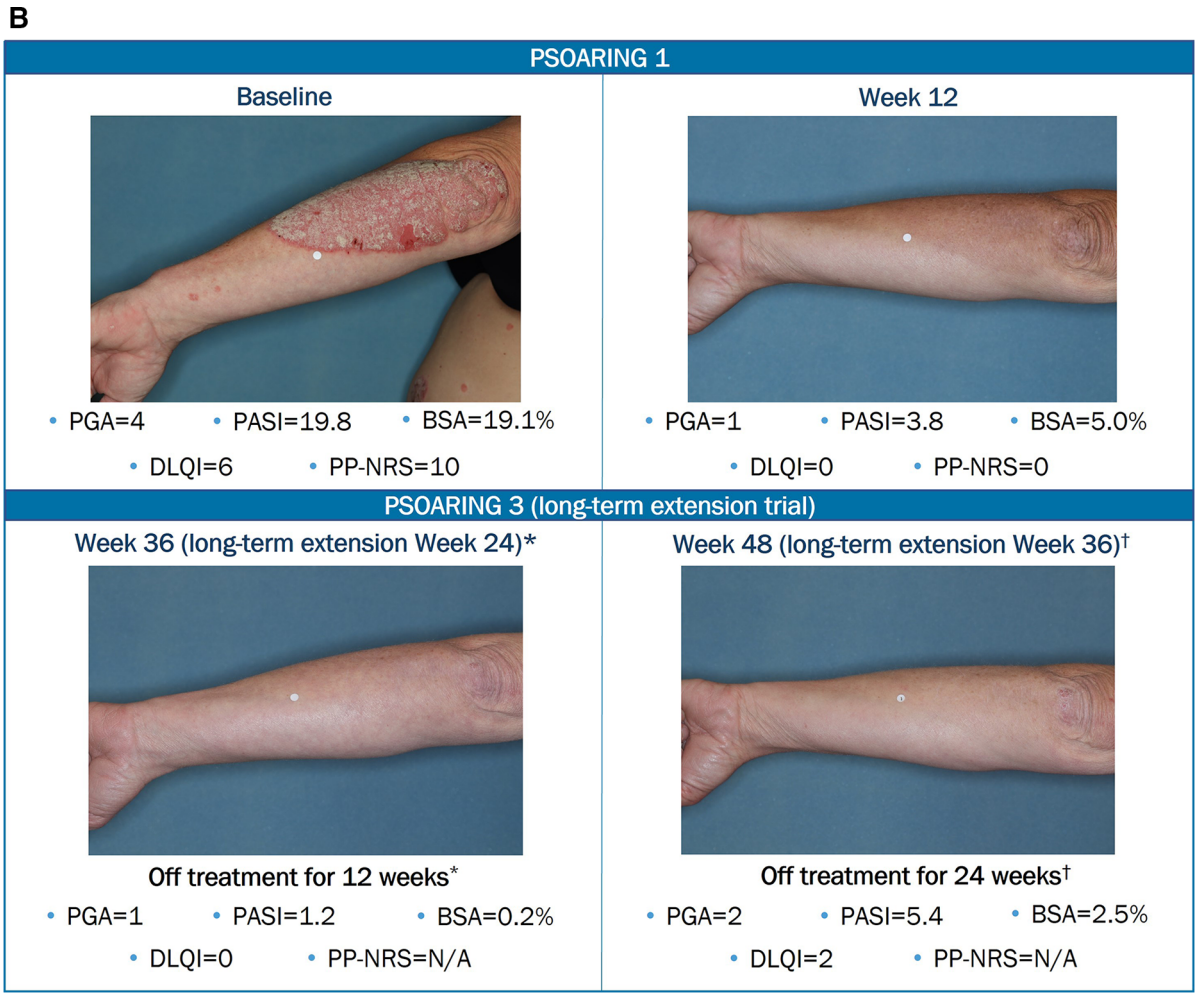

Fig. 5 continued

common TEAEs were folliculitis, contact dermatitis, and upper respiratory tract infection [8]. On the basis of findings in earlier clinical trials of tapinarof cream [9, 20], folliculitis and contact dermatitis were designated as dermatologic AESIs, and are illustrated in Figs. 9 and 10, respectively; investigators were specifically trained to proactively look for these AESIs. Folliculitis and contact dermatitis were identified by investigators and graded using Common Terminology Criteria for Adverse Events (CTCAE), where grade 1 corresponds to "mild," grade 2 to "moderate," grade 3 to "severe," grade 4 to "life-threatening," and grade 5 to "fatal." Trial drug adjustments that were permitted to address AEs included dose change, treatment interruption, and permanent discontinuation of treatment. Dose change included stopping trial treatment application to specific body areas (e.g., site of folliculitis) while continuing application to other body areas. A treatment interruption involved stopping drug entirely for a period of time.

FOLLICULITIS

All cases of folliculitis in PSOARING 1 and 2 were mild or moderate, except for one severe (grade 3) event. The trial discontinuation rate

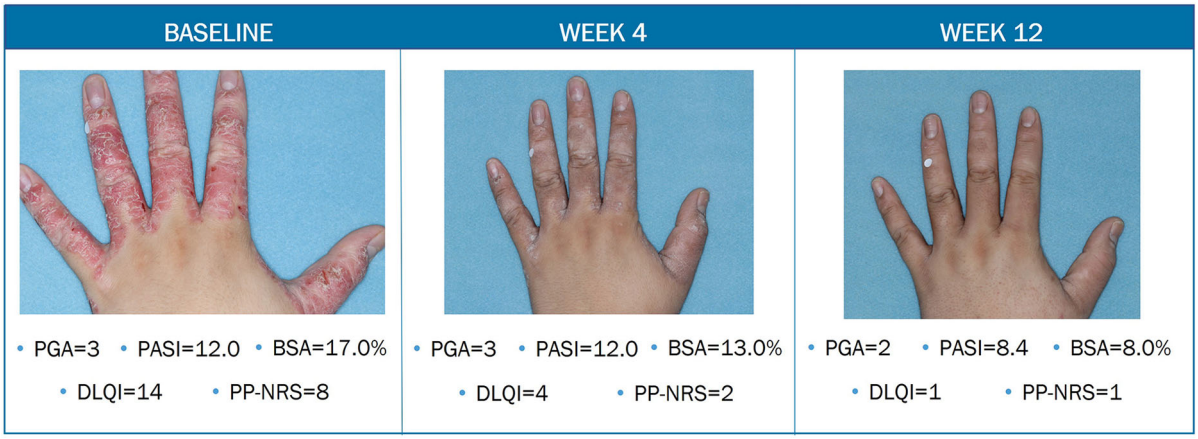

Fig. 6 Clinical response of a patient with moderate plaque psoriasis treated with tapinarof cream who achieved improvements in PGA, PASI, BSA, and patient-reported outcomes in PSOARING 2. Hand: improvements in PGA, PASI, BSA, and PRO endpoints in a patient who failed to meet the regulatory endpoint of a PGA score of 0 or 1 with a 2-grade improvement. At baseline, markedly indurated, erythematous, scaling plaques on the dorsal digits and between the fingers are seen. Fissures and bleeding are visible, indicative of the loss of mechanical pliability of the skin and "fissuring" resulting when the digits are flexed. At week 4, the erythema and induration have significantly improved, with complete clearance of the hand at week 12. Despite the presence of residual disease elsewhere, improvements in DLQI from 14 to 1 and PP-NRS from 8 to an itch-free state (1) at week 12 indicate a favorable impact of tapinarof therapy on QoL and itch. Image is a representative lesion from one tapinarof-treated patient from the PSOARING 2 trial. PGA, PASI, and BSA are global efficacy assessments. Individual results may vary. Intertriginous skin (sites in which opposing skin surfaces are in contact when the patient is at rest) includes areas between the fingers (shown in images above). *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *PASI* Psoriasis Area and Severity Index, *PGA* Physician Global Assessment, *PP-NRS* Peak Pruritus Numerical Rating Scale, *PRO* patient-reported outcome, *QD* once daily, *QoL* quality of life

due to folliculitis was low: 1.8% in PSOARING 1 and 0.9% in PSOARING 2. The majority of patients who experienced a folliculitis event did not require dose change (58.8–67.2%), treatment interruption (75.4–82.5%), or concomitant medication (65.6–73.8%). The mean time to first onset of folliculitis was approximately 30–32 days across trials. Across the 52-week PSOARING program, 86–92% of folliculitis events occurred at treatment application sites. Figure 9 shows a patient with a typical mild (grade 1) case of folliculitis (Fig. 9a) and the one patient graded as having severe folliculitis (grade 3) (Fig. 9b) occurring with tapinarof treatment in PSOARING 1 and 2.

The close-up view of the skin in Fig. 9b indicates the morphologic progression with evidence of cornification/scaling at the follicular ostia and mild erythema, suggesting inflammation. Although not required by the protocol, all folliculitis cultures obtained by the investigator and reported to the trial sponsor were negative for bacteria, yeast, and fungi, consistent with a "non-infectious folliculitis" etiology. This is consistent with most cases of folliculitis requiring no intervention or interruption of therapy and being self-limited.

The images in Fig. 9 indicate that the events identified as folliculitis in these trials may be more closely associated morphologically with keratosis pilaris. This could be explained by increased follicular cornification with subsequent plugging, resulting in mild to moderate, non-infectious papules occurring perilesionally to tapinarof application areas. AhR regulates the epidermal differentiation complex (EDC), and tapinarof has been shown to repair the skin barrier through activation and upregulation of stratum corneum components, including filaggrin, hornerin, and involucrin [21]. This

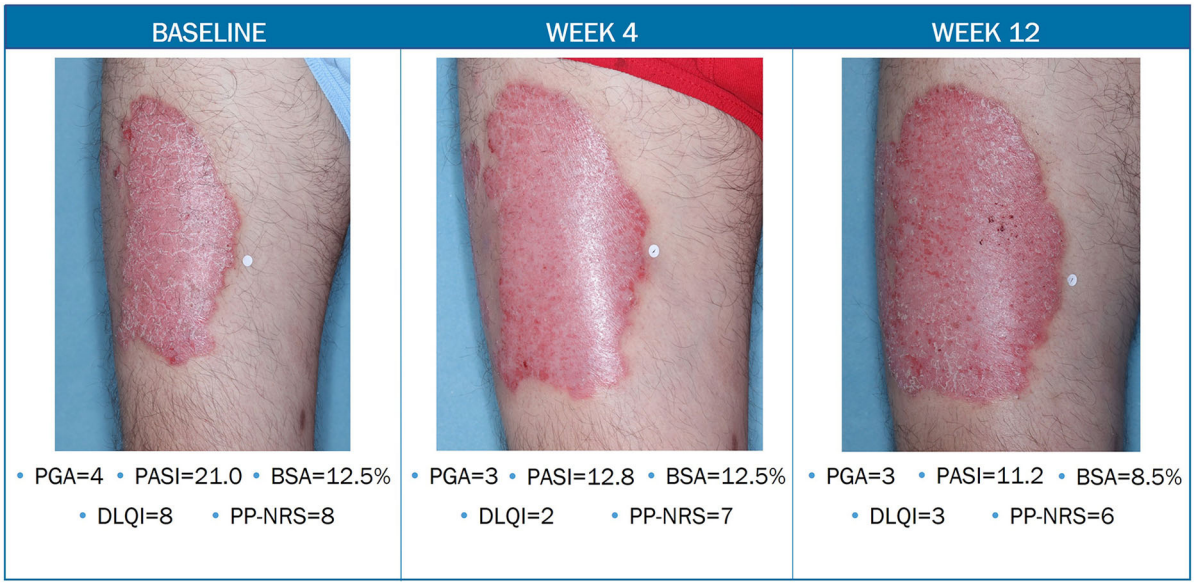

Fig. 7 Clinical response of a patient with severe plaque psoriasis treated with vehicle cream QD in PSOARING 2. Thigh (anterior view): at baseline, a well-circumscribed erythematous plaque with scaling is present on the thigh. No significant improvement in this lesion is observed in either size or morphology during 12 weeks of vehicle treatment. Image is a representative lesion of one vehicle-treated patient from the PSOARING 2 trial. PGA, PASI, and BSA are global efficacy assessments. Individual results may vary. *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *PASI* Psoriasis Area and Severity Index, *PGA* Physician Global Assessment, *PP-NRS* Peak Pruritus Numerical Rating Scale, *QD* once daily

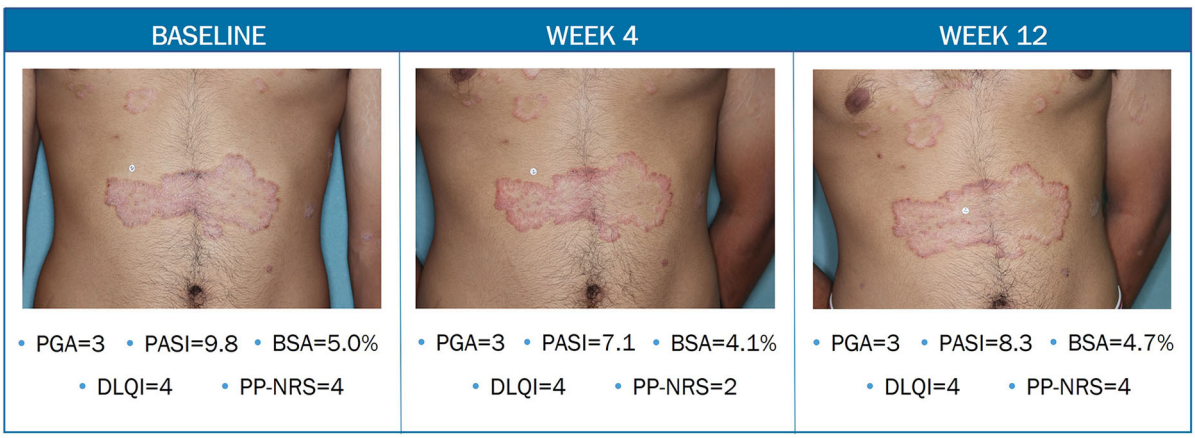

Fig. 8 Clinical response of a patient with moderate plaque psoriasis treated with vehicle cream QD in PSOARING 2. Chest and abdomen: this patient experienced no improvement in PGA score, BSA affected, or PROs. At baseline, well-circumscribed erythematous plaques with scale are present on the chest and abdomen. No significant improvement in these lesions is observed in either size or morphology during 12 weeks of vehicle treatment. Image is a representative lesion of one vehicle-treated patient from the PSOARING 2 trial. PGA, PASI, and BSA are global efficacy assessments. Individual results may vary. *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *PASI* Psoriasis Area and Severity Index, *PGA* Physician Global Assessment, *PP-NRS* Peak Pruritus Numerical Rating Scale, *PRO* patient-reported outcome, *QD* once daily

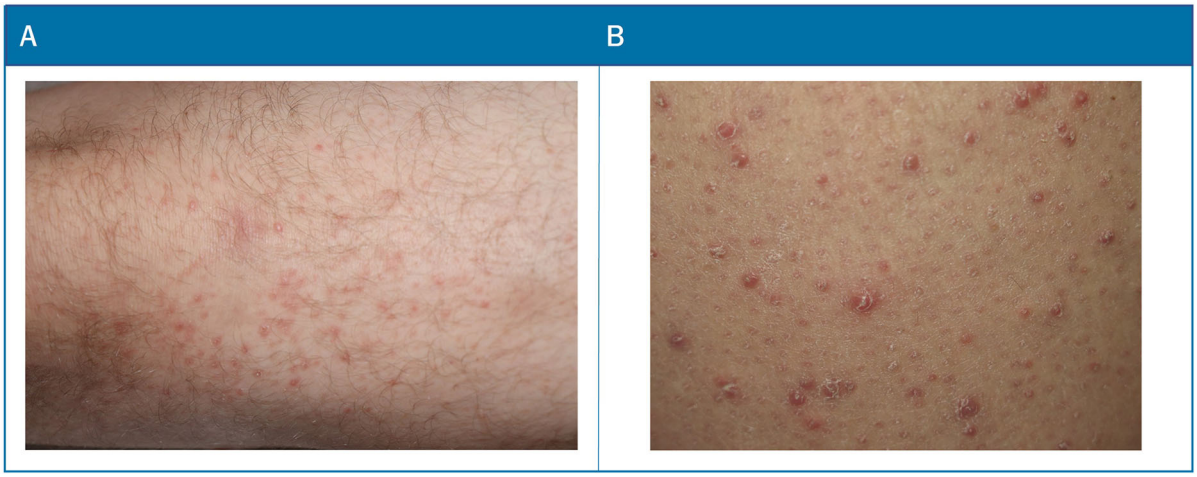

Fig. 9 Folliculitis in two tapinarof-treated patients in PSOARING 1 and 2: (**a**) mild (CTCAE grade 1) and **b** severe (CTCAE grade 3). Punctate erythematous follicular scaling macules and papules in the morphology are reminiscent of keratosis pilaris. In the grade 3 image shown in (**b**), a progression of morphologies from minimal perifollicular scale to erythematous follicular scaling papules can be seen. *CTCAE* Common Terminology Criteria for Adverse Events

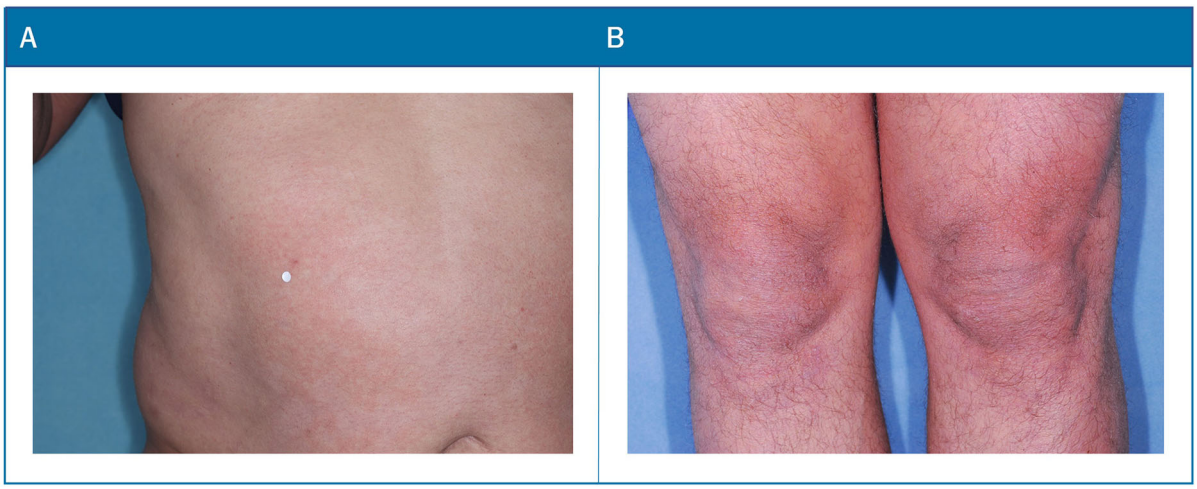

Fig. 10 Moderate contact dermatitis (CTCAE grade 2) on the torso (**a**) and knees (**b**) of two tapinarof-treated patients in PSOARING 1 and 2. Ill-defined erythema of the abdomen, reminiscent of an atopic phenotype, is observed on the torso (**a**); whereas a more discrete-bordered erythema is present perilesionally to cleared psoriasis plaques affecting the knees (**b**). *CTCAE* Common Terminology Criteria for Adverse Events

upregulation of barrier components suggests that folliculitis may be an on-target effect of tapinarof.

During these trials, the use of therapeutic interventions was reported by investigators in a limited number of patients. These interventions included topical antibiotics, systemic antibiotics, antihistamines, and transient interruption of drug application at those sites exhibiting folliculitis. With the exception of temporary interruption in trial drug use, there was insufficient information to determine if these

interventions had any impact on the natural resolution of folliculitis.

It is helpful to instruct patients on the proper use of the medication including once daily application of a thin layer of cream to affected skin, washing hands after application (unless the cream is for treatment of the hands), and minimizing application to non-lesional skin. In general, when folliculitis occurs with tapinarof treatment, it is typically mild and self-limited, and does not require intervention or dose changes.

In these trials, the majority of treatment-emergent follicular reactions were consistent with those previously reported, being self-limited and requiring no interventions or overall treatment interruptions. Temporary interruption of drug application to sites of folliculitis appears to be an effective management strategy. Intriguingly, the hypothesis that increased cornification of the follicular epithelium and follicular plugging underlie the mechanism for this keratosis pilaris-like effect suggests that in those cases where additional intervention is requested, local application of keratolytics and/or topical retinoids could be effective management strategies.

CONTACT DERMATITIS

All cases of contact dermatitis were mild or moderate (grade 1 or 2), except for one severe (grade 3) event. Trial discontinuation rates due to contact dermatitis were low: 1.5% in PSOARING 1 and 2.0% in PSOARING 2. The majority of patients in PSOARING 1 and 2 who experienced contact dermatitis did not require dose reduction (90–100%) or treatment interruption (64.7–75%). The mean time of first onset of contact dermatitis was 36–43 days across the trials. Across the 52-week PSOARING program, 82–94% of contact dermatitis events occurred at treatment application sites. Figure 10 shows examples of moderate (grade 2) contact dermatitis in two tapinarof-treated patients from PSOARING 3.

Of interest, patients who experienced contact dermatitis showed distribution mainly in focal areas and sporadic distribution at sites of tapinarof cream application. The limited distribution of contact dermatitis at tapinarof application sites, and the observation that re-application of tapinarof cream after resolution of dermatitis did not uniformly re-elicit the dermatitis, suggest that this dermatitis may not represent allergic contact dermatitis due to tapinarof cream. A non-allergic contact dermatitis observation is further supported by (i) the absence of positive patch tests in response to treatment with tapinarof cream in 240 healthy volunteers during the contact sensitization dermal safety trial, and (ii) relative to the phase 3 psoriasis trials, the lower incidence of contact dermatitis observed in the randomized, vehicle-controlled tapinarof dose-ranging phase 2b AD trial [7, 8, 20, 22]. The low incidence of contact dermatitis in the phase 2b AD trial is interesting because the barrier defect associated with AD would be expected to increase the risk of contact dermatitis in patients with AD. Patch tests were not performed in the PSOARING trial program.

An alternative hypothesis for the above is that the observations of sporadic dermatitis in response to treatment with tapinarof cream may represent phenotypic switching analogous to what has been reported with psoriasis biologics [23]. It has been speculated that targeting Th1 and Th17 cytokines may prompt a transient shift to a Th2-dominated immune response, causing an atopic eczema phenotype [23]. Similar to targeted biologics, focal treatment with tapinarof cream may suppress Th1/Th17 inflammation to a sufficient degree to induce a transient Th2 shift in some patients with psoriasis.

LIMITATIONS OF CASE PHOTOGRAPHY APPROACH

In the PSOARING program, documenting patients' psoriasis using case photography was an optional part of the protocols, and investigators at centers with suitable capabilities could choose to participate. Patient agreement to be photographed was not a requirement for trial participation. Patient photography generally focused on a representative lesion in selected

patients, whereas efficacy assessments were based on validated endpoints reflecting the totality of patients' psoriasis disease burden (reflected by the PGA, PASI, and %BSA evaluations).

CONCLUSIONS

As a result of the unique mechanism of action and clinical profile of tapinarof, medical photography showing outcomes is important to facilitate optimal use of this new therapy in routine care for patients with plaque psoriasis who may benefit. Integration of high-quality case photographs has been shown to enhance clinical practice and support clinical decision-making [24]. In the PSOARING clinical trials, tapinarof cream 1% QD demonstrated significant efficacy and noticeable improvement in psoriasis disease activity and QoL in patients with mild to severe plaque psoriasis, based on the pre-specified regulatory endpoints shown in the case photography.

In PSOARING 1 and 2, patients with clinical responses that met regulatory endpoints also experienced rapid, clinically meaningful improvements with topical tapinarof monotherapy that exceeded consensus treatment goals set for combination therapy, including biologic and systemic therapy (cases 1–4). Many patients with clinical responses not meeting the regulatory endpoints still experienced meaningful and visible improvements in disease activity and QoL (case 6).

PSOARING 3 demonstrated that intermittent or continuous treatment with tapinarof was well tolerated for up to 1 year, with high rates (40.9%; n = 312/763) of complete disease clearance, a remittive effect of approximately 4 months while off therapy after achievement of a PGA score of 0 (clear), and no evidence of tachyphylaxis even while on intermittent therapy [8]. Patients treated with tapinarof cream experienced remittive periods with effective disease control off therapy (case 5A and 5B).

The incidence and severity of AEs remained consistent across trials. The occurrence of AESIs, folliculitis and contact dermatitis, was closely followed in these trials, with investigators trained to proactively look for these AESIs. Trial discontinuation rates due to folliculitis and contact dermatitis were low, and the majority of patients did not have any treatment interruptions or interventions to treat either folliculitis or contact dermatitis. Folliculitis, when it occurred, was generally characterized by mild inflammation at the application site(s), which was non-infectious, self-limited, and did not interfere with therapy [25]. The majority of folliculitis cases were not painful, tender, or itchy, and were not associated with infection. Most patients in PSOARING 1 and 2 who experienced a contact dermatitis event remained on therapy and elected to enroll into PSOARING 3. Of interest, contact dermatitis was not reported in the psoriasis maximal usage trial of tapinarof cream 1% or in four dermal safety trials [12, 22].

Events defined as "folliculitis" in these trials were morphologically similar to keratosis pilaris; whereas, the observed "contact dermatitis" was not consistent with allergic contact dermatitis due to tapinarof cream and may represent phenotypic switching analogous to outcomes observed with some biologic psoriasis therapies [23].

In summary, tapinarof is a novel topical treatment option for patients with mild to severe plaque psoriasis, with no restrictions regarding duration of use; application site, including sensitive and intertriginous areas; and extent of BSA affected. Tapinarof cream 1% QD has the potential to transform the care of patients with plaque psoriasis and is under investigation for the treatment of psoriasis in children down to 2 years of age, and for AD in adults and children down to 2 years of age.

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Data Availability. Data from with these trials are proprietary and not publicly available but may be made available, with conditions, upon reasonable request and with permission from the sponsor.

Declarations

Conflict of Interest. Seemal R. Desai has served as a consultant and investigator for Dermavant Sciences, Inc.; he also serves in multiple other leadership and industry roles unrelated to tapinarof cream 1%. Linda Stein Gold has served as a consultant, and/or has received payment for the development of educational presentations, and/or has received grants from Amgen, Arcutis, Bristol Myers Squibb, Dermavant Sciences, Inc., Eli Lilly, LEO Pharma, Ortho Dermatologics, Pfizer, and UCB Biopharma. Michael C. Cameron has served as a consultant, advisor, or speaker for AbbVie, Bristol Myers Squibb, Dermavant Sciences, Inc., Eli Lilly, EPI Health, Evelo Biosciences, Incyte, Journey Medical, LEO Pharma, Regeneron, and Ortho Pharmaceuticals. Alexandra Golant has received consulting or speaking fees from AbbVie, Amgen, Arcutis, Dermavant Sciences, Inc., Eli Lilly, Evelo Biosciences, Incyte, Janssen, LEO Pharma, Regeneron, and Sanofi. G. Michael Lewitt has served as a consultant, speaker, investigator, or advisory board member and/or has received grants from AbbVie, Amgen, Inc., Bristol Myers Squibb, Dermavant Sciences, Inc., DermTech, Eli Lilly, Galderma, LEO Pharma, Janssen, Novan, Inc., Pfizer, Ortho Dermatologics, and UCB Biopharma. Matthew J. Bruno has served as a consultant and/or received payment for promotional presentations from AbbVie, Almirall, Bristol Myers Squibb, Dermavant Sciences, Inc., EPI Health, Journey Medical Corporation, Mayne Pharma, Medimetriks Pharmaceuticals, Pfizer, Regeneron/Sanofi-Genzyme, and Sun Pharmaceuticals. George Martin has served as a speaker and/or consultant and/or has been involved in scientific advisory boards for AbbVie, Almirall, Alumis, Bristol Myers Squibb, Celgene, Dermavant Sciences, Inc., DUSA/Sun, Eli Lilly, Evelo, Galderma, Horizon, Incyte, Janssen, LEO Pharma, Nobelpharma, Ortho/Bausch Health, Organogenesis, Pfizer, Trevi, and UCB Biopharma. Philip M. Brown, David S. Rubenstein, Victoria Butners, and Anna M. Tallman are employees of Dermavant Sciences, Inc., with stock options.

Ethical Approval. The trials were conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. Approval was obtained from the local ethics committee or institutional review board for each trial center. All the patients provided written informed consent and photographic release.

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