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ORIGINAL RESEARCH

Rapid Improvements in Itch with Tapinarof Cream 1% Once Daily in Two Phase 3 Trials in Adults with Mild to Severe Plaque Psoriasis

Leon Kircik · Matthew Zirwas · Shawn G. Kwatra · G. Michael Lewitt · Holly Glover · Tomas Chao · Philip M. Brown · David S. Rubenstein · Anna M. Tallman

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ABSTRACT

Introduction: Patients with psoriasis report pruritus as their most bothersome symptom. Tapinarof cream 1% once daily demonstrated significant efficacy versus vehicle and was well tolerated in adults with mild to severe plaque psoriasis in two 12-week trials: PSOARING 1 (NCT03956355) and PSOARING 2 (NCT03983980). Here, we present patient-reported pruritus outcomes from these trials.

Methods: Outcomes included a Peak Pruritus Numerical Rating Scale (PP-NRS) score of 0 or 1 (itch-free state); Dermatology Life Quality Index (DLQI) itch item scores; and Psoriasis Symptom Diary (PSD) itch item scores.

Results: Analyses included 683 tapinarof- and 342 vehicle-treated patients. At baseline, mean pruritus scores were similar across trials with only 7–11% of patients reporting an itch-free state. At week 12, the proportion of tapinarof-

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L. Kircik (✉)
Icahn School of Medicine at Mount Sinai, 5 E. 98th St., 5th Fl., New York, NY 10029, USA
e-mail: wedoderm@yahoo.com

M. Zirwas
DOCS Dermatology, 2359 E Main St, Bexley, OH 43209, USA
e-mail: matt.zirwas@gmail.com

S. G. Kwatra
Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: skwatra1@jhmi.edu

G. M. Lewitt
Illinois Dermatology Institute, Chicago, IL, USA
e-mail: gmlewitt@illinoisderm.com

H. Glover
Metroplex Dermatology, Arlington, TX, USA
e-mail: hollysueglover@gmail.com

T. Chao
Atlanta North Dermatology, Woodstock, GA, USA
e-mail: tomasjchao@aol.com

P. M. Brown · D. S. Rubenstein · A. M. Tallman
Dermavant Sciences, Inc., 3300 Paramount Parkway, Suite 150, Morrisville, NC 27560, USAP. M. Brown
e-mail: phil.brown@dermavant.com
D. S. Rubenstein
e-mail: david.rubenstein@dermavant.com
A. M. Tallman
e-mail: anna.tallman@dermavant.com

treated patients achieving an itch-free state was 50% in both trials compared with 32% ($P = 0.0007$) and 27% ($P < 0.0001$) in the vehicle groups. Improvements were apparent at the earliest assessments with continued improvement over the course of the trials. There were rapid and statistically significant improvements in the proportion of patients with a $\geq$ 4-point improvement in PP-NRS for tapinarof-treated patients versus vehicle from week 2 with 68% vs 46% ($P = 0.0004$) and 60% vs 31% ($P = 0.0001$) at week 12 achieving a response in each trial. Significantly greater reductions in itch with tapinarof versus vehicle were also demonstrated at week 12 for DLQI itch item 1 ($P = 0.0026$ and $P < 0.0001$), PSD item 1 (both $P < 0.0001$), and PSD item 2 (both $P < 0.0001$).

Conclusion: Tapinarof was highly efficacious in reducing pruritus across multiple patient-reported outcome measures, with rapid, statistically significant, and clinically meaningful improvements. The high proportion of patients achieving the treatment target of an itch-free state at week 12 (50%) is a noteworthy clinical outcome for a non-steroidal topical cream in the treatment of mild to severe plaque psoriasis.

Trial Registration: Clinical trial registration information: NCT03956355, NCT03983980.

Keywords: Itch; Pruritus; Phase 3 PSOARING trials; Plaque psoriasis; Tapinarof cream 1% QD; Topical therapy; Aryl hydrocarbon receptor agonist

Key Summary Points

Why carry out the study?

Pruritus (itch) is reported to be the most bothersome symptom by patients with psoriasis.

Tapinarof cream 1% once daily (QD) demonstrated significant efficacy versus vehicle and was well tolerated in adults with mild to severe plaque psoriasis in two 12-week pivotal phase 3 trials, PSOARING 1 and 2.

What was learned from the study?

Tapinarof cream 1% QD demonstrated rapid, clinically meaningful, and statistically significant improvements across multiple patient-reported pruritus assessments.

Improvements in pruritus with tapinarof were seen from the earliest visit at week 2, and significantly more tapinarof-treated patients achieved an itch-free state at week 12 compared with vehicle.

Tapinarof cream 1% QD is efficacious for the treatment of pruritus in adults with plaque psoriasis, with no limitations on location, extent, or duration of use.

INTRODUCTION

Psoriasis is a chronic, inflammatory skin disease that affects approximately 2% of people worldwide [1]. Pruritus affects 60–90% of patients with psoriasis and substantially impacts health-related quality of life [2–5]. Itching can negatively affect patients' physical activity, sleep, functioning, and psychological well-being [2–5]. In the Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey that included 1005 US patients, itch was reported to be the most important factor contributing to disease severity; however, it was considered less important by physicians [6].

Pruritic sensations can be experienced anywhere on the skin or mucosa and are induced by activation of peripheral sensory nerve fibers distributed in the skin and processed in multiple areas of the brain [3]. Cytokines involved in the pathogenesis of psoriasis, including interleukin (IL)-17 and IL-23, have also been implicated as mediators of itch [7, 8]. IL-17 may directly or indirectly influence itch by interacting with neurons to enhance nociceptive effects and/or modulate the sensitivity to sensory perception [3, 9].

The pattern and intensity of pruritus are generally associated with the location and

severity of psoriatic plaques, and relief from itch symptoms often coincides with clearance of plaques [3]. Topical corticosteroids are an integral part of the psoriasis therapeutic armamentarium and can be effective for itch; however, some patients do not respond to corticosteroids [10]. Moreover, many approved topical medications, including corticosteroids, tazarotene, and vitamin D analogs, have restrictions listed in their prescribing information on the duration, total surface area, and location of treatment [11]. Well-known cutaneous adverse effects such as atrophy, striae, and telangiectasias, as well potential systemic adverse events, prevent the optimal long-term and extensive application of corticosteroids to all areas affected by disease [12]. When treatment is curtailed accordingly, symptoms (including itch) commonly recur. Similarly, few approved topical options are suitable for sensitive skin in areas such as the face and genitals.

Moisturizers and oral antihistamines can provide acute relief but have limited long-term efficacy and their mechanisms of action are not disease-specific (i.e., pruritus in psoriasis is generally cytokine- rather than histamine-mediated) [3, 13, 14]. Antihistamines are also associated with adverse effects, including anticholinergic effects and dizziness [15].

Tapinarof (VTAMA®; Dermavant Sciences, Inc.) is a first-in-class, non-steroidal, topical aryl hydrocarbon receptor (AhR) agonist approved by the US Food and Drug Administration for the treatment of plaque psoriasis in adults [16]. Tapinarof is approved for first- or later-line treatment of psoriasis of any severity, and may be used alone or adjunctively with other prescription psoriasis medications. Tapinarof prescribing information carries no warnings or contraindications and places no restrictions on the duration of use, extent of body surface area treated, or body sites to which treatment can be applied [16]. Tapinarof is also 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.

Tapinarof binds to and activates AhR, and has been shown to downregulate proinflammatory T helper cell 17 cytokines, including IL-17A and IL-17F; normalize skin barrier proteins, including filaggrin and loricrin; and increase antioxidant activity through activation of the AhR–nuclear factor erythroid 2-related factor-2 (Nrf2) pathway [17, 18]. The mechanism of action underlying efficacy in pruritus reported in patients with psoriasis treated with tapinarof, while not fully known, potentially involves downregulating inflammatory signaling cascades, including IL-17 and Th2 cytokines that are known to be pruritogens [17, 18].

Tapinarof cream 1% once daily (QD) demonstrated statistically significant efficacy versus vehicle and was well tolerated in adults with mild to severe plaque psoriasis in two 12-week, pivotal phase 3 trials, PSOARING 1 (NCT03956355) and PSOARING 2 (NCT03983980) [19]. Efficacy continued to improve in PSOARING 3 (NCT04053387), the long-term extension trial, with a high rate of complete disease clearance (Physician Global Assessment [PGA] = 0; 40.9%; n = 312/763). There was an approximately 4-month remittive effect (maintenance of a PGA score of 0 [clear] or 1 [almost clear]) off therapy after first achieving complete disease clearance, and durability of response for up to 52 weeks with continuous or intermittent therapy [20].

Here, we report post hoc analyses of patient-reported pruritus outcomes from the PSOARING 1 and PSOARING 2 trials.

METHODS

Trial Design

PSOARING 1 and 2 were two identical phase 3, multicenter, randomized, double-blind, vehicle-controlled trials that evaluated the efficacy and safety of tapinarof cream 1% QD in adults with mild to severe plaque psoriasis. Eligible patients were randomized 2:1 to receive tapinarof cream 1% QD or vehicle QD for 12 weeks (Fig. S1 in the electronic supplementary material).

The trials were conducted in compliance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. Approval was obtained from local ethics committees or institutional review boards for each center. All

patients provided prior written informed consent.

Participants

Full inclusion and exclusion criteria for PSOARING 1 and 2 have been previously reported [19]. Patients were aged 18–75 years with chronic plaque psoriasis; had a PGA score of 2 (mild), 3 (moderate), or 4 (severe) at baseline; and body surface area involvement of ≥ 3 to $\leq 20\%$.

Outcome Measures and Statistical Analyses

Pruritus was assessed by the proportion of patients achieving an itch-free state, defined as a Peak Pruritus Numerical Rating Scale (PP-NRS) score of 0 or 1 at week 12. The PP-NRS is evaluated on an 11-point scale, where 0 indicates "no itch" and 10 indicates "worst imaginable itch" within the last 24 h [21]. The mean change in pruritus from baseline at week 12 was also assessed using the PP-NRS score, Psoriasis Symptom Diary (PSD) items 1 (itching severity) and 2 (bothered by itching), and DLQI itch item 1 score. PSD items 1 and 2 assess the severity, bother, and functional impact of itch, rated on an 11-point scale, where 0 indicates "absent" and 10 indicates "worst imaginable" [22]. DLQI item 1 (assessing itch, soreness, painfulness, or stinging) evaluates the impact of itch on quality of life; it is scored on a 4-point scale, where 0 indicates "not at all" and 3 indicates "very much" [23]. PP-NRS total score and PSD items 1 and 2 scores were assessed for improvement from baseline at weeks 2, 4, 8, and 12. DLQI item 1 score was assessed for improvement from baseline at weeks 4 and 12.

Statistical Analyses

Post hoc pruritus outcomes were evaluated on the basis of the intention-to-treat population using observed cases. The proportion of patients achieving a PP-NRS score of 0 or 1, indicating an itch-free state, was compared between treatment groups at baseline and weeks 2, 4, 8, and 12 using the Cochran–Mantel–Haenszel analysis stratified by baseline PGA score. Continuous variables were analyzed using an analysis of covariance model, with randomized treatment as a main effect, baseline PGA score as a covariate, and baseline value of the endpoint as a continuous covariate. The treatment effect is presented as least squares mean values.

RESULTS

Baseline Patient Demographics and Disease Characteristics

Baseline demographics and disease severity, including pruritus, were similar across groups in both trials (Table 1). Approximately 80% of patients had a PGA score of 3 (moderate) and a mean Psoriasis Area Severity Index (PASI) score of 9 at baseline [19]. Mean baseline PP-NRS scores were 5.7–6.1 across all groups in PSOARING 1 and 2, with only 7.0–10.6% of patients reporting an itch-free state at baseline (PP-NRS = 0 or 1). Mean baseline DLQI item 1 scores were 1.8–1.9, and mean PSD item 1 and 2 scores were 5.6–6.0 and 5.5–5.7, respectively, across both trials.

PP-NRS Total Score and PP-NRS Response

Significantly greater improvements in mean PP-NRS total scores (measured on an 11-point scale) were observed for patients treated with tapinarof compared with vehicle as early as week 2, the earliest assessment ($P = 0.0162$ and $P < 0.0001$; PSOARING 1 and 2, respectively; Fig. 1). Improvements continued through week 4 ($P = 0.0003$ and $P < 0.0001$), week 8 ($P = 0.0001$ and $P < 0.0001$), and at week 12, the final assessment, the mean reductions in PP-NRS scores were -3.9 vs -2.9 ($P = 0.0002$) in PSOARING 1 (Fig. 1a) and -3.0 vs -1.4 ($P < 0.0001$) in PSOARING 2 (Fig. 1b) for tapinarof versus vehicle, respectively.

Significantly more tapinarof-treated patients had a PP-NRS response, defined as at least a 4-point reduction in PP-NRS total score, at week 2 ($P = 0.0282$ and $P = 0.0152$;

Table 1 Baseline patient demographics and disease characteristics

	PSOARING 1		PSOARING 2	
	Tapinarof 1% QD (*n* = 340)	**Vehicle QD (*n* = 170)**	**Tapinarof 1% QD (*n* = 343)**	**Vehicle QD (*n* = 172)**
Age, years, mean (SD)	49.8 (13.7)	49.1 (13.3)	50.0 (13.1)	50.0 (13.7)
Male, *n* (%)	213 (62.6)	86 (50.6)	188 (54.8)	102 (59.3)
Weight, kg, mean (SD)	91.7 (24.6)	92.8 (22.7)	92.9 (24.3)	89.6 (19.9)
BMI, kg/m^2, mean (SD)	31.4 (7.8)	32.5 (7.6)	31.8 (7.7)	30.7 (6.3)
PP-NRS total score, mean (SD)	5.7 (2.9)	6.1 (2.8)	5.9 (2.7)	6.1 (2.8)
Score of 0 or 1, *n* (%)[a]	36 (10.6)	13 (7.6)	24 (7.0)	15 (8.7)
DLQI total score, mean (SD)	8.2 (5.8)	8.7 (5.9)	8.5 (5.9)	8.6 (5.9)
Item 1, mean (SD)[b]	1.8 (0.9)	1.9 (0.8)	1.8 (0.8)	1.9 (0.8)
PSD total score, mean (SD)	73.1 (41.2)	74.9 (43.0)	74.0 (38.4)	76.0 (41.2)
Item 1, mean (SD)[c]	5.6 (2.7)	5.9 (2.7)	5.8 (2.6)	6.0 (2.8)
Item 2, mean (SD)[c]	5.5 (2.9)	5.7 (3.0)	5.6 (2.8)	5.7 (3.0)

Intention-to-treat population

BMI body mass index, *DLQI* Dermatology Life Quality Index, *PP-NRS* Peak Pruritus Numerical Rating Scale, *PSD* Psoriasis Symptom Diary, *QD* once daily, *SD* standard deviation

[a]PP-NRS is scored on an 11-point scale, where 0 and 1 indicates "no itch" and 10 indicates "worst imaginable itch" [21]

[b]The DLQI item 1 (assessing itch, soreness, painfulness, or stinging) evaluates the impact of itch on quality of life; it is scored on a 4-point scale rating, where 0 indicates "not at all" and 3 indicates "very much" [23]

[c]PSD items 1 (itching severity) and 2 (bothered by itching) are rated on an 11-point scale, where 0 indicates "absent" and 10 indicates "worst imaginable" [22]

PSOARING 1 and 2, respectively; Fig. 2). The proportion of patients with a PP-NRS response was also significantly higher with tapinarof than vehicle at week 4 ($P = 0.0016$ and $P < 0.0001$), week 8 ($P = 0.0002$ and $P < 0.0001$), and at week 12, where 68% vs 46% in PSOARING 1 ($P = 0.0004$) and 60% vs 31% ($P < 0.0001$) PSOARING 2 achieved a response with tapinarof versus vehicle, respectively.

Itch-Free State

The proportion of patients in an itch-free state was significantly higher compared with vehicle as early as the first assessment (week 2) in PSOARING 1 ($P = 0.0194$) and at every assessment thereafter in both trials: week 4 ($P = 0.0026$ and $P = 0.0004$), week 8 ($P = 0.0001$ and $P < 0.0001$), and week 12 ($P = 0.0007$ and $P < 0.0001$), in PSOARING 1 and 2, respectively (Fig. 3). At week 12, a significantly higher proportion of tapinarof-treated patients (50% in both trials) achieved an itch-free state (defined as a PP-NRS score of 0 or 1) compared with vehicle (32% and 27%; $P = 0.0007$ and $P < 0.0001$ for PSOARING 1 and 2, respectively).

DLQI Itch Item Score

Significant improvements in DLQI item 1 scores (measured on a 4-point scale) were demonstrated with tapinarof versus vehicle at week 4,

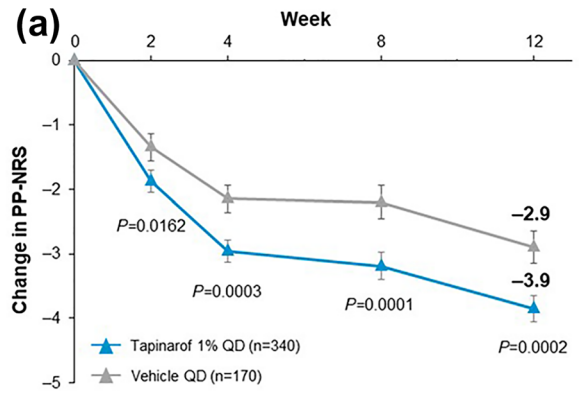

Fig. 1 Early, statistically significant, and continued improvement in PP-NRS score from baseline in **a** PSOARING 1 and **b** PSOARING 2. Intention-to-treat population, observed cases. Least squares mean (standard error). *PP-NRS* Peak Pruritus Numerical Rating Scale, *QD* once daily

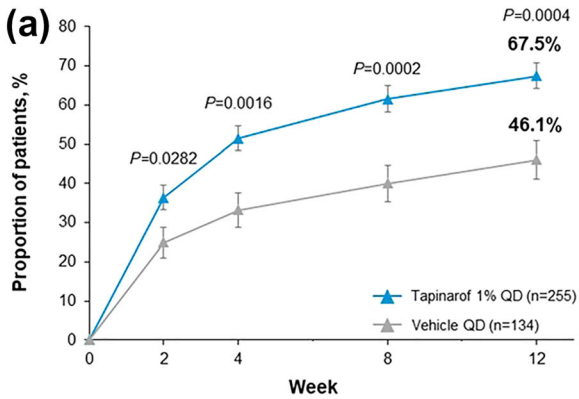

Fig. 2 Early and statistically significant achievement of a minimum 4-point improvement in PP-NRS from baseline to week 12 with tapinarof cream 1% QD in **a** PSOARING 1 and **b** PSOARING 2. Intention-to-treat population[a], observed cases. Mean proportion (standard error). [a]Only includes patients with baseline PP-NRS $\geq$ 4. *PP-NRS* Peak Pruritus Numerical Rating Scale, *QD* once daily

the earliest visit on which the DLQI was assessed ($P = 0.0003$ and $P < 0.0001$; Fig. 4), and week 12, the final assessment ($P = 0.0026$ and $P < 0.0001$), in PSOARING 1 and 2, respectively.

PSD Itch Scores

Mean improvements in itch severity score (PSD item 1; measured on an 11-point scale) with tapinarof were significantly greater versus vehicle as early as week 2, the earliest PSD assessment ($P < 0.0001$ for PSOARING 2; Fig. 5). Statistically significant improvements were also reported at weeks 4 and 8 ($P = 0.0003$ for PSOARING 1 and $P < 0.0001$ for PSOARING 2, for both weeks), and at week 12 (both $P < 0.0001$).

Patients also reported being significantly less bothered by itching (PSD item 2; measured on an 11-point scale) with tapinarof versus vehicle as early as week 2, ($P = 0.0022$ for PSOARING 1 and $P < 0.0001$ for PSOARING 2; Fig. 6). Mean improvements from baseline with tapinarof in PSD item 2 score were also significant versus vehicle at week 4 ($P < 0.0001$ for both), week 8

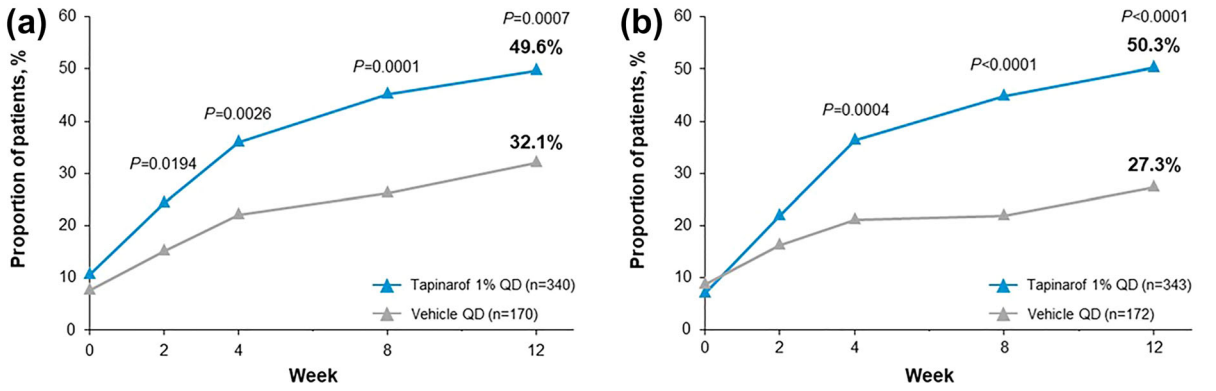

Fig. 3 Rapid and statistically significant achievement of an itch-free state (PP-NRS score of 0 or 1) with tapinarof cream 1% QD in **a** PSOARING 1 and **b** PSOARING 2. Intention-to-treat population, observed cases. *PP-NRS* Peak Pruritus Numerical Rating Scale, *QD* once daily

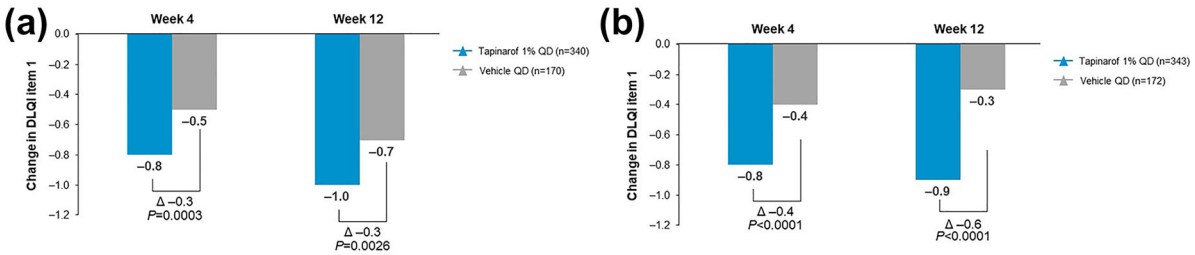

Fig. 4 Statistically significant improvement in DLQI itch item 1[a] rating from baseline at weeks 4 and 12 in **a** PSOARING 1 and **b** PSOARING 2. [a]DLQI item 1 evaluates itch, soreness, painfulness, or stinging on a 4-point scale rating, where 0 indicates "not at all" and 3 indicates "very much" impact on quality of life. Intention-to-treat population, observed cases. Least squares mean (standard error). *DLQI* Dermatology Life Quality Index, *QD* once daily

($P = 0.0009$ for PSOARING 1 and $P < 0.0001$ for PSOARING 2), and week 12 (both $P < 0.0001$).

Safety

Safety data for PSOARING 1 and 2 have been previously reported; most treatment-emergent adverse events (TEAEs) were mild or moderate in severity and did not lead to trial discontinuation [19]. The most common TEAEs (≥ 2% in any group) were folliculitis, nasopharyngitis, contact dermatitis, headache, upper respiratory tract infection, pruritus, and viral upper respiratory tract infection [19].

DISCUSSION

Tapinarof cream 1% QD demonstrated rapid, statistically significant, and clinically meaningful reductions in pruritus in patients with mild to severe plaque psoriasis in the pivotal phase 3 trials, PSOARING 1 and PSOARING 2. Tapinarof cream demonstrated a consistent safety profile across these and previously reported clinical trials and was efficacious and well tolerated for up to 1 year in a long-term extension trial (PSOARING 3) [19, 20, 24–26].

The importance of pruritus as a prevalent and burdensome psoriasis symptom is gaining acceptance as an outcome in clinical trials [27]. Left uncontrolled, pruritus can substantially reduce well-being and quality of life of patients with psoriasis [2–5]. Patients treated with

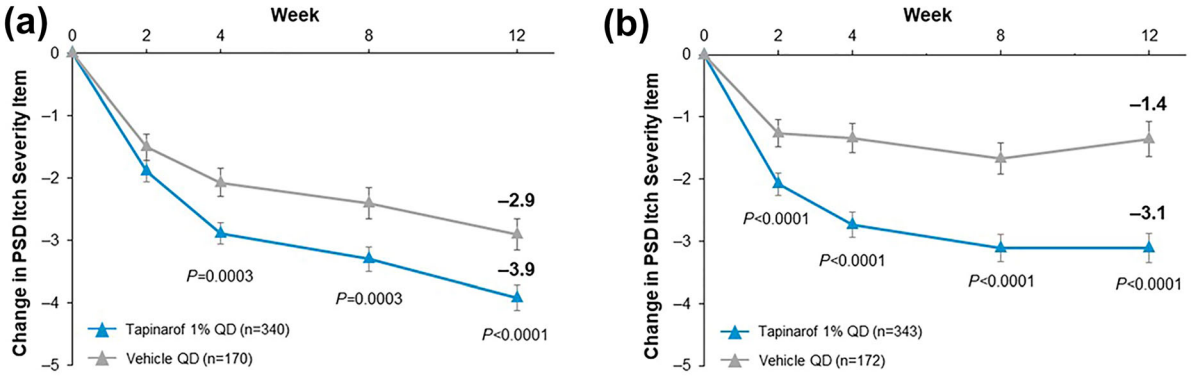

Fig. 5 Early, statistically significant, and sustained improvement in PSD itch severity item rating from baseline at weeks 2, 4, 8, and 12 in **a** PSOARING 1 and **b** PSOARING 2. Intention-to-treat population, observed cases. Least squares mean (standard error). *PSD* Psoriasis Symptom Diary, *QD* once daily

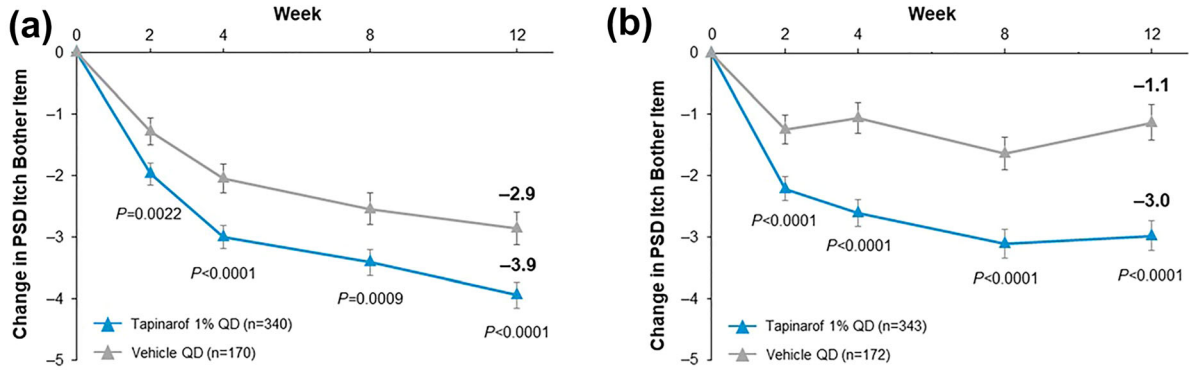

Fig. 6 Rapid and statistically significant improvement in PSD itch bother item rating from baseline at weeks 2, 4, 8, and 12 in **a** PSOARING 1 and **b** PSOARING 2. Intention-to-treat population, observed cases. Least squares mean (standard error). *PSD* Psoriasis Symptom Diary, *QD* once daily

tapinarof in PSOARING 1 and 2 reported significant and clinically relevant improvements in pruritus compared with vehicle-treated patients. These improvements were apparent at the earliest assessments (week 2) with continued improvement over the course of the trials. At week 12, the proportion of tapinarof-treated patients achieving an itch-free state (a PP-NRS score of 0 or 1) was 50% compared with 27–32% in the vehicle groups ($P = 0.0007$ for PSOARING 1; $P < 0.0001$ for PSOARING 2).

The relief from pruritus with tapinarof cream demonstrated in this analysis is consistent with previously reported improvements in total PP-NRS scores and PP-NRS responses (a clinically relevant 4-point improvement) at week 12 [19]. In addition to the significant efficacy demonstrated on the PP-NRS, rapid and significant improvements were demonstrated with tapinarof on all additional patient-reported pruritus outcome measures compared with vehicle.

The evaluations on the DLQI item 1 and the PSD itch items were performed to explore if the clinically significant efficacy demonstrated with tapinarof on the PP-NRS scale was consistent with these life-quality subscales. It should be noted that the PP-NRS is a well-defined and reliable patient-reported outcome measure for evaluating the intensity of pruritus, whereas the DLQI and PSD (and their subscales) are not itch-

specific nor validated to detect clinically relevant differences in itch. More research is needed on the assessment of itch in clinical trials of psoriasis, and on the correlation of scales such as the PP-NRS and QoL instruments, such as the DLQI and PSD.

The vehicle effect in these trials was 46% and 31% with vehicle, compared with 68% and 60% with tapinarof in each trial (both $P < 0.001$), based on the proportion of patients who achieved at least a 4-point improvement in PP-NRS from baseline to week 12. This endpoint reflects improvement in itch among patients with significant itch at baseline, as patients were required to have a PP-NRS score of at least of 4 at baseline. Despite any vehicle effect, the magnitude of improvement in the active arms, and the differences versus vehicle, underscore the clinical relevance of tapinarof therapy in the treatment of itch.

CONCLUSIONS

More attention to the efficacy of treatments for pruritus in psoriasis is warranted. Here we evaluated pruritus using several different rating scales and endpoints to help inform clinicians about the benefit of tapinarof and improve methods for the evaluation of treatments for psoriasis.

Tapinarof cream 1% QD demonstrated rapid, clinically meaningful, and statistically significant improvements across multiple patient-reported outcome measures in both PSOARING 1 and 2 for all pruritus assessments. Improvements in pruritus with tapinarof cream were demonstrated from the earliest visit through week 12. The statistically significant proportion of patients achieving the treatment target of an itch-free state is a noteworthy clinical outcome in the treatment of plaque psoriasis with a topical cream.

The similar, statistically significant, improvements in pruritus with tapinarof observed across outcome measures in this large cohort of patients support the previously reported efficacy of tapinarof cream in the treatment patients with mild to severe plaque psoriasis [19, 20, 24–26].

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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

Conflicts of Interest. Leon Kircik has served as a consultant, speaker, investigator, or advisory board member for Abbott Laboratories, AbbVie, Ablynx, Aclaris, Acambis, Allergan, Inc., Almirall, Amgen, Inc., Anacor Pharmaceuticals, AnaptysBio, Arcutis Biotherapeutics, Arena Pharmaceuticals, Assos Pharmaceuticals, Astellas Pharma US, Inc., Asubio Pharmaceuticals, Bausch Health, Berlex Laboratories (Bayer HealthCare Pharmaceuticals), Biogen Idec, BioLife, Biopelle, Bristol Myers Squibb, Boehringer Ingelheim, Breckenridge Pharma, Cassiopea SpA, Centocor, Inc., Cellceutix, Cipher Pharmaceuticals, Coherus BioSciences, Colbar LifeScience, Combinatrix, Connetics

Corporation, Coria Laboratories, Dermavant Sciences, Inc., Dermira, Dermik Laboratories, Dow Pharmaceutical Sciences, Inc., Dr. Reddy's Laboratories, DUSA Pharmaceuticals, Embil Pharmaceutical Co. Ltd., Eli Lilly, EOS, Exeltis, Ferndale Laboratories, Inc., Ferrer, Foamix Pharmaceuticals, Galderma, Genentech, Inc., GlaxoSmithKline, Glenmark Pharmaceuticals, Healthpoint, Ltd, Idera Pharmaceuticals, Incyte, Intendis, Innocutis, Innovail, ISDIN, Johnson & Johnson, Kyowa Kirin, Laboratory Skin Care Inc., LEO Pharma, L'Oréal, 3M, Maruho Co., Ltd., Medical International Technologies, Merck, Medicis Pharmaceutical Corp., Merz Pharma, NanoBio, Novartis AG, Noven Pharmaceuticals, Nucryst Pharmaceuticals Corp., Obagi, Onset Dermatologics, Ortho Neutrogena, Pediapharma, Pfizer, Promius Pharma, PuraCap, Pharmaderm, QLT, Inc., Quinnova Pharmaceuticals, Quatrix, Regeneron, Sanofi, Serono (Merck Serono International SA), SkinMedica, Inc., Stiefel Laboratories, Inc., Sun Pharma, Taro Pharmaceutical Industries, Toler Rx, Triax Pharmaceuticals, UCB Pharma, Valeant Pharmaceuticals Intl., Warner Chilcott, XenoPort, and ZAGE. Matthew Zirwas has served as an advisor, consultant, investigator, owner, or speaker for AbbVie, All Free Clear, Amgen, Inc., AnaptysBio, Arcutis Biotherapeutics, Aseptic MD, Biocon, Cara Therapeutics, Concert Pharmaceuticals, Dermavant Sciences, Inc., Edessa Biotech, Eli Lilly, EPI Health, Evelo Biosciences, Fitbit, Galderma, Genentech, Inc., Incyte, L'Oréal, LEO Pharma, Level Ex, LUUM, Novartis, Oculus Innovative Sciences, Peloton, Pfizer, Regeneron Pharmaceuticals, Sanofi, Sun Pharma, Trevi Therapeutics, UCB Pharma, and Vial. Shawn G. Kwatra has served as an investigator, advisory board member, or consultant for AbbVie, Aslan Pharmaceuticals, Arcutis Biotherapeutics, Castle Biosciences, Celldex Therapeutics, Galderma, Genzada Pharmaceuticals, Incyte, Johnson & Johnson, LEO Pharma, Novartis Pharmaceuticals Corporation, Pfizer, Regeneron Pharmaceuticals, and Sanofi. G. Michael Lewitt has served as a consultant, speaker, investigator, or advisory board member for 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, Orthodermatologics, and UCB Pharma. Holly Glover has served as a consultant, speaker, investigator, or advisory board member of AbbVie, Almirall, Bristol Myers Squibb, Cassiopea SpA, Dermavant Sciences, Inc., Eli Lilly, Galderma, Incyte, ISDIN, LEO Pharma, Pfizer, and Sun Pharma. Tomas Chao has served as an advisor and speaker for Dermavant Sciences, Inc. Philip M. Brown, David S. Rubenstein, 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 patients provided written informed consent.

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