Tapinarof cream 1% once daily: Significant efficacy in the treatment of moderate to severe atopic dermatitis in adults and children down to 2 years of age in the pivotal phase 3 ADORING trials

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Background: Tapinarof cream 1% once daily (QD), a topical aryl hydrocarbon receptor agonist, downregulates pro-inflammatory Th2 cytokines, upregulates skin-barrier components, and reduces oxidative stress.

Objective: To assess tapinarof efficacy and safety in adults and children down to 2 years of age with atopic dermatitis (AD).

Methods: Eight hundred and thirteen patients were randomized to tapinarof or vehicle QD in two 8-week phase 3 trials.

Results: The primary efficacy endpoint, Validated Investigator Global Assessment for Atopic Dermatitis score of 0 or 1 and ≥2-grade improvement from baseline at Week 8, was met with statistical significance in both trials: 45.4% versus 13.9% and 46.4% versus 18.0% (tapinarof vs vehicle; both $P < .0001$). Significantly superior Eczema Area and Severity Index 75 (EASI75) responses were also observed with tapinarof versus vehicle at Week 8: 55.8% versus 22.9% and 59.1% versus 21.2% (both $P < .0001$). Rapid improvements in patient-reported pruritus were also significant with tapinarof versus vehicle. Common adverse events (≥5%) of folliculitis, headache, and nasopharyngitis were mostly mild or moderate, with lower discontinuations due to adverse events in the tapinarof groups than with vehicle.

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Limitations: Long-term efficacy was not assessed.

Conclusion: Tapinarof demonstrated highly significant efficacy and favorable safety and tolerability in a diverse population of patients with AD down to 2 years of age. (J Am Acad Dermatol 2024;91:457-65.)

Key words: atopic dermatitis; atopic eczema; aryl hydrocarbon receptor agonist; randomized controlled phase 3 trials; tapinarof cream 1% QD; topical therapy.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disease characterized by intense pruritus and eczematous lesions that substantially impact sleep and quality of life.[1-4] AD is burdensome and prevalent, affecting approximately 16.5 million adults and 9.6 million children in the US.[5,6] The trajectory of AD is variable, with flares being an integral feature of the disease course.

Due to the burden and heterogeneity of AD, there is a need for safe, efficacious, nonsteroidal, topical therapies that can be used by all patients, including very young children, without the limitations of current topical medications.[7]

Corticosteroids and phosphodiesterase-4 (PDE4) inhibitors are first-line topical treatment options for AD, with calcineurin inhibitors and Janus kinase (JAK) inhibitors in second-line.[8] Safety and tolerability issues of topical corticosteroids are usually associated with inappropriate long-term use or high-potency agents; adverse events (AEs) may include skin atrophy, striae, telangiectasia, ecchymosis, dyspigmentation, hirsutism, and withdrawal phenomena.[9-11] Topical PDE4 and calcineurin inhibitors are associated with local tolerability issues, including application site pain, burning, or stinging.[12-14] Only one topical medication (a calcineurin inhibitor) is approved to treat severe AD, restricted to second-line short-duration use in immunocompetent individuals.[13] The only approved topical JAK inhibitor carries a boxed warning and has restrictions based on age (≥12 years) and maximum body surface area (BSA) treated (<20%).[15] All approved topical PDE4, calcineurin, and JAK inhibitors for AD are indicated for twice-daily application, which can be a barrier to adherence.[12-15]

Tapinarof (VTAMA, Dermavant Sciences, Inc) is a nonsteroidal, topical aryl hydrocarbon receptor (AhR) agonist approved for the treatment of plaque psoriasis in adults[16-18] and under investigation for the treatment of plaque psoriasis in children (NCT05172726). In adults and adolescents with moderate to severe AD, tapinarof cream 1% once daily (QD) demonstrated efficacy versus vehicle, based on the primary outcome measure of an Investigator Global Assessment (IGA) score of clear (IGA = 0) or almost clear (IGA = 1) and a minimum 2-grade improvement from baseline at Week 12, and was well tolerated in a previous phase 2b trial (NCT02564055).[19,20] Efficacy was maintained 4 weeks after stopping treatment, indicating a possible off-therapy remittive effect.[20]

CAPSULE SUMMARY

- Tapinarof is effective in the treatment of atopic dermatitis in a diverse population of patients down to 2 years of age.
- Tapinarof is a nonsteroidal topical medication with the potential to be used for the treatment of atopic dermatitis without restrictions on sites of application or total area treated.

AD pathogenesis includes dermal inflammation, epithelial barrier dysfunction, oxidative stress, changes in AhR signaling, and reduced nuclear factor erythroid 2-related factor 2 (Nrf2) activity.[21-23] Type 2 pro-inflammatory cytokines implicated in AD include interleukin (IL)-4, IL-5, IL-13, and the pruritogenic cytokine, IL-31.[24] Tapinarof reduces inflammation and normalizes skin barrier function by ligand-dependent activation of AhR, resulting in downregulation of inflammatory Th2 cytokines implicated in AD, modulation of keratinocyte differentiation, and increased expression of skin-barrier components, including proteins (filaggrin, loricrin, hornerin, and involucrin) and ceramides.[25,26] Additionally, tapinarof increases cytoprotective antioxidant responses to reduce oxidative stress in AD, through the Nrf2 pathway and by direct reactive oxygen species scavenging.[26]

Tapinarof cream demonstrated minimal-to-no systemic absorption under maximal usage conditions, using a highly sensitive assay, including in children down to 2 years of age with extensive AD, when applied over a high BSA affected (up to 90%)[27] and in adults with plaque psoriasis and extensive disease.[28] Tapinarof cream pharmacokinetics are consistent with localized skin-targeted effects, a low potential for systemic AEs, and no drug–drug interactions.[17,27,28]

Here, we report results of ADORING 1 and ADORING 2, two double-blind, randomized, vehicle-controlled phase 3 trials (NCT05014568, NCT05032859), assessing the efficacy and safety of

Abbreviations used:

AD:	atopic dermatitis
AE:	adverse event
AESI:	adverse events of special interest
AhR:	aryl hydrocarbon receptor
BSA:	body surface area
EASI:	Eczema Area and Severity Index
EASI75:	≥75% improvement in Eczema Area and Severity Index score
IGA:	Investigator Global Assessment
IL:	interleukin
JAK:	Janus kinase
MI:	multiple imputation
Nrf2:	nuclear factor erythroid 2-related factor 2
PDE4:	phosphodiesterase-4
PP-NRS:	Peak Pruritus Numerical Rating Scale
QD:	once daily
TEAE:	treatment-emergent adverse event
vIGA-AD:	Validated Investigator Global Assessment for Atopic Dermatitis

tapinarof cream 1% QD in adults and children down to 2 years of age with AD.

METHODS

The trials were conducted in compliance with Good Clinical Practice and the Helsinki Declaration, with ethical approval from relevant institutional review boards. Patients (or parents/legal guardians) provided informed consent. All authors contributed to data interpretation, drafting, critical feedback, and final approval of the manuscript. The sponsor designed, funded, and oversaw the conduct of the trials.

Trial design

ADORING 1 and 2 were identically designed, phase 3, randomized, double-blind, vehicle-controlled, multicenter trials that evaluated the efficacy and safety of tapinarof cream 1% QD or vehicle cream QD in patients with AD down to 2 years of age. After a 30-day screening period, eligible patients were randomly assigned 2:1 to tapinarof or vehicle cream. Patients were stratified so a majority had moderate disease at baseline, defined as a Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD)* score of 3, and at least 10% had severe AD (vIGA-AD of 4). Patients were stratified to maintain a minimum of 15% enrollment in each age group (2-6, 7-11, 12-17, and ≥18 years) with adults comprising a maximum of 20%.

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Assessments

Clinical assessments occurred at screening, baseline, and Weeks 1, 2, 4, and 8. Additional telephone assessments for AEs were conducted at Weeks 3 and 6. After completion, eligible patients could enroll in an open-label, long-term extension trial, ADORING 3 (NCT05142774).

Participants

Patients were adults and children down to 2 years of age with a diagnosis of AD by Hanifin and Rajka criteria and a vIGA-AD of ≥3, an Eczema Area and Severity Index (EASI) score ≥6, and 5% to 35% BSA involvement at screening and baseline.[29]

Trial treatment

Patients (or caregivers) applied a thin layer of cream QD to affected areas, including sensitive and intertriginous skin, new lesions, and lesions that improved or cleared during the trials. Patients recorded the time of application and Peak Pruritus Numerical Rating Scale (PP-NRS) score in a daily diary. Treating the scalp was permitted but not required; efficacy analyses excluded scalp assessments. Use of other AD therapies was not permitted, except for nonmedicated emollients on nonlesional skin at least 30 minutes after applying trial cream.

Efficacy endpoints

The primary efficacy endpoint was the proportion of patients with a vIGA-AD response, defined as a vIGA-AD score of 0 (clear) or 1 (almost clear) and ≥2-grade improvement from baseline at Week 8.

Key secondary endpoints included the proportion of patients with ≥75% improvement in EASI score from baseline at Week 8 (EASI75), and the proportion aged ≥12 years with a baseline PP-NRS score ≥4 who achieved a PP-NRS response, defined as a ≥4-point reduction in the average weekly PP-NRS total score from baseline at Week 8. The PP-NRS, a well-defined, reliable patient-reported outcome validated for use in patients aged ≥12 years with moderate or severe AD,[30] can be completed by caregivers in patients younger than 12 years. PP-NRS response rates were stratified for patients ≥12 years, <12 years, and the overall population.

Safety evaluation

Safety assessments included incidence of treatment-emergent AEs (TEAEs), vital signs, and physical and laboratory tests. Investigators specifically monitored AEs of special interest (AESIs), predefined as follicular events, contact dermatitis, and headache, based on previous trials.[19,27,28] Follicular event AESIs were

determined by investigators and were not limited to folliculitis, including, for example, follicular eczema and keratosis pilaris-like follicular plugging.

Statistical analysis

Enrollment of 400 patients in each trial was estimated to provide 97.2% power to detect a significant difference (two-sided P value $< .05$), assuming 45% of patients in the tapinarof arms and 25% in the vehicle arms achieved the primary endpoint. Power was calculated using a Fisher's exact test sample size calculation. Power calculations assumed 15% of patients receiving tapinarof cream and 30% receiving vehicle cream would be lost to follow-up at Week 8.

The primary efficacy endpoint and other dichotomous endpoints were analyzed using a Cochran–Mantel–Haenszel test stratified by baseline vIGA-AD and age group. Efficacy endpoints were based on the intention-to-treat population. The primary estimand of interest was focused on the composite estimand (treatment effect measured by the ratio of vIGA-AD response rates at Week 8) in the active treatment versus vehicle-control arms. Patients who prematurely discontinued treatment due to AEs or lack of efficacy and patients using prohibited medications with significant impact on efficacy evaluations prior to Week 8 were considered treatment failures. Investigator assessments only included data collected at in-person visits.

Missing data were handled using multiple imputation (MI), in which 100 imputations were generated using the PROC MI procedure of SAS version 9.4.

RESULTS

Patients

ADORING 1 was conducted at 67 sites and ADORING 2 at 62 sites in the US or Canada. Both trials started in September 2021. ADORING 1 completed in March 2023. ADORING 2 completed in February 2023. In total, 602 and 540 patients were screened and 407 and 406 were randomized in ADORING 1 and 2, respectively (Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/g6455cpd93/2).

Demographic and disease characteristics were balanced across the arms of each trial at baseline (Table I). Overall, 80% of patients were pediatric (<18 years). At baseline, 89.9% and 84.0% of patients in ADORING 1 and 2, respectively, had a vIGA-AD of 3 (moderate). Corresponding mean EASI scores were 12.5 and 13.3; and mean PP-NRS scores were 6.7 and 6.8.

Primary and secondary efficacy endpoints

At Week 8, significantly more patients treated with tapinarof than vehicle achieved the primary efficacy endpoint of a vIGA-AD response in both trials: 45.4% in the tapinarof arm compared with 13.9% with vehicle in ADORING 1 ($P < .0001$), and 46.4% versus 18.0% in ADORING 2 ($P < .0001$) (Fig 1).

At Week 8, statistically significant differences in favor of tapinarof were also demonstrated in both trials for the key secondary efficacy endpoint of EASI75 response: 55.8% of tapinarof-treated patients versus 22.9% for vehicle in ADORING 1 ($P < .0001$), and 59.1% versus 21.2% in ADORING 2 ($P < .0001$) (Supplementary Fig 2A, available via Mendeley at https://data.mendeley.com/datasets/g6455cpd93/2).

Greater improvements in itch were reported in the tapinarof compared with vehicle groups, with a statistically significant improvement in PP-NRS response in the tapinarof arms compared with vehicle in patients aged ≥12 years: 55.8% versus 34.2% in ADORING 1 ($P = .0366$), and 52.8% versus 24.1% in ADORING 2 ($P = .0015$) (Supplementary Fig 2B, available via Mendeley at https://data.mendeley.com/datasets/g6455cpd93/2). Significantly superior PP-NRS responses were reported in the tapinarof groups in patients aged <12 years (60.7% vs 28.0% [$P = .0001$] in ADORING 1, and 60.0% vs 40.8% [$P = .0414$] in ADORING 2) (Supplementary Fig 3A, available via Mendeley at https://data.mendeley.com/datasets/g6455cpd93/2) and overall (61.1% vs 34.0% [$P < .0001$] in ADORING 1, and 57.4% vs 33.0% [$P < .0001$] in ADORING 2) (Supplementary Fig 3B, available via Mendeley at https://data.mendeley.com/datasets/g6455cpd93/2).

Case photography

Figure 2 shows a target lesion of an 8-year-old, White male patient with moderate baseline AD (vIGA-AD = 3) treated with tapinarof who achieved a vIGA-AD response at Week 8. Marked and rapid improvement was observed in this intertriginous skin area, with improvements in signs of disease as early as Week 2 (Supplementary Fig 4, available via Mendeley at https://data.mendeley.com/datasets/g6455cpd93/2). By Week 4, there are no signs of erythema, induration, or oozing, and no signs of disease or postinflammatory pigmentation changes visible through Week 8. Improvements in the target lesion correspond to global assessments of disease, and the primary efficacy endpoint was achieved as early as Week 2, and an itch-free state (PP-NRS score of 0 or 1) at Week 8.

Table I. Baseline patient demographics and clinical characteristics*

Characteristic	ADORING 1		ADORING 2	
	Tapinarof 1% QD (*n* = 270)	Vehicle QD (*n* = 137)	Tapinarof 1% QD (*n* = 271)	Vehicle QD (*n* = 135)
Age, mean years	15.6 ± 16.62	15.6 ± 16.49	16.4 ± 16.24	16.7 ± 16.05
Age group, years (*n*, %)				
2-6	76 (28.1)	39 (28.5)	65 (24.0)	32 (23.7)
7-11	75 (27.8)	37 (27.0)	64 (23.6)	32 (23.7)
12-17	67 (24.8)	34 (24.8)	89 (32.8)	44 (32.6)
≥18	52 (19.3)	27 (19.7)	53 (19.6)	27 (20.0)
Male sex (*n*, %)	130 (48.1)	66 (48.2)	117 (43.2)	58 (43.0)
Weight, kg	46.7 ± 27.3	47.7 ± 27.7	51.5 ± 29.1	54.0 ± 32.0
BMI, kg/m^2	21.4 ± 6.3	22.1 ± 6.6	22.7 ± 7.5	23.3 ± 8.3
Fitzpatrick skin type (*n*, %)				
I	9 (3.3)	7 (5.1)	11 (4.1)	4 (3.0)
II	66 (24.4)	22 (16.1)	52 (19.2)	28 (20.7)
III	60 (22.2)	31 (22.6)	50 (18.5)	33 (24.4)
IV	67 (24.8)	30 (21.9)	71 (26.2)	31 (23.0)
V	44 (16.3)	40 (29.2)	63 (23.2)	27 (20.0)
VI	24 (8.9)	7 (5.1)	24 (8.9)	12 (8.9)
Race† (*n*, %)				
White	152 (56.3)	79 (57.7)	124 (45.8)	58 (43.0)
Black or African American	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)
American Indian or Alaska Native	2 (0.7)	0	0	2 (1.5)
Native Hawaiian or Pacific Islander	0	0	1 (0.4)	0
Multiple races	14 (5.2)	5 (3.6)	6 (2.2)	2 (1.5)
Not reported	6 (2.2)	5 (3.6)	6 (2.2)	3 (2.2)
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	12.2 ± 5.0	12.9 ± 5.6	13.5 ± 5.6	13.1 ± 4.7
BSA affected, mean %	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 y‖	6.5 ± 2.4	6.3 ± 2.3	6.3 ± 2.4	6.5 ± 2.2
<12 y	7.0 ± 2.3	6.6 ± 2.5	7.1 ± 2.3	7.4 ± 1.8

BMI, Body mass index; *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.

*Plus–minus (±) values are standard deviations. Percentages may not total 100 because of rounding.

†Race was reported by the patient.

‡vIGA-AD score is assessed on a scale from 0 to 4, with higher scores indicating more severe atopic dermatitis.

§EASI score ranges from 0 to 72, with higher scores indicating more severe atopic dermatitis, and assesses the degree of erythema, edema/papulation, excoriation, and lichenification (each scored from 0 to 3 separately) for each of 4 body regions, with adjustment for the %BSA involved for each body region relative to the whole body.

‖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.[21]

Safety

Common TEAEs (≥5% in any arm) were folliculitis, headache, and nasopharyngitis (Table II). Most TEAEs were mild or moderate and were associated with low discontinuation rates. There were few serious TEAEs and none were considered treatment related. Trial discontinuation rates due to AEs were lower with tapinarof than vehicle (ADORING 1: 1.9% vs 3.6%; ADORING 2: 1.5% vs 3.0%).

Rates of contact dermatitis AESIs were lower with tapinarof than with vehicle in both trials: 1.5% versus 2.2% (ADORING 1) and 1.1% versus 1.5% (ADORING 2). Contact dermatitis events were all mild or moderate, with no grade 3 (severe) events, and led to few trial or treatment discontinuations (0.7% vs 1.5% and 0.0% vs 0.8%, respectively).

Follicular event AESIs were reported in 10.0% of patients receiving tapinarof and 0.7% receiving

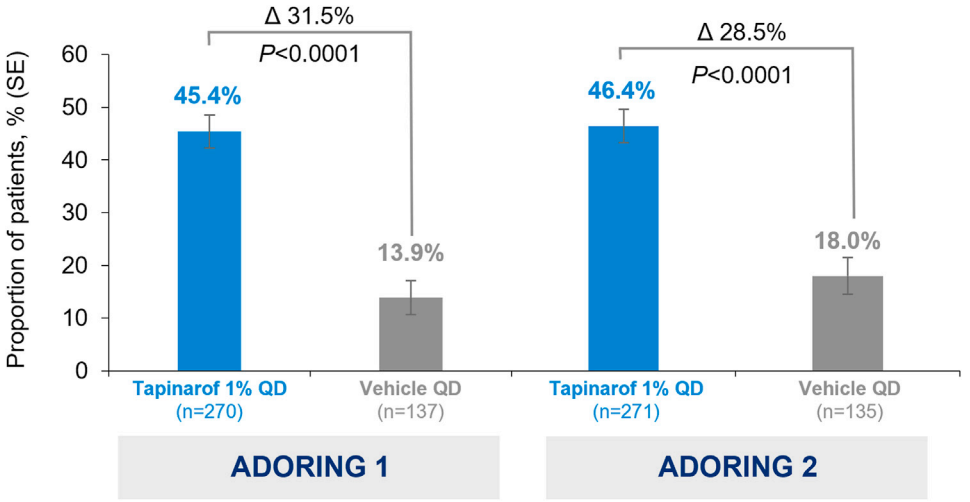

Fig 1. Statistically significant responses on primary endpoint of vIGA-AD response* at Week 8. Intention-to-treat population, MI estimand. *vIGA-AD response is defined as a score of 0 (clear) or 1 (almost clear) and at least a 2-grade improvement from baseline. *MI*, Multiple imputation; *QD*, once daily; *SE*, standard error (represented by length of vertical whiskers); *vIGA-AD*, Validated Investigator Global Assessment for Atopic Dermatitis.

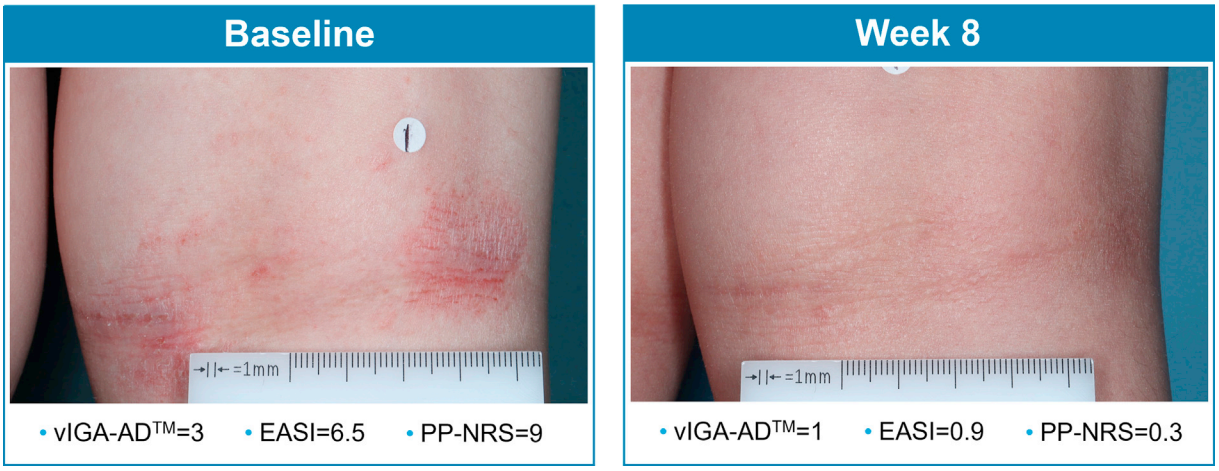

Fig 2. Rapid response to tapinarof cream 1% QD treatment in an 8-year-old, white male patient achieving the primary efficacy endpoint at Week 2. An 8-year-old, White male patient with moderate AD at baseline who was treated with tapinarof 1% cream QD. Rapid resolution of erythema and lichenification of the target lesion in the popliteal fossa was observed. Alongside the visible improvement in this intertriginous skin area, overall disease burden was rapidly and significantly improved, as reflected by improvements in vIGA-AD, EASI, and PP-NRS as early as Week 2, continuing through Week 8. Supplementary Fig 4, available via Mendeley at https://data.mendeley.com/datasets/g6455cpd93/2, shows clinical photographs with all assessments (baseline and Weeks 2, 4, and 8). Clinical photography of target lesions was performed in a subset of patients at selected sites. For individuals who consented to photography, a target lesion was selected by the investigator for serial photography prior to the first application of investigational product. vIGA-AD, EASI, and PP-NRS scores are global assessments that reflect the burden of disease across the whole body. *AD*, Atopic dermatitis; *EASI*, Eczema Area Severity Index; *PP-NRS*, Peak Pruritus Numerical Rating Scale; *QD*, once daily; *vIGA-AD*, Validated Investigator Global Assessment for Atopic Dermatitis.

vehicle in ADORING 1, and 8.9% versus 1.5% in ADORING 2. Most follicular events in the tapinarof groups were mild (77.8%, n = 21/270; and 83.3%, n = 20/271, respectively), with no severe (grade 3) events. Low rates of both trial and treatment discontinuation were associated with follicular events across tapinarof and vehicle groups in each trial (0.4% vs 0.0% and 0.0% vs 0.0%, respectively).

Table II. Adverse events (safety population)*

Characteristic	ADORING 1		ADORING 2	
Patients, *n* (%)	**Tapinarof 1% QD (*n* = 270)**	**Vehicle QD (*n* = 137)**	**Tapinarof 1% QD (*n* = 271)**	**Vehicle QD (*n* = 133)**
Any adverse event	123 (45.6)	35 (25.5)	100 (36.9)	28 (21.1)
Serious adverse event†	3 (1.1)	0	2 (0.7)	0
TEAE leading to trial discontinuation	5 (1.9)	5 (3.6)	4 (1.5)	4 (3.0)
Treatment-related TEAEs				
Any	34 (12.6)	9 (6.6)	32 (11.8)	9 (6.8)
Serious	0	0	0	0
Adverse events of special interest‡				
Contact dermatitis	4 (1.5)	3 (2.2)	3 (1.1)	2 (1.5)
Grade 3	0	0	0	0
Led to trial discontinuation	2 (0.7)	2 (1.5)	0	1 (0.8)
Follicular event§	27 (10.0)	1 (0.7)	24 (8.9)	2 (1.5)
Grade 3	0	0	0	0
Led to trial discontinuation	1 (0.4)	0	0	0
Headache	19 (7.0)	3 (2.2)	4 (1.5)	0
Grade 3	1 (0.4)	0	0	0
Led to trial discontinuation	1 (0.4)	1 (0.7)	0	0
Any TEAE (≥5%)				
Folliculitis	22 (8.1)	1 (0.7)	22 (8.1)	2 (1.5)
Headache	19 (7.0)	3 (2.2)	4 (1.5)	0
Nasopharyngitis	13 (4.8)	7 (5.1)	4 (1.5)	1 (0.8)

MedDRA, Medical Dictionary for Regulatory Activities; *QD*, once daily; *TEAE*, treatment-emergent adverse event.

*Each patient with an adverse event was counted only once for each MedDRA preferred term. Severity was based on the Common Terminology Criteria for Adverse Events (version 5.0), where Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe or medically significant but not immediately life-threatening; Grade 4 = Life-threatening consequences; Grade 5 = Death related to adverse event.

†No serious adverse events were considered by the investigators to be related to tapinarof 1% cream.

‡No adverse events of special interest were graded 4 or 5 (considered either life-threatening or related to death).

§Events of folliculitis, follicular eczema, keratosis pilaris, and application site folliculitis were categorized as follicular events (adverse events of special interest).

Headache AESIs were reported by 7.0% of patients receiving tapinarof and 2.2% receiving vehicle in ADORING 1; and by 1.5% and 0.0%, respectively, in ADORING 2. Headache was generally mild, transient, and considered unrelated to trial treatment. There was only one report of severe headache across trials, which did not lead to trial discontinuation. Trial and treatment discontinuations due to headache were low across the arms of both trials (0.4% vs 0.7% and 0.0% vs 0.0%, respectively).

DISCUSSION

Tapinarof 1% cream QD demonstrated statistically significant and clinically meaningful efficacy in the treatment of AD compared with vehicle on the primary endpoint in adults and children down to 2 years of age. Statistically significant and clinically meaningful efficacy in favor of tapinarof was confirmed across key secondary endpoints, including pruritus.

Tapinarof was well tolerated in patients down to 2 years of age, demonstrating a favorable and predictable safety profile, consistent with previous trials in AD[19,20] and plaque psoriasis.[17,18] AEs were mostly mild and associated with discontinuation rates that were lower in the tapinarof groups compared with vehicle. Rates of the AESIs in these trials, which included children as young as 2 years, were generally lower than (or consistent with) rates previously reported in adults with plaque psoriasis.[17,18] While rates of headache were generally low and not considered treatment-related by investigators, it is possible that variations across groups in the incidence of headache may be treatment related. However, no relationship has been found between headache and tapinarof plasma exposure, even with maximal usage in extensive disease.[27,28] The mechanism by which tapinarof cream 1% may be associated with headache in a small percentage of patients is, therefore, unknown and it is difficult to infer the cause of the variations reported.

Tapinarof was effective across a diverse population, with an age range of 2 to 81 years (80% pediatric patients), and approximately 50% with skin of color

based on self-reported race and Fitzpatrick skin type (IV, V, and VI). While rapid improvements in AD were demonstrated in 8 weeks, the long-term extension trial, ADORING 3, will assess the efficacy and safety of tapinarof cream in AD across the spectrum of severity, including patients with mild or more severe AD, and assessment of the potential remittive effect observed in both a phase 2b trial in AD and a long-term phase 3 trial in plaque psoriasis.[18-20] Eligible participants from ADORING 1 and 2 who enrolled in the long-term extension trial, ADORING 3, will be evaluated for up to 48 weeks. A high proportion of eligible patients from ADORING 1 and 2 (91%) elected to enroll in ADORING 3.

In these 8-week trials, tapinarof cream 1% QD was superior to vehicle in the treatment of AD in adults and children. Tapinarof potentially fills a gap in the treatment armamentarium for a highly effective, nonsteroidal topical that can be used down to 2 years of age without restrictions on the severity of disease, duration of use, total BSA treated, or sites of application.

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Conflicts of interest

Dr Silverberg has received honoraria as a consultant and/or advisory board member for AbbVie, Alamar, Aldena, Amgen, AObiome, Arcutis, Arena, Asana, Aslan, BioMX, Biosion, Bodewell, Boehringer Ingelheim, Bristol Myers Squibb, Cara, Castle Biosciences, Celgene, Connect Biopharma, Corevitas, Dermavant Sciences, Inc, Dermira, Dermtech, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, LEO Pharma, Menlo, Novartis, Optum, Pfizer, RAPT, Recludix, Regeneron, Sanofi-Genzyme, Shaperon, TARGET-RWE, Union, and UpToDate; speaker for AbbVie, Eli Lilly, LEO Pharma, Pfizer, Regeneron, and Sanofi-Genzyme; and institution received grants from Galderma, Incyte, and Pfizer. Dr Eichenfield has served as a consultant, advisor, or investigator for AbbVie, Amgen, Apogee, Arcutis, Aslan, Bausch, Bristol Myers Squibb, Castle Biosciences, Dermavant Sciences, Inc, Eli Lilly, Forté, Galderma, Incyte, Janssen, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi-Genzyme, and UCB Pharma. Dr 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. Dr 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. Dr Bissonnette has served as a consultant/investigator/advisory board member for AbbVie, Alumis, Almirall, Amgen, AnaptysBio, Arcutis, Aristea, Bausch Health, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Myers Squibb, Dermavant Sciences, Inc, Eli Lilly, Escalier, Janssen, Kyowa Kirin, LEO Pharma, Nimbus, Novartis, Pfizer, Regeneron, Sienna, and UCB Biopharma; and is an employee and shareholder of Innovaderm Research. Dr Papp has served as a consultant/speaker/scientific officer/has attended advisory boards for, or received grants or honoraria from AbbVie, Akros, Amgen, Anacor, Arcutis, Astellas, Bausch Health/Valeant, Baxalta, Boehringer Ingelheim, Bristol Myers Squibb, Can-Fite Biopharma, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly, Evelo, Galapagos, Galderma, Genentech, Gilead, GlaxoSmithKline, Janssen, Kyowa Kirin, LEO Pharma, Medimmune, Meiji Seika Pharma, Merck (MSD), Merck-Serono, Mitsubishi Pharma, Moberg Pharma, Novartis, Pfizer, PRCL Research, Regeneron, Roche, Sanofi-Aventis/Genzyme, Sun Pharma, Takeda, and UCB Biopharma. Dr Browning has served as an investigator for AbbVie, Acelyrin, Amgen, Arcutis, Dermavant, Inc, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron, Sanofi, UCB Pharma, and Vyne; and as a speaker for Regeneron, Pfizer, and Krystal. Dr Kwong is a consultant, speaker, or principal investigator for AbbVie, Almirall, Amgen, Arcutis, Dermavant Sciences, Inc, Eli Lilly, Galderma, Incyte, L'Oréal, Novartis, Novum, Ortho, Pfizer, Regeneron/Sanofi, Sun, Verrica, and UCB Pharma. Dr Korman has served as an investigator and speaker for Abbott Labs, Genentech and Astellas; received grants and honoraria; served on the advisory board and was an investigator for Centocor; received grants and residency/fellowship program funding; and was investigator and speaker for Amgen, receiving grants and honoraria. Dr Brown, Dr Rubenstein, Dr Piscitelli, Dr Somerville, and Dr Tallman are employees of Dermavant Sciences, Inc, with stock options. Dr Hebert has received research support paid to the medical school from AbbVie, Arcutis, Dermavant Sciences, Inc, and Pfizer; and honoraria received from Alphyn, Apogee, Arcutis, Dermavant Sciences, Inc, Galderma, GSK, Incyte, LEO Pharma, Novan, Ortho Dermatologics, Pfizer, Sun Pharma, and Verrica; and from Sanofi Regeneron and Ortho Dermatologics as part of data safety monitoring boards. Dr 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.

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