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 ORIGINAL ARTICLE

Rapid Onset of Itch Relief With Tapinarof in Two Phase 3 Trials in Atopic Dermatitis

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ABSTRACT

Background: In the ADORING 1 and 2 phase 3 trials, tapinarof cream 1% once daily (QD) demonstrated significant efficacy and was well tolerated in adults and children down to 2 years of age with atopic dermatitis (AD). Here we evaluate the time to onset of itch relief in the trials.

Methods: Eight hundred thirteen (813) patients were randomized to tapinarof cream 1% or vehicle QD for 8 weeks. Pruritus relief was assessed by Peak Pruritus Numerical Rating Scale (PP-NRS) scores (daily and by visit at weeks 1, 2, 4, and 8).

Results: Mean baseline PP-NRS scores in ADORING 1 and 2 were 6.7 and 6.8, respectively. Greater reductions in mean daily PP-NRS scores were observed for tapinarof vs vehicle as early as day 1, 24 hours after initial application (–1.2 vs –1.0; pooled post hoc analysis), with significant improvements at day 2 (–1.6 vs –1.1, P=0.0115). Daily pruritus improvements continued through week 8. Significantly greater reductions in mean weekly PP-NRS scores with tapinarof vs vehicle were demonstrated at week 1 in ADORING 1, –2.0 vs –1.2 (P<0.0001) and ADORING 2, –2.0 vs –1.3 (P=0.0010), continuing through week 8, –4.1 vs –2.6 and –4.1 vs –2.4 (both P<0.0001).

Conclusion: Tapinarof demonstrated rapid and clinically meaningful pruritus relief in patients with AD, with improvements starting 24 hours after initial application and statistically significant improvements at day 2.

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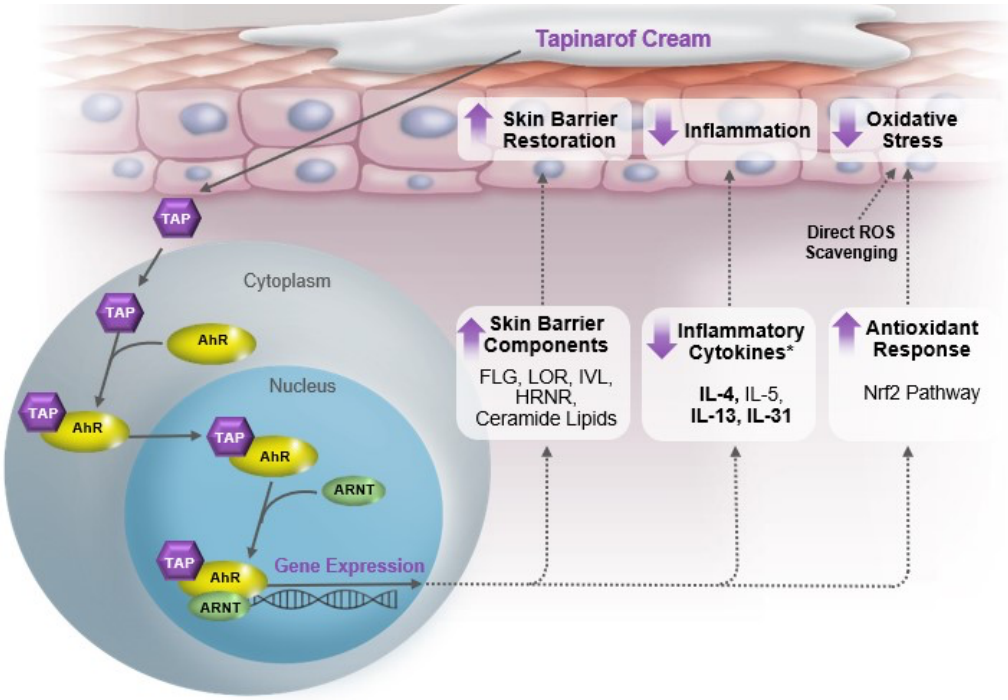
INTRODUCTION

Atopic dermatitis (AD) is a chronic relapsing-remitting condition that affects approximately 25% of children and 7% to 10% of adults globally.[1] Pruritus (itch) is the most bothersome symptom for patients with AD, substantially impacting sleep and health-related quality of life (QoL).[2,3]

Pruritus is stimulated by the activation of pruriceptive sensory neurons and can be experienced anywhere on the skin or mucosa.[4] Cytokines involved in AD pathogenesis, including interleukin (IL)-4, IL-13, and IL-31, are also implicated as pruritus mediators.[5-8] IL-4, IL-13, and IL-31 may directly or indirectly influence pruritus through activation of sensory neurons.[5,7,8] Semaphorin 3A is a nerve repulsion factor that inhibits sensory nerve growth; increased epidermal nerve density and decreased semaphorin 3A levels are associated with pruritus in patients with AD.[9,10]

Important goals of AD treatment include the rapid relief of core symptoms including pruritus, with sustained efficacy, and rapid healing of skin lesions.[11] Topical corticosteroids (TCSs) are a mainstay of treatment and are generally efficacious when used as directed, but are associated with adverse events (AEs) that can limit their use.[12,13,14,15] TCS effectiveness may also be limited by the potential for tachyphylaxis (loss of response).[16,17] Furthermore, TCSs have restrictions relating to patient age, duration, and extent of use, and use in specific anatomic locations.[16,18] Consequently, TCS use is often restricted,

FIGURE 1. Proposed mechanism of action of tapinarof.



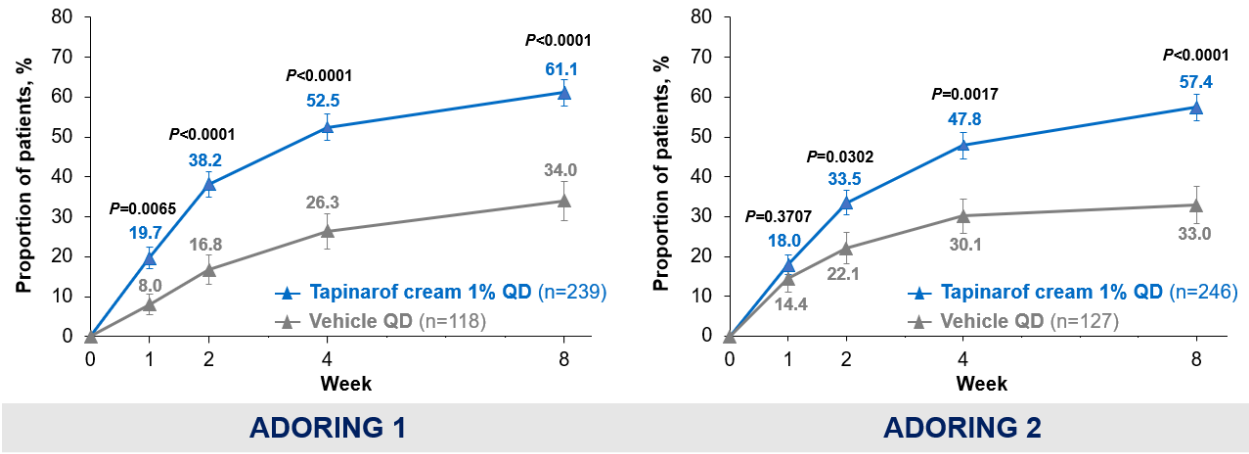
Adapted from the *Journal of the American Academy of Dermatology*; 84(4); Bissonnette R, Stein Gold L, Rubenstein DS, Tallman AM, Armstrong A; Tapinarof in the treatment of psoriasis: a review of the unique mechanism of action of a novel therapeutic aryl hydrocarbon receptor-modulating agent; p.1065; Copyright (2021), with permission from Elsevier.
*Tapinarof binds to and activates AhR to downregulate proinflammatory cytokines, including IL-4, IL-13, and IL-31, that are implicated in itch.
AhR, aryl hydrocarbon receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; FLG, filaggrin; HRNR, hornerin; IL, interleukin; IVL, involucrin; LOR, loricrin; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; TAP, tapinarof.

especially in sensitive skin areas; and low-potency TCSs with variable efficacy are often used in infants and children who are at increased risk of systemic absorption and AEs.[12,19] Topical calcineurin inhibitors (tacrolimus and pimecrolimus) and crisaborole (a topical phosphodiesterase-4 inhibitor), while efficacious, may be associated with AEs, including application site burning, stinging, and pain, and have restrictions on long-term use.[20,21] The topical Janus kinase inhibitor ruxolitinib has warnings and restrictions based on age, duration of therapy, and maximum body surface area (BSA) treated.[21-24]

Tapinarof (VTAMA®; Dermavant Sciences, an Organon Company) is a non-steroidal, topical aryl hydrocarbon receptor (AhR) agonist approved by the United States Food and Drug Administration for the treatment of AD in adults and children down to age 2 years, and for the treatment of plaque psoriasis in adults, with no warnings, contraindications, precautions, drug-drug interactions, or restrictions on location, extent, or duration of use.[25] AhR plays a role in multiple signaling pathways involved in skin homeostasis, immune responses, and epithelial barrier function.[26] Tapinarof binds to and activates AhR to downregulate pro-inflammatory cytokines IL-4, IL-13, IL-31, IL-5, which are implicated in AD, to restore the skin barrier through upregulation of skin barrier components (filaggrin, loricrin, hornerin, involucrin, and ceramides), and to reduce oxidative stress in the skin (Figure 1).[26] Clinically meaningful improvements in pruritus with tapinarof were demonstrated in patients with AD and psoriasis, likely through downregulating inflammatory signaling cascades.[26-28] Tapinarof has also been shown to upregulate semaphorin 3A, which is associated with a reduction in pruritus.[9,10]

Tapinarof cream 1% once daily (QD) was superior to vehicle in improving pruritus across multiple patient-reported outcome measures in 2 randomized, vehicle-controlled phase 3 trials in adults with mild to severe plaque psoriasis (PSOARING 1, NCT03956355; PSOARING 2, NCT03983980).[27] In ADORING 1 and ADORING 2, 2 randomized, vehicle-controlled phase 3 trials in adults and children down to age 2 years with AD, tapinarof cream 1% QD demonstrated significant efficacy and was well tolerated.[28] A Peak Pruritus Numerical Rating Scale (PP-NRS) response was defined as a ≥4-point reduction in the mean weekly PP-NRS total score from baseline in ADORING 1 and ADORING 2. At week 8, a PP-NRS response was achieved by significantly higher proportions of patients in all tapinarof groups vs vehicle in both trials (Figure 2).[28] Significant improvements were demonstrated in patients aged ≥12 years, 55.8% vs 34.2% (P=0.0366) and 52.8% vs 24.1% (P=0.0015); in

FIGURE 2. Early and statistically significant achievement of a minimum 4-point improvement in PP-NRS from baseline through week 8 with tapinarof cream 1% QD in ADORING 1 and 2.



Proxy-completion by parent or caregiver for patients aged <12 years, self-completion for patients aged ≥12 years.
Intention-to-treat, observed cases. Mean (standard error).
PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily.

those aged <12 years, 60.7% vs 28.0% (*P*=0.0001) and 60.0% vs 40.8% (*P*=0.0414); and in all patients, 61.1% vs 34.0% (*P*<0.0001) and 57.4% vs 33.0% (*P*<0.0001), in ADORING 1 and 2, respectively.[28]

Given the importance of pruritus relief for patients with AD, we further investigated the kinetics of onset of itch relief in these phase 3 trials of tapinarof cream in patients down to age 2 years with AD.

MATERIALS AND METHODS

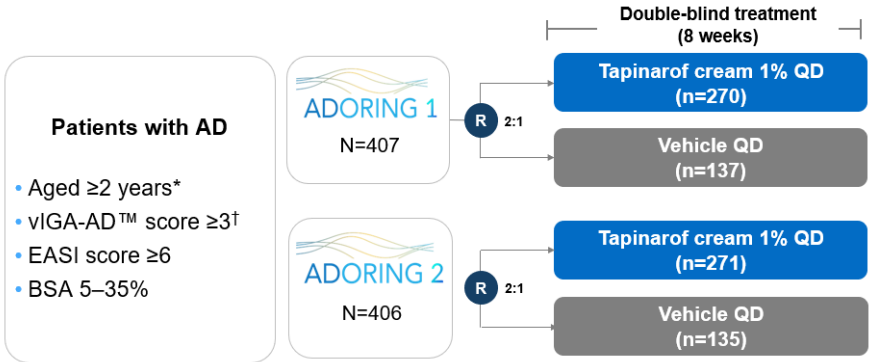
Trial Design and Treatment

In ADORING 1 and 2 – 2 identically designed phase 3, double-blind, randomized, vehicle-controlled trials – patients with moderate to severe AD were randomized 2:1 to tapinarof cream 1% or vehicle QD for 8 weeks (Figure 3). Following the double-blind period, eligible patients could enroll in an open-label, long-term trial (ADORING 3) or complete a follow-up visit 1 week after treatment ended (week 9). The trials were conducted according to Good Clinical Practice and the Declaration of Helsinki. Approval was obtained from all local ethics committees or institutional review boards. All patients provided written informed consent.

Participants

Key inclusion and exclusion criteria for ADORING 1 and 2 were previously reported.[28] Patients were adults and children down to age 2 years with an AD diagnosis by Hanifin and Rajka criteria,[29] with a Validated Investigator Global Assessment for Atopic Dermatitis™ (vIGA-AD™) score of ≥3 (moderate or severe), an Eczema Area and Severity Index (EASI) score of ≥6, and BSA involvement of 5% to 35% at screening and baseline.

FIGURE 3. ADORING 1 and 2 trial design.



*A minimum of ~15% of patients were enrolled into the following age groups: 2–6 years, 7–11 years, 12–17 years, and ≥18 years. Adults (aged ≥18 years) comprised a maximum of approximately 20% of enrolled patients.
†Patients with a vIGA-AD™ score of 4 (severe) represented a minimum of ~10% of the total randomized population; the remainder had a vIGA-AD™ score of 3 (moderate).
BSA, body surface area; EASI, Eczema Area and Severity Index; QD, once daily; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis™.

Outcome Measures

Pruritus was assessed by the mean change from baseline in daily PP-NRS scores and at each visit (weeks 1, 2, 4, 6, and 8). The PP-NRS uses an 11-point scale (0 indicates "no itch" and 10 indicates "worst imaginable itch" within the last 24 hours).[30] Weekly PP-NRS scores were the mean of the prior 7 days' scores, including the visit day. Patients or parents/caregivers recorded pruritus assessments in a daily diary. Patients aged ≥12 years self-completed the PP-NRS; parents/caregivers completed it for patients <12 years. A minimal clinically important difference (MCID) for improvement in PP-NRS from baseline is generally considered 4 points (a PP-NRS response); however, studies have shown that a 2-point difference may also be considered clinically meaningful in AD.[6,31] Safety evaluations included incidence of treatment-emergent AEs (TEAEs).[28]

Statistical Analyses

PP-NRS endpoints were based on the intention-to-treat population. Analyses were based on individual data from each trial, except evaluation of daily itch which was assessed using a post hoc pooled analysis to identify the earliest achievement of significant improvements vs vehicle. Continuous variables were analyzed using an analysis of covariance model, with baseline vIGA-AD™ score and age group as covariates, and PP-NRS baseline value as a continuous covariate. The treatment effect is presented as least squares means. Missing data were handled using multiple imputation (MI).

RESULTS

Baseline Patient Demographics and Disease Characteristics

Baseline demographics and disease severity, including pruritus, were similar across groups for the diverse population in ADORING 1 and 2 (Table 1).[28] Overall, 80% of patients were

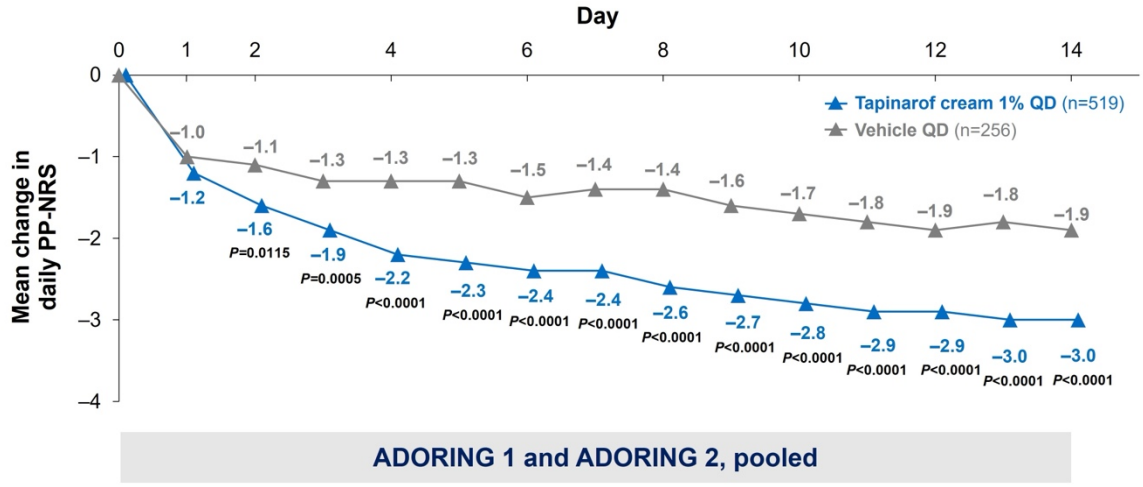
TABLE 1.

Baseline Patient Demographics and Clinical Characteristics for ADORING 1 and 2

Characteristic	ADORING 1		ADORING 2	
	Tapinarof Cream 1% QD (n=270)	Vehicle QD (n=137)	Tapinarof Cream 1% QD (n=271)	Vehicle QD (n=135)
Age, years, mean (SD)	15.6 (16.6)	15.6 (16.5)	16.4 (16.2)	16.7 (16.1)
Age group, n (%)				
2–6 years	76 (28.1)	39 (28.5)	65 (24.0)	32 (23.7)
7–11 years	75 (27.8)	37 (27.0)	64 (23.6)	32 (23.7)
12–17 years	67 (24.8)	34 (24.8)	89 (32.8)	44 (32.6)
≥18 years	52 (19.3)	27 (19.7)	53 (19.6)	27 (20.0)
Male, n (%)	130 (48.1)	66 (48.2)	117 (43.2)	58 (43.0)
Race*, n (%)				
White	152 (56.3)	79 (57.7)	124 (45.8)	58 (43.0)
Black	70 (25.9)	38 (27.7)	95 (35.1)	47 (34.8)
Asian	26 (9.6)	10 (7.3)	39 (14.4)	23 (17.0)
Other groups†	16 (5.9)	5 (3.6)	7 (2.6)	4 (3.0)
Not reported	6 (2.2)	5 (3.6)	6 (2.2)	3 (2.2)
Fitzpatrick skin type, n (%)				
I–III	135 (50.0)	60 (43.8)	113 (41.7)	65 (48.1)
IV–VI	135 (50.0)	77 (56.2)	158 (58.3)	70 (51.9)
vIGA-AD™ score, n (%)				
3 (Moderate)	244 (90.4)	122 (89.1)	228 (84.1)	113 (83.7)
4 (Severe)	26 (9.6)	15 (10.9)	43 (15.9)	22 (16.3)
EASI score, mean (SD)	12.2 (5.0)	12.9 (5.6)	13.5 (5.6)	13.1 (4.7)
BSA affected, mean (SD)	16.5 (8.7)	17.7 (9.5)	17.1 (8.7)	15.8 (7. 9)
PP-NRS‡ total score, mean (SD)				
All	6.8 (2.3)	6.5 (2.4)	6.7 (2.4)	6.9 (2.1)
≥12 years	6.5 (2.4)	6.3 (2.3)	6.3 (2.4)	6.5 (2.2)
<12 years	7.0 (2.3)	6.6 (2.5)	7.1 (2.3)	7.4 (1.8)

*Race was patient reported.
†"Other groups" comprised American Indian or Alaska Native, Native Hawaiian or Pacific Islander, or multiple races.
‡The PP-NRS is a well-defined and reliable patient-reported outcome measure for evaluating the intensity of pruritus in the previous 24 hours on a scale of 0 to 10 (with 0 being "no itch" and 10 being "worst itch imaginable"). The PP-NRS is validated for use in patients aged ≥12 years with moderate to severe AD.
AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area and Severity Index; PP-NRS, Peak Pruritus-Numerical Rating Scale; QD, once daily; SD, standard deviation; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis™.

FIGURE 4. Rapid reduction in pruritus with tapinarof cream 1% QD as early as 24 hours after first application, the first assessment, in a pooled post hoc analysis of ADORING 1 and 2.



Time is days after first application. ADORING 1 and 2 post hoc pooled data showing a numerical reduction in pruritus with tapinarof vs vehicle at day 1, 24 hours after first application, with a significant improvement from day 2.
Intention-to-treat, observed cases. P-values not adjusted for multiple comparisons.
PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily.

children (aged <18 years). At baseline, 83.7% to 90.4% of patients had a vIGA-AD™ of 3 (moderate), mean EASI scores were 12.2 to 13.5, and mean BSA was 15.8% to 17.7% across all groups.

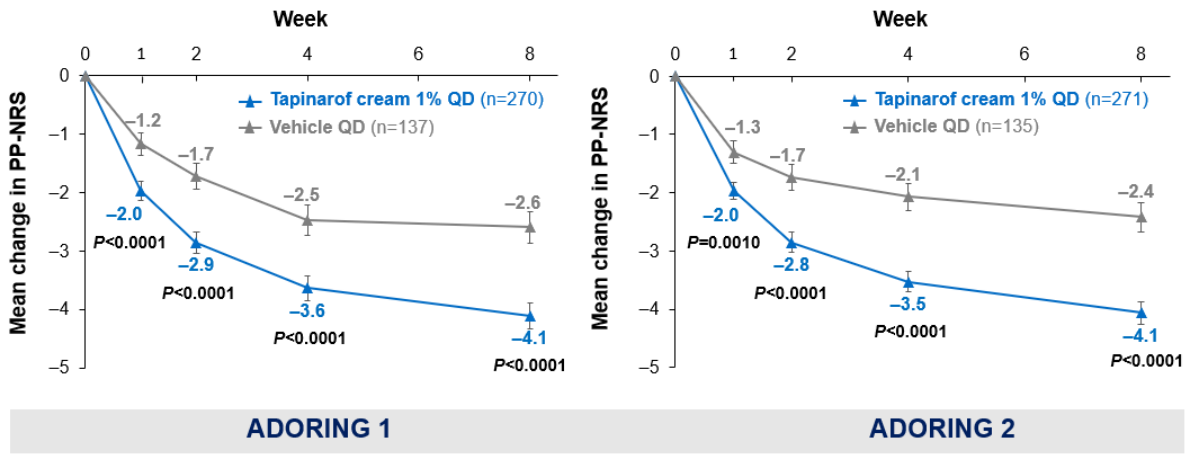
Mean Change From Baseline in Daily PP-NRS Score

Numerically greater reductions in mean (standard deviation [SD]) daily PP-NRS scores were observed with tapinarof vs vehicle as early as day 1, 24 hours after initial application (–1.2 [2.2] vs –1.0 [2.1]), in a pooled post hoc analysis of ADORING 1 and 2 (Figure 4). Significant improvement in mean daily itch (SD) with tapinarof vs vehicle were demonstrated starting from day 2 (–1.6 [2.3] vs –1.1 [2.0], *P*=0.0115) (Figure 4). Significant improvements in daily PP-NRS scores with tapinarof vs vehicle continued through the first 2 weeks (day 14: –3.0 [2.7] vs –1.9 [2.5], *P*<0.0001), and through week 8 (day 56: –4.1 [2.8] vs –2.5 [3.0], *P*<0.0001).

Mean Change From Baseline in Weekly PP-NRS Score

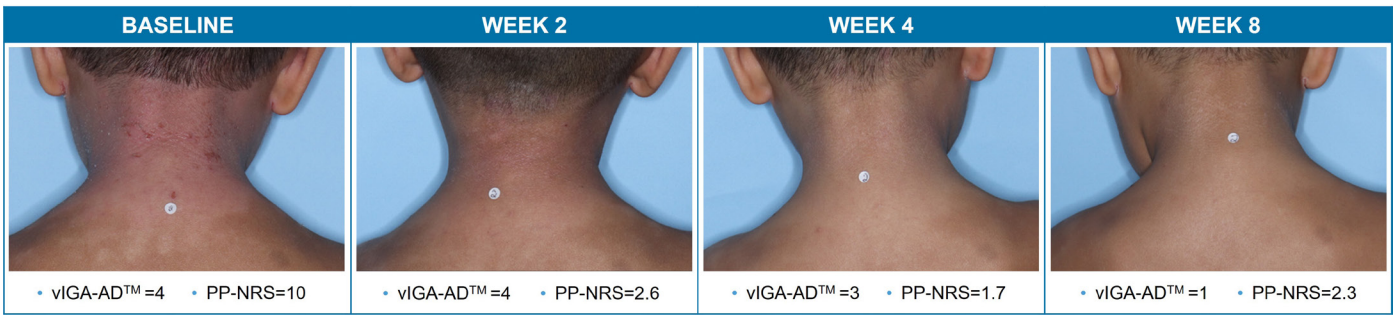
Significant reductions in mean weekly PP-NRS scores were demonstrated with tapinarof vs vehicle as early as week 1 (–2.0 vs –1.2 [*P*<0.0001] and –2.0 vs –1.3 [*P*=0.0010]), the earliest measured time point, in ADORING 1 and 2, respectively (Figure 5).

FIGURE 5. Rapid and significant reduction in pruritus with tapinarof cream 1% QD from baseline through week 8 in ADORING 1 and 2.



Intention-to-treat, observed cases. Least squares mean (standard error).
PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily.

FIGURE 6. Achievement of the ≥4-point MCID in PP-NRS within 24 hours after first application*, with improvement maintained through the end of the trial in a 3-year-old patient with AD treated with tapinarof cream 1% QD.



Example of one representative target lesion in a tapinarof-treated patient from the ADORING 1 trial. Individual results may vary.
*A PP-NRS score of 3 was achieved 24 hours after first application of tapinarof cream.
Weekly PP-NRS scores are the mean of daily scores for the previous 7 days.
AD, atopic dermatitis; MCID, minimal clinically important difference; PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily; vIGA-AD™, Validated Investigator Global Assessment for Atopic Dermatitis™.

Significant improvements in mean weekly PP-NRS scores (tapinarof vs vehicle) continued through week 2 (both $P<0.0001$) and week 4 (both $P<0.0001$); and at week 8 the mean reductions in PP-NRS scores were –4.1 vs –2.6 and –4.1 vs –2.4 (both $P<0.0001$). The tapinarof groups surpassed the MCID (≥4-point reduction in mean PP-NRS score from baseline) at week 8.

Achievement of an Early PP-NRS Response

Significantly more patients treated with tapinarof vs vehicle achieved a PP-NRS response (≥4-point improvement in weekly mean PP-NRS total score) at week 1, the first assessment, in ADORING 1 (19.7% vs 8.0%, $P=0.0065$), and at week 2 in ADORING 2 (33.5% vs 22.1%, $P=0.0302$) (Figure 2).

Case Photography

The 3-year-old patient in Figure 6 had severe AD (vIGA-AD™ =4) and severe pruritus (PP-NRS=10) at baseline. He achieved the primary endpoint (vIGA-AD™ of clear [0] or almost clear [1] and ≥2-grade improvement) at week 8 (Figure 6). Pruritus reduction surpassed the minimal clinically important ≥4-point improvement in PP-NRS 24 hours after initial application of tapinarof (daily PP-NRS=3). Achievement of the PP-NRS response continued consistently through week 8.

Safety

Safety data for these trials were previously reported.[28] Most TEAEs were mild or moderate in severity and consistent with previous trials; the most common TEAEs (≥5%, any group) were folliculitis, headache, and nasopharyngitis. Trial discontinuation rates due to TEAEs were lower with tapinarof than vehicle (ADORING 1: 1.9% vs 3.6%; ADORING 2: 1.5% vs 3.0%).

DISCUSSION

Tapinarof cream 1% QD monotherapy demonstrated rapid, statistically significant, and clinically meaningful reductions in pruritus in a diverse population of patients down to age 2 years with AD in the ADORING 1 and 2 phase 3 trials. Tapinarof was well tolerated overall, and trial discontinuation rates were lower with tapinarof than with vehicle. Tapinarof demonstrated a consistent safety profile across these and previously reported trials.[28,32,33]

Pruritus is the most burdensome symptom for patients with AD, especially young children, regardless of disease severity. Left uncontrolled, pruritus can substantially impact well-being and health-related QoL.[2,3] The impact of AD on sleep is largely mediated through pruritus and scratching.[34] The association between attention-deficit/hyperactivity disorder and AD in children has been suggested to be mediated through sleep disturbance.[35] In adults with AD, sleep disturbance, likely due to chronic pruritus, increases the risk of anxiety and depression.[36] Consequently, treating AD in both adults and children with therapies that provide rapid pruritus relief could improve sleep and reduce risks of long-term sequalae. More data are needed to confirm this hypothesis.

Tapinarof decreases pro-inflammatory cytokines, particularly IL-31, a key pruritus mediator in AD, and restores the skin barrier (Figure 1).[6,26] Additionally, targeting AhR to modulate multiple inflammatory pathways provides a potential rationale for the high and consistent efficacy of tapinarof across this large, diverse population.[26,37]

Patients treated with tapinarof in ADORING 1 and 2 reported significant and clinically relevant improvements in pruritus vs vehicle. At week 8, improvements in weekly PP-NRS scores with tapinarof vs vehicle were –4.1 vs –2.6 (P<0.0001) in ADORING 1 and –4.1 vs –2.4 (P<0.0001) in ADORING 2, surpassing the MCID of ≥4 points (Figure 5). Pooling daily PP-NRS scores in a post hoc analysis confirmed that improvements with tapinarof were apparent as early as day 1, 24 hours after initial application, with significance demonstrated at 48 hours, continuing through week 8 (Figure 4).

Pruritus relief demonstrated with tapinarof is consistent with previously reported improvements in total PP-NRS scores and PP-NRS responses (a clinically meaningful ≥4-point improvement) at week 12 in adults with mild to severe plaque psoriasis in the PSOARING 1 and 2 phase 3 trials.[32]

A limitation of these analyses was that earliest achievement of significant improvements in daily itch was assessed using a post hoc pooled analysis. Strengths of the trial design include a large, diverse patient population, especially regarding age and race, and the prespecified use of the PP-NRS, a well-defined, reliable patient-reported outcome measure.

Tapinarof is a once-daily non-steroidal cream that rapidly reduced pruritus in a diverse population with AD. Tapinarof cream 1% QD can be used without restrictions on duration of use, extent of BSA treated, or sites of application in adults and children down to age 2 years with AD.

DISCLOSURES

Eric L. Simpson reports grants and fees for participation as a consultant and principal investigator from Eli Lilly and Company, LEO Pharma, Pfizer, and Regeneron; grants for participation as a principal investigator from Galderma and Merck & Co.; and fees for consultant services from AbbVie, Boehringer Ingelheim, Dermavant Sciences, Inc., Incyte, Forte Bio, Pierre Fabre Dermo, and Sanofi-Genzyme.

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Robert Bissonnette has served as an advisory board member, consultant, speaker, and/or investigator for, and receives honoraria and/or grants from AbbVie, Amgen, Apogee, Arcutis, Areteia, Asana BioSciences, Bellus, BioMimetix, Bluefin, Biomedicine, Boehringer Ingelheim, Boston Pharma, CARA Therapeutic, Dermavant Sciences, Inc., Eli Lilly, Escient, Evidera, Fresh Tracks (Brickell), Galderma, GlaxoSmithKline, Incyte, Inmagene Bio, Janssen, LEO Pharma, Merck, Novartis, Opsidio, Pfizer, RAPT Therapeutic, Sanofi, Sitryx, Target RWE, Vyne Therapeutics, and Zencor. He is an employee and shareholder of Innovaderm Research.

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.

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Philip M. Brown, Stephen C. Piscitelli, and Anna M. Tallman are employees of Dermavant Sciences, an Organon Company.

David S. Rubenstein is a former employee of Dermavant Sciences, Inc.

Lawrence F. Eichenfield has served as a consultant, advisor, or investigator for AbbVie, Amgen, Apogee, Arcutis, Aslan, Bausch, Bristol Myers Squib, Castle Biosciences, Dermavant Sciences, Inc., Eli Lilly, Forté, Galderma, Incyte, Janssen, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi-Genzyme, and UCB Pharma.

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