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Efficacy and safety of tapinarof cream once daily in Japanese pediatric patients with atopic dermatitis: a 60-week phase 3 trial consisting of an 8-week, double-blind, vehicle-controlled period and a 52-week, open-label extension period

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Background: In Japan, tapinarof cream (an aryl hydrocarbon receptor agonist) is approved for the treatment of atopic dermatitis (AD) in patients aged ≥12 years.
Methods: In Japanese pediatric patients aged 2–11 years with AD, we conducted a 60-week phase 3 trial of tapinarof cream, consisting of an 8-week, double-blind, vehicle-controlled period (DB period) and a 52-week, open-label extension period (OL period). Eligible patients (N = 162) were randomized to tapinarof cream 0.5% (n = 107) or vehicle cream (n = 55) in the DB period; subsequently, all patients who entered the OL period (n = 151) received tapinarof cream 0.5%.
Results: At week 8 in the DB period, the proportion of patients with ≥75% improvement from baseline in Eczema Area and Severity Index (EASI) score (EASI-75 response, the primary endpoint) was significantly higher in the tapinarof group than in the vehicle group (52.59% vs. 12.60%, $p < 0.0001$). The proportion of patients who achieved an Investigator's Global Assessment score of 0 (clear) or 1 (almost clear) with ≥ 2-grade improvement from baseline at week 8 (IGA treatment success, a key secondary endpoint) was 26.2% in the tapinarof group and 1.8% in the vehicle group. In the OL period, improvements in efficacy endpoints continued through week 60 with treatment. In the tapinarof group, EASI-75 response rate was 75.8% at week 32% and 80.2% at week 60, and IGA treatment success rate was 48.5% at week 32, and 56.3% at week 60. Across the DB and OL periods, no treatment-related serious adverse events (AEs) were reported, and all treatment-related AEs were mild or moderate. The most common treatment-related AEs included folliculitis and acne.
Conclusion: Tapinarof cream was effective and well tolerated for up to 60 weeks in the treatment of Japanese pediatric patients aged 2–11 years with AD.

KEYWORDS
aryl hydrocarbon receptor (AhR), atopic dermatitis, pediatric patients, phase 3 trial, tapinarof

Introduction

Atopic dermatitis (AD) is a chronic, recurring, inflammatory skin disease characterized by eczematous lesions and intense pruritus [1]. The pathogenesis of AD is multifactorial, which includes genetic and environmental factors, skin barrier dysfunction, and immune dysregulation [2–4]. AD is more prevalent in children, affecting 7%–10% of adults and up to 25% of children worldwide [5]. In Japan, AD has been reported to affect 5%–27% of preschool children and 5%–15% of elementary school children [1]. AD is known as a burdensome disease and substantially impairs sleep and quality of life for children and their guardians [6–8].

In the guidelines for the management of AD in Japan, the primary goal of treatment is to reach and maintain stable conditions, where signs and symptoms of AD are absent or minimal without disturbance of daily activities and no drug therapy is required [1]. Although systemic therapies including biologics can be used for the treatment of refractory moderate-to severe AD, topical therapies are the mainstay of treatment for most patients with AD across a wide range of disease severity. Topical corticosteroids are the most common anti-inflammatory drug, especially for the treatment of acute flares of AD; however, their long-term use can be limited by potential adverse reactions, such as skin atrophy [1]. In the last several years, new nonsteroidal topical drugs, such as Janus kinase inhibitors and phosphodiesterase-4 inhibitors, have become available for the treatment of AD. Given the multifactorial nature of AD, however, there remains a need for efficacious and safe topical treatment options with new mechanisms of action.

Tapinarof is a nonsteroidal, topical aryl hydrocarbon receptor (AhR) agonist [9]. By activation of AhR, tapinarof downregulates inflammatory cytokines associated with AD and upregulates skin-barrier components [9, 10]. In a clinical trial, tapinarof was shown to potentially improve skin barrier function in patients with AD, as assessed by stratum corneum hydration and transepidermal water loss [11]. Additionally, tapinarof activates the nuclear factor erythroid 2 related factor 2 pathway, leading to upregulated antioxidant enzymes and reduced oxidative stress [9, 12].

Tapinarof cream 1% is approved for the treatment of AD in patients aged ≥2 years in the United States [13] and the United Arab Emirates [14] and in patients aged ≥12 years in Japan [15]. For pediatric AD patients in Japan, a phase 2 trial of tapinarof cream 0.5% and 1% was conducted in patients aged 2–11 years, and tapinarof cream 0.5% was selected for further investigation in this population [16]. A phase 3 trial was designed to confirm the efficacy of tapinarof cream 0.5% in a larger pediatric population and to evaluate its long-term efficacy and safety for up to 60 weeks. Here, we report the results of the phase 3 trial of tapinarof cream 0.5% in Japanese pediatric patients aged 2–11 years with AD.

Materials and methods

Trial design

This trial was conducted between August 2023 and March 2025 at 27 sites in Japan (Japan Registry of Clinical Trials (https://jrct.mhlw.go.jp/), jRCT2031230139) in compliance with the guidelines for Good Clinical Practice and the provisions of the Declaration of Helsinki. At each trial site, the protocol was approved by the relevant institutional review board. All legal guardians (and patients, when possible) provided written informed consent before any trial-related procedures.

This trial consisted of an 8-week, randomized, double-blind, vehicle-controlled period (double-blind [DB] period) and a 52-week, open-label extension period (open-label [OL] period) (Figure 1). At the initiation of the DB period, patients were randomized 2:1 to receive tapinarof cream 0.5% or vehicle cream. A computer-generated randomization was performed with a dynamic allocation method to balance for age category (2–6 years and 7–11 years) and Investigator's Global Assessment (IGA) score [17, 18]. After completing all assessments at week 8, patients transitioned to the OL period. When patients experienced worsening of AD in the DB period, they could transition to the OL period early at week 4 or later (defined as the early transition visit) at the investigator's discretion (i.e., no objective criteria were predefined for early transition). In the OL period, all patients received tapinarof cream 0.5%.

Patients

Eligible patients were aged 2–11 years and had a clinical diagnosis of AD according to the criteria of the Japanese Dermatological Association [1]. At screening and baseline, patients were required to have an IGA score of 2 (mild), 3 (moderate), or 4 (severe); an Eczema Area and Severity Index (EASI) score [17–20] of ≥5 (excluding the hairy scalp); and affected body surface area (BSA) of 5%–30% (excluding the hairy scalp). Patients were excluded if they had a significant dermatologic or inflammatory condition that would interfere with the trial assessments, had an acute active skin infection, or used AD therapies within the indicated period before baseline (e.g., phototherapy within 4 weeks, topical corticosteroids within 2 weeks or 1 week; Supplementary Table S1).

Trial treatment

Legal guardians (and patients, when possible) were instructed to apply a thin layer of trial treatment once daily (QD) to all AD lesions (except for the hairy scalp), including newly appearing lesions. When AD lesions cleared, application to the areas was continued in the DB period but could be interrupted at the investigator's discretion in the OL period. Therapies that were indicated for AD or that may have been effective in treating AD were prohibited during the trial (Supplementary Table S1). In the OL period, however, these therapies could be used at the investigator's discretion as rescue therapy when no improvement from baseline was observed in AD lesions.

Trial assessments

The assessments of IGA, EASI, and percent of BSA affected were performed by the investigators at each trial visit. The 5-point IGA, ranging from 0 (clear) to 4 (severe), was used. The Patient-Oriented Eczema Measure (POEM) [21, 22] was completed by legal guardians

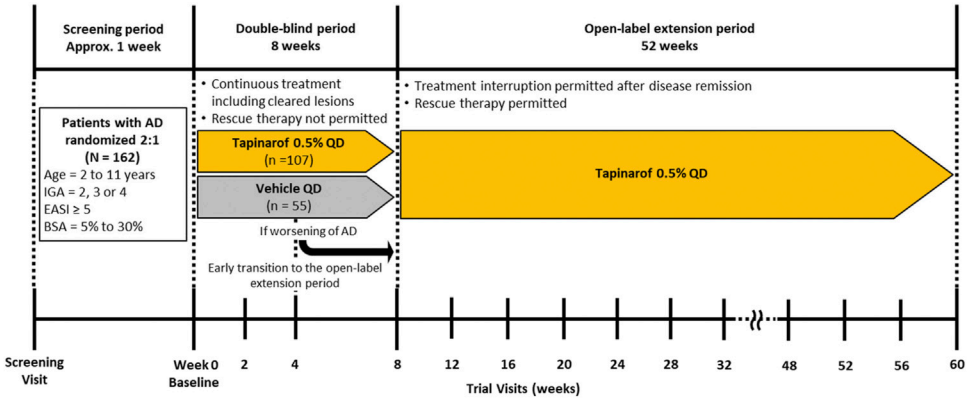

FIGURE 1
Trial design. AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; QD, once daily.

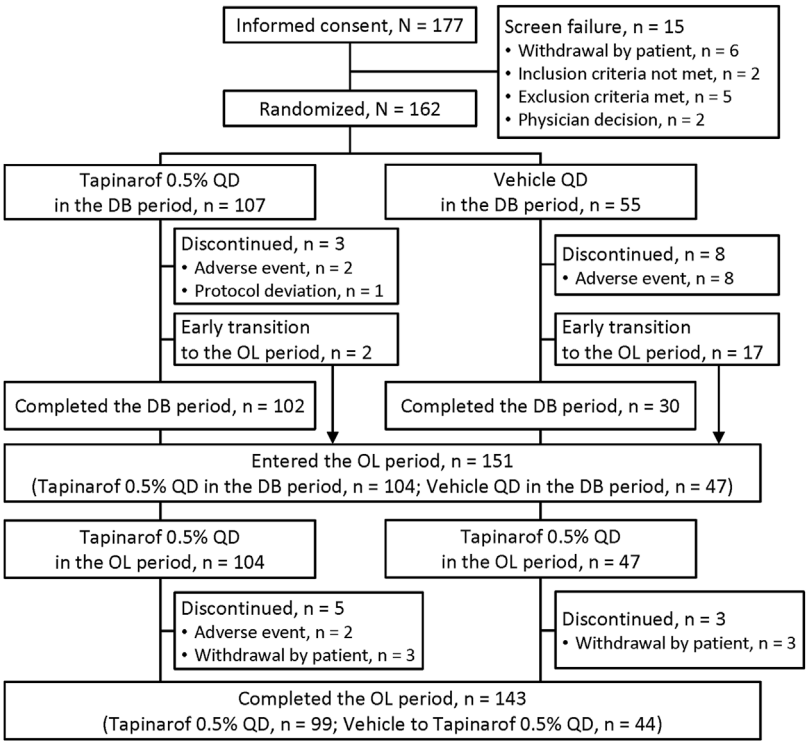

FIGURE 2
Patient disposition. DB, double-blind; OL, open-label; QD, once daily.

at each trial visit. The pruritus score is a 5-point scale ranging from 0 to 4 [23], with higher score indicating more severe itch, and was completed by legal guardians (or patients, when possible). The daytime and nighttime pruritus scores were recorded in the diary twice daily at bedtime and upon awakening, respectively, in the DB period and were assessed at each trial visit in the OL period.

In the DB period, the primary endpoint was the proportion of patients with ≥75% improvement from baseline in EASI score (EASI-75) at week 8. Key secondary endpoints were the mean percent change from baseline in EASI score and the proportion of patients who achieved IGA treatment success, defined as an IGA score of 0 (clear) or 1 (almost clear) with ≥ 2-grade improvement from baseline at week 8. Other secondary endpoints included the proportion of patients with ≥50% and ≥90% improvement from baseline in EASI score (EASI-50 and EASI-90, respectively), the proportion of patients with an IGA score of 0 or 1, the mean change

TABLE 1 Patient demographics and baseline disease characteristics.

	Tapinarof 0.5% (n = 107)	Vehicle (n = 55)
Age, mean (SD), years	7.0 (2.7)	7.0 (2.8)
Age category, n (%)		
2–6 years	50 (46.7)	25 (45.5)
7–11 years	57 (53.3)	30 (54.5)
Male, n (%)	55 (51.4)	27 (49.1)
Weight, mean (SD), kg	25.1 (10.5)	25.3 (10.6)
BMI, mean (SD), kg/m^2	16.6 (2.8)	16.8 (2.9)
Disease duration, mean (SD), years	4.2 (2.8)	4.5 (3.0)
EASI score, mean (SD)	10.9 (4.3)	10.7 (3.9)
IGA score, n (%)		
2: Mild	40 (37.4)	19 (34.5)
3: Moderate	65 (60.7)	34 (61.8)
4: Severe	2 (1.9)	2 (3.6)
BSA affected, mean (SD), %	18.0 (6.5)	18.1 (7.0)
POEM score, mean (SD)	10.8 (4.9)	10.7 (5.7)
Pruritus score, mean (SD)		
Daytime[a]	2.2 (0.7)	2.1 (0.9)
Nighttime[a]	1.7 (0.6)	1.6 (0.9)
Maximum[b]	2.3 (0.7)	2.2 (0.8)

Data based on the full analysis set in the DB period. Patient demographics and baseline characteristics in the overall trial period are provided in Supplementary Table S2.
Abbreviations: BMI, body mass index; BSA, body surface area; DB, double-blind; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; POEM, Patient Oriented Eczema Measure; SD, standard deviation.
[a]The baseline values for daytime and nighttime pruritus scores were respectively defined as the mean values of daily daytime and nighttime pruritus scores obtained during 7 days prior to the initiation of trial treatment.
[b]The maximum pruritus score on an assessment day was defined as the greater of the daytime and nighttime scores. The baseline value for maximum pruritus score was defined as the mean value of daily maximum pruritus scores obtained during 7 days prior to the initiation of trial treatment.

from baseline in percent of BSA affected, the mean change from baseline in POEM score, and the mean change from baseline in daytime, nighttime, and maximum pruritus scores. The maximum pruritus score on an assessment day is defined as the greater of the daytime and nighttime scores. Across the DB and OL periods (overall trial period), most of the above endpoints were used for long-term efficacy assessments.

Safety assessments included the incidence and severity of adverse events (AEs), clinical laboratory parameters, and vital signs. Trough concentrations of tapinarof were determined in plasma samples collected at weeks 4, 8, 32, and 60.

Statistical analyses

In the phase 2 trial of tapinarof in Japanese pediatric patients with AD [16], EASI-75 response rate at week 8 was 65.0% in the tapinarof 0.5% group and 15.0% in the vehicle group (patients with missing data were treated as nonresponders). On the basis of this result, a sample size of 63 patients (42 patients in the tapinarof 0.5% group, 21 patients in the vehicle group) would provide at least 90% power to detect a significant difference in the primary endpoint between the groups with a Fisher's exact test (2-sided p value of <0.05). However, to ensure an adequate number of patients for long-term safety assessments, the target sample size was determined to be 150 patients (100 patients in the tapinarof 0.5% group, 50 patients in the vehicle group).

For the DB period, the primary analyses of efficacy were performed in the full analysis set, which consisted of all randomized patients who received at least 1 application of trial treatment and underwent the assessment of EASI score at least once. For patients who underwent early transition to the OL period, data corresponding to those at week 8 after the transition were handled as missing in the primary and key secondary endpoint analyses of the DB period. EASI-75 response rate at week 8 (the primary endpoint) was analyzed on the basis of 100 datasets where missing data were imputed by the multiple imputation with the fully conditional specification (FCS) model. The FCS model successively imputed missing data from week 2 to week 8, using linear regression models including the treatment group, baseline value, and post baseline values as covariates. The Cochran–Mantel–Haenszel test stratified by baseline IGA score (2 or ≥3) was performed at the 2-sided significance level of 5%. The common between-group difference in the rate and its 95% CI (Sato method [24]) were calculated by combining the between-group differences in each baseline IGA score stratum. The mean percent change from baseline in EASI score at week 8 (a key secondary endpoint) was analyzed with mixed effect models for repeated measures. The mixed effect models for

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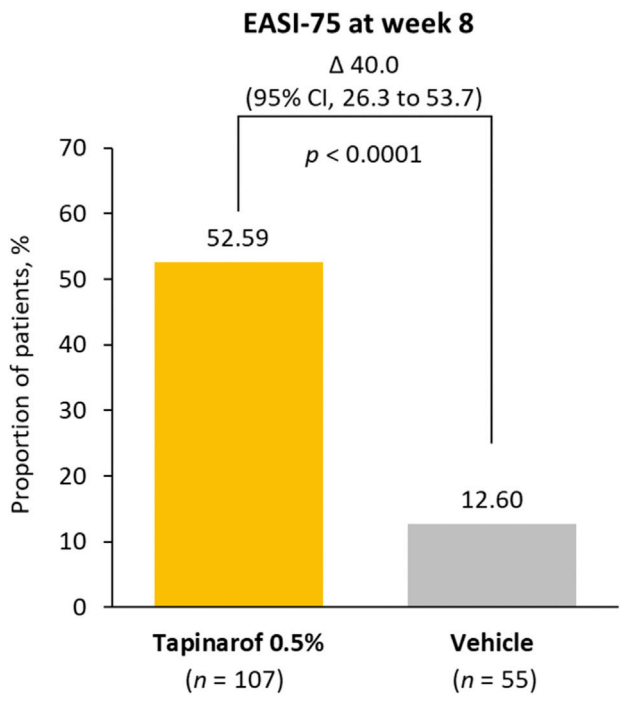

FIGURE 3
The primary endpoint: EASI-75 response rate at week 8. EASI-75 was defined as ≥ 75% improvement from baseline in EASI score and was analyzed on the basis of 100 data sets where missing data were imputed by multiple imputation. CI, confidence interval; EASI, Eczema Area and Severity Index.

repeated measures included fixed effects for treatment group, analysis visit, treatment group by analysis visit interaction, patient as a random effect, and baseline score as a continuous covariate, with an unstructured variance-covariance structure for the random effects. IGA treatment success at week 8 (the other key secondary endpoint) was analyzed on the basis of the first dataset out of 100 datasets where missing data were imputed by the multiple imputation with the FCS model. Other secondary endpoints were analyzed on the basis of observed cases (OC) where missing data were not imputed. Except for the primary endpoint, no formal statistical tests were performed for comparisons between the groups.

For the overall trial period, the efficacy analyses were performed in the efficacy analysis population, which consisted of all patients who received at least 1 application of tapinarof cream and underwent the efficacy assessment at least once (i.e., vehicle-treated patients who discontinued the trial during the DB period [by week 8] were excluded from the analyses). Efficacy endpoints were analyzed on the basis of OC where missing data were not imputed. Data obtained after initiation of rescue therapy were included in the analyses. For patients who underwent early transition to the OL period, the data at each visit after the transition were assigned according to the specified analysis window.

The safety analyses were performed in the safety analysis population, which consisted of all patients who received at least 1 application of trial treatment for the DB period and who received at least 1 application of tapinarof cream for the overall trial period. The pharmacokinetic analyses were performed in the pharmacokinetic analysis population, which consisted of all patients who had plasma concentration data of tapinarof (including plasma concentration below the lower limit of quantification [LLOQ, 50.0 pg/mL]) at ≥ 1 time point for the overall trial period.

Results

Patients

At the initiation of the DB period, 162 patients were randomized to tapinarof (n = 107) or vehicle (n = 55). The 8-week treatment in the DB period was completed by 102 patients in the tapinarof group and 30 patients in the vehicle group. Because of worsening of AD, 2 patients in the tapinarof group and 17 patients in the vehicle group underwent the early transition visit and transitioned to the OL period early, before week 8. A total of 151 patients entered the OL period, and 143 patients completed the trial. The primary reasons for trial discontinuation were AEs and withdrawal by patients (Figure 2).

No apparent differences between treatment groups were noted in the demographics and baseline disease characteristics. At baseline, approximately 60% of patients had a baseline IGA score of 3 (moderate), and few patients had an IGA score of 4 (severe) (2 patients in each group). The mean (SD) baseline EASI score was 10.9 (4.3) in the tapinarof group and 10.7 (3.9) in the vehicle group (Table 1; Supplementary Table S2).

In the OL period, rescue therapy was used at least once by approximately 20% of patients. The rescue therapy used was topical corticosteroids only; no other topical or systemic rescue therapy was performed (Supplementary Table S3). Although treatment with tapinarof could be interrupted at the investigator's discretion in the OL period after clearance of AD lesions, the duration of exposure to tapinarof was ≥48 weeks in approximately 80% of patients, indicating that most patients continued treatment with tapinarof after the clearance.

Efficacy

In the DB period, significantly more patients achieved the primary endpoint, EASI-75 response rate at week 8, in the tapinarof group (52.59%) than in the vehicle group (12.60%), with a between-group difference of 40.0 percent points (95% CI, 26.3 to 53.7; $p < 0.0001$) (Figure 3). Greater improvements in the key secondary endpoints were noted in the tapinarof group. At week 8, the least-squares mean percent change from baseline in EASI score was −68.28% in the tapinarof group and −23.01% in the vehicle group, with a between-group difference of −45.27 percent points (95% CI, −59.48 to −31.06) (Figure 4). At week 8, IGA treatment success rate was 26.2% in the tapinarof group and 1.8% in the vehicle group, with a between-group difference of 24.4 percent points (95% CI, 13.2–34.0) (Figure 4). Representative clinical images of patients who achieved IGA treatment success are presented in Supplementary Figure S1. Greater improvements in the tapinarof group were also noted in other secondary endpoints (Supplementary Figure S2), and the maximum pruritus score decreased rapidly in the tapinarof group (Figure 5).

In the tapinarof group, EASI-75 response and IGA treatment success rates continued to increase after week 8. EASI-75 response rate was 53.4% at week 8, 75.8% at week 32, and 80.2% at week 60;

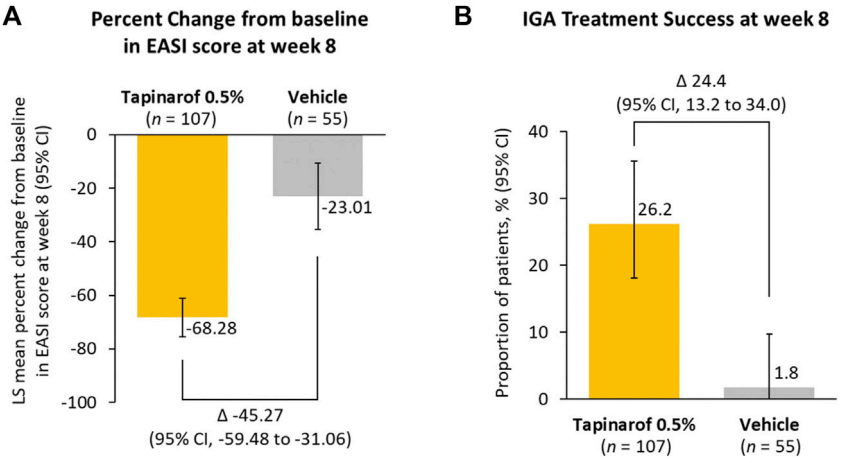

FIGURE 4
Key secondary endpoints. **(A)** Percent change from baseline in EASI score at week 8, **(B)** IGA treatment success rate at week 8. Percent change from baseline in EASI score at week 8 was analyzed with the mixed effect models for repeated measures. IGA treatment success was defined as an IGA score of 0 or 1 with ≥ 2-grade improvement from baseline and was analyzed on the basis of the first data set of 100 data sets where missing data were imputed by multiple imputation. Data are presented with exact 95% CIs. CI, confidence interval; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; LS, least-squares.

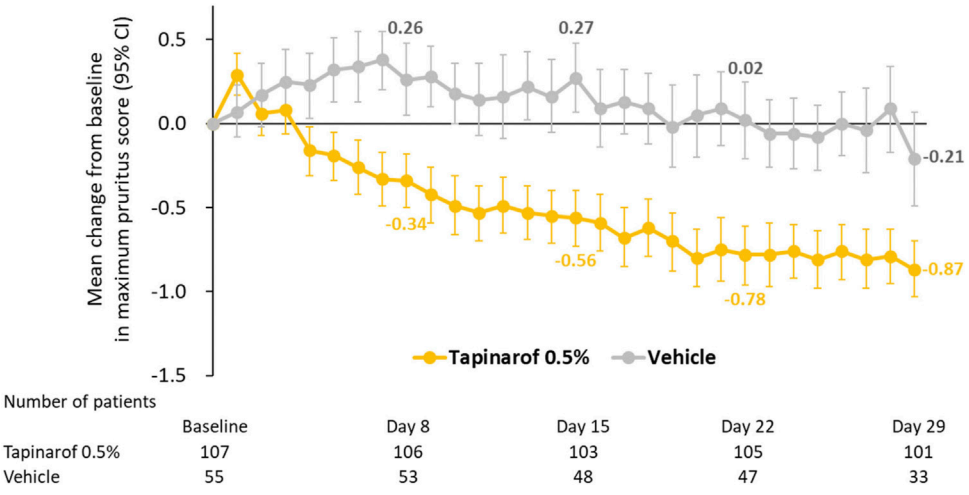

FIGURE 5
Mean daily change in maximum pruritus score from baseline to week 4. The maximum pruritus score on an assessment day was defined as the greater of the daytime and nighttime scores. The baseline value for maximum pruritus score was defined as the mean value of daily maximum pruritus scores obtained during 7 days prior to the initiation of trial treatment. CI, confidence interval.

IGA treatment success rate was 24.3% at week 8, 48.5% at week 32, and 56.3% at week 60. In the vehicle-to-tapinarof group (patients who received vehicle cream in the DB period), these rates increased rapidly after switching to tapinarof. EASI-75 response rate was 21.3% at week 8, 84.8% at week 32, and 82.8% at week 60; IGA treatment success rate was 4.3% at week 8, 54.3% at week 32, and 62.1% at week 60. In both groups, the increased rates were maintained through week 60 (Figure 6). Similarly, improvements in the other efficacy endpoints were maintained through week 60 (Supplementary Table S4). No apparent differences in efficacy results were noted between the age categories (2–6 years and 7–11 years) (Supplementary Table S5).

Safety

In the DB period, AEs were reported in 78 of 107 (72.9%) patients in the tapinarof group and in 41 of 55 (74.5%) patients in the vehicle group (Table 2). No serious or severe AEs were reported in either group. The most common AEs included nasopharyngitis (36.4%), influenza (14.0%), and AD (5.6%, mostly reported as worsening of AD) in the tapinarof group and AD (43.6%), nasopharyngitis (25.5%), influenza (10.9%), and contact dermatitis (5.5%) in the vehicle group. Treatment-related AEs were reported in 6.5% of patients in the tapinarof group and in 3.6% of patients in the vehicle group. The most common treatment-

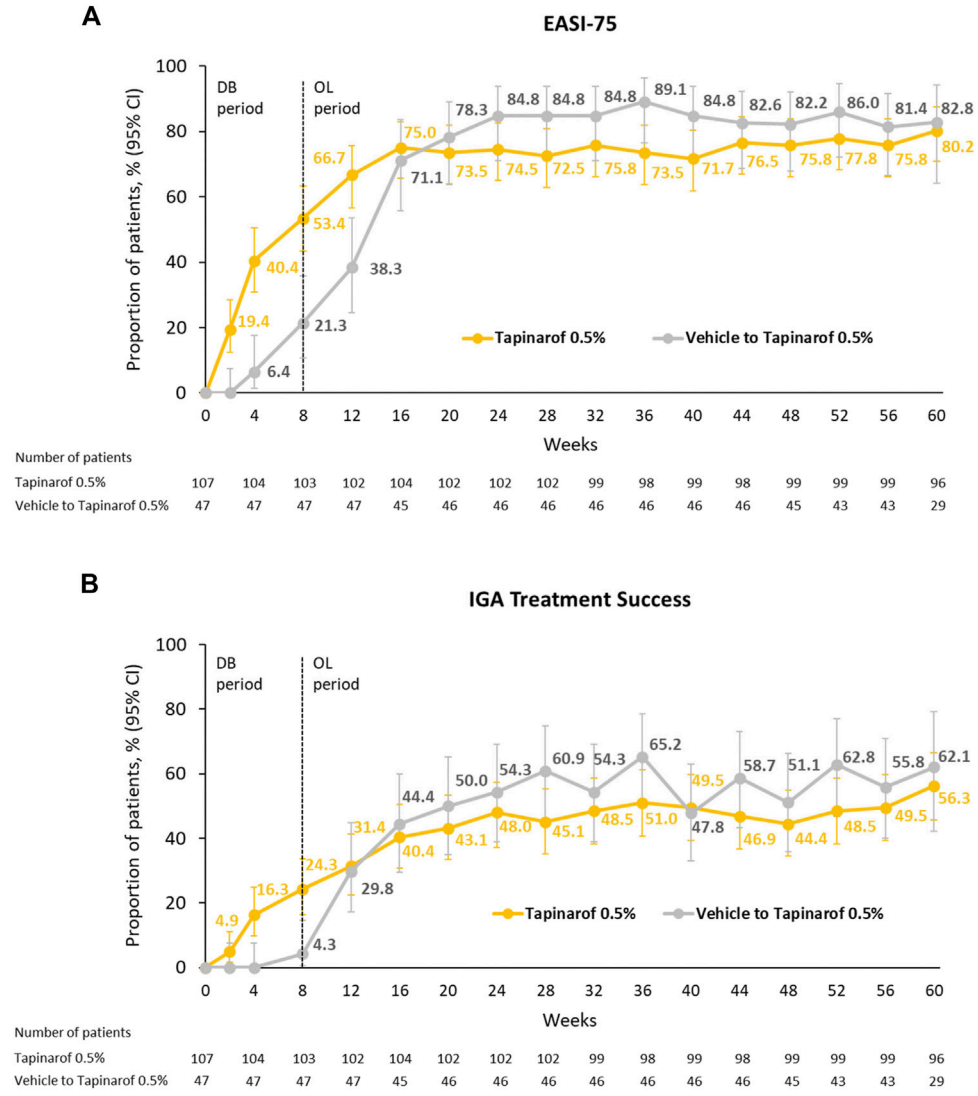

FIGURE 6
Proportion of patients with **(A)** EASI-75 and **(B)** IGA treatment success in the overall trial period. EASI-75 was defined as ≥ 75% improvement from baseline in EASI score. IGA treatment success was defined as an IGA score of 0 or 1 with ≥ 2-grade improvement from baseline. In the vehicle-to-tapinarof group, patients switched from vehicle cream to tapinarof cream 0.5% at week 8 or the early transition visit. The early transition visits occurred in 17 patients between week 4 and before week 8; therefore, the data at week 8 for the vehicle-to-tapinarof group included those after the initiation of treatment with tapinarof from the 17 patients. Data were analyzed on the basis of OC where missing data were not imputed and are presented with exact 95% CIs. CI, confidence interval; DB, double-blind; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; OC, observed cases; OL, open-label.

related AEs included application site folliculitis (2.8%) in the tapinarof group and AD (3.6%) in the vehicle group. The incidence of trial discontinuations due to AEs was lower in the tapinarof group (1.9%) than in the vehicle group (14.5%). The most common AE leading to trial discontinuation was AD, which was reported 1.9% of patients in the tapinarof group and 12.7% of patients in the vehicle group.

In the total safety analysis population of the overall trial period, AEs were reported in 150 of 154 (97.4%) patients (Table 2). One serious AE (tibia fracture) and one severe AE (liver function test increased) were reported but were considered unrelated to tapinarof. The majority of AEs were mild or moderate. Common AEs occurring in ≥5% of patients are provided in Supplementary Table S6. The most common AEs included nasopharyngitis (67.5%), influenza (37.7%), AD (16.9%), and skin papilloma (16.2%). Treatment-related AEs were reported in 14.3% of patients. The most common treatment-related AEs included application site folliculitis (4.5%), acne (3.9%), and application site acne and AD (2.6% each). The most common AE leading to trial discontinuation was AD (2.6%).

The incidence of AEs did not increase with continued treatment over 60 weeks (Supplementary Table S7). In the subgroup analysis by age category (2–6 years [younger group] and 7–11 years [older group]) (Supplementary Table S8), the incidence of acne was numerically higher in the older group (15.3%) than in the younger group (4.3%). However, more than half of acne events in the older group were considered unrelated to tapinarof, and there

TABLE 2 Summary of adverse events.

	DB period		Overall trial period[a] (n = 154)
	Tapinarof 0.5% (n = 107)	Vehicle (n = 55)	
Any AEs	78 (72.9)	41 (74.5)	150 (97.4)
Serious AEs[b]	0	0	1 (0.6)
Severe AEs[c]	0	0	1 (0.6)
Treatment-related AEs	7 (6.5)	2 (3.6)	22 (14.3)
AEs leading to discontinuation	2 (1.9)	8 (14.5)	4 (2.6)
Most common AEs (occurring in ≥10% of patients in the overall trial period)			
Nasopharyngitis	39 (36.4)	14 (25.5)	104 (67.5)
Influenza	15 (14.0)	6 (10.9)	58 (37.7)
AD	6 (5.6)	24 (43.6)	26 (16.9)
Skin papilloma	3 (2.8)	0	25 (16.2)
Gastroenteritis	2 (1.9)	2 (3.6)	22 (14.3)
Pyrexia	1 (0.9)	0	19 (12.3)
Asthma	2 (1.9)	2 (3.6)	18 (11.7)
Arthropod sting	1 (0.9)	2 (3.6)	17 (11.0)
Acne	0	0	16 (10.4)
Most common treatment-related AEs (occurring in ≥2 patients in the overall trial period)			
Application site folliculitis	3 (2.8)	0	7 (4.5)
Acne	0	0	6 (3.9)
Application site acne	0	0	4 (2.6)
AD	1 (0.9)	2 (3.6)	4 (2.6)
Folliculitis	0	0	3 (1.9)
AEs leading to discontinuation			
AD	2 (1.9)	7 (12.7)	4 (2.6)
Eczema impetiginous	0	0	1 (0.6)
Pityriasis rosea	0	1 (1.8)	0

Data are presented as number of patients (percentage). The AE terms reported by the investigator were coded using Medical Dictionary for Regulatory Activities V.26.0. Common AEs occurring in ≥5% of patients are provided in Supplementary Table S6.

Abbreviations: AD, atopic dermatitis; AE, adverse event; DB, double-blind.

[a]The Safety analysis population in the overall trial period included the data from patients who received at least 1 application of tapinarof cream 0.5% in the overall trial period. For patients who received vehicle cream in the DB period, AEs that occurred in the DB period (vehicle-treated period) were excluded from the analyses.

[b]One serious AE, tibia fracture, was considered unrelated to treatment.

[c]One severe AE, liver function test increased, was considered unrelated to treatment.

did not appear to be a large difference in the incidence of tapinarof-related acne between the age groups (4.7% in the older group vs. 2.9% in the younger group). No clinically significant changes over time were noted in clinical laboratory parameters or vital signs. Additionally, the plasma concentration of tapinarof was below the LLOQ (50 pg/mL) in ≥80% of patients at each time point (Supplementary Table S9).

Discussion

The efficacy results from the DB period (8-week treatment) demonstrated that tapinarof cream 0.5% was superior to vehicle cream in treating AD in Japanese pediatric patients. Treatment with tapinarof resulted in improvements in efficacy endpoints, such as EASI-75 response and IGA treatment success rates, by week 8. The favorable results in the primary and key secondary endpoints were supported by patient-reported outcomes, including POEM and pruritus scores. Improvements in POEM score were noted from week 2 onwards, and pruritus relief was also noted shortly after the initiation of treatment with tapinarof. Taken together, these results indicate that treatment with tapinarof can improve signs and symptoms of AD experienced by patients as well as AD severity assessed by the investigators.

In the overall trial period (up to 60-week treatment), efficacy analyses were based on OC without imputation for missing data, rescue topical corticosteroids were used in approximately 20% of

patients during the OL period, and treatment with tapinarof could be interrupted after lesion clearance. Although long-term efficacy data should be interpreted with these limitations, improvements in efficacy endpoints were maintained through week 60, indicating that tapinarof can be used for long-term management of AD in the population. The efficacy results of this trial were generally consistent with those of phase 3 trials of tapinarof cream 1% in Japanese adolescent and adult patients (≥12 years of age) with AD [25].

Tapinarof cream 0.5% was well tolerated for up to 60 weeks of treatment. No treatment-related serious AEs were reported. Except for one severe AE that was considered unrelated to treatment, all the AEs were mild or moderate. The incidence of trial discontinuations due to AEs was low in patients treated with tapinarof (2.6% in the overall trial period). The most common treatment-related AEs included folliculitis and acne, which were also commonly reported in the phase 3 trials in adolescent and adult patients (≥10% for each event) [25], and none led to trial discontinuations in the present trial. Folliculitis and acne observed with tapinarof appear to be morphologically similar to keratosis pilaris [26, 27] and can be associated with increased follicular cornification with subsequent plugging, resulting from the upregulation of stratum corneum components, including filaggrin, hornerin, and involucrin [9].

Headache was also a common tapinarof-related AE in the phase 3 trials in adolescent and adult patients (≥10%) and generally occurred early in treatment (the median time of first onset: 2.0 days), whereas the event was reported in only 3.2% of patients in the present trial and occurred after 32 weeks of treatment, and none was considered related to tapinarof. Contact dermatitis was reported in 6.5% of patients in the present trial, and the event in only one patient (0.9%) was considered related to tapinarof. One tapinarof-related AE of skin hypopigmentation was reported, and no other AEs associated with pigmentary changes were reported.

Overall, the incidence of tapinarof-related AEs was lower in the present trial than in the phase 3 trials in adolescent and adult patients. This finding may be attributed to the difference in strength of tapinarof (0.5% vs. 1%); however, no apparent differences in the incidence of these AEs were noted between the strengths of tapinarof in the phase 2 trial [16]. Further investigation in more patients with AD is still required to characterize the safety profile of tapinarof.

This trial has some limitations. First, most patients enrolled in this trial had a baseline IGA score of 2 (mild) or 3 (moderate), whereas few patients had a baseline IGA score of 4 (severe) (Table 1). In the tapinarof group, both 2 patients with a baseline IGA score of 4 achieved the primary endpoint (EASI-75 at week 8); nonetheless, further investigation in patients with severe AD is warranted. Second, because of a relatively small number of patients enrolled in this trial, the interpretation of data from subgroup analyses (e.g., disease severity, age) was limited. Third, as vehicle cream was used as the comparator in the DB period, the superiority of tapinarof over current topical therapies for pediatric patients with AD is uncertain. Fourth, although this trial evaluated the efficacy and safety of tapinarof for up to 60 weeks, further investigation with longer duration of treatment is warranted given the chronic course of AD. Lastly, AD is also prevalent in patients aged <2 years, but they were not included in this trial. A 52-week phase 3 trial in patients aged 3 to <24 months is ongoing in Japan (Japan Registry of Clinical Trials [https://jrct.mhlw.go.jp/], jRCT2031250138).

In summary, in the 8-week treatment, tapinarof cream 0.5% QD was superior to vehicle cream in treating AD in Japanese pediatric patients. The efficacy response to tapinarof cream was maintained for up to 60 weeks of treatment. Tapinarof cream was well tolerated over the 60-week treatment period. The incidence of trial discontinuations due to AEs was low, and most AEs were mild or moderate. The most common treatment-related AEs included folliculitis and acne. The trial results indicate that tapinarof cream can provide a novel topical treatment option for Japanese pediatric patients aged 2–11 years with AD.

Data availability statement

The datasets presented in this article are not readily available because they contain information that could compromise the privacy of trial patients. Requests to access the datasets should be directed to SF, shuichi.fukasawa@shionogi.co.jp.

Ethics statement

The trial involving humans was approved by the relevant institutional review board at each trial site. The trial was conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this trial was provided by the participants' legal guardians/next of kin.

Author contributions

AI and GT contributed to conceptualization and design of the trial. RM, SF, and SY contributed to management of the trial and data collection. All authors contributed to the article and approved the submitted version.

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Conflict of interest

AI has received advisory board honoraria, consulting fees or speaker honoraria from AbbVie, Eli Lilly

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Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/jcia.2026.17307/full#supplementary-material

References

1. Saeki H, Ohya Y, Arakawa H, Ichiyama S, Katsunuma T, Katoh N, et al. Executive summary: japanese guidelines for atopic dermatitis (ADGL) 2024. *Allergol Int* (2025) 74(2):210–21. doi: 10.1016/j.alit.2025.01.003

2. Otsuka A, Nomura T, Rerknimitr P, Seidel JA, Honda T, Kabashima K. The interplay between genetic and environmental factors in the pathogenesis of atopic dermatitis. *Immunol Rev* (2017) 278(1):246–62. doi: 10.1111/imr.12545

3. Egawa G, Kabashima K. Multifactorial skin barrier deficiency and atopic dermatitis: essential topics to prevent the atopic March. *J Allergy Clin Immunol* (2016) 138(2): 350–8.e1. doi: 10.1016/j.jaci.2016.06.002

4. Werfel T, Allam JP, Biedermann T, Eyerich K, Gilles S, Guttman-Yassky E, et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J Allergy Clin Immunol* (2016) 138(2):336–49. doi: 10.1016/j.jaci.2016.06.010

5. Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. *Nat Rev Dis Primers* (2018) 4(1):1. doi: 10.1038/s41572-018-0001-z

6. Carroll CL, Balkrishnan R, Feldman SR, Fleischer AB, Jr, Manuel JC. The burden of atopic dermatitis: impact on the patient, family, and society. *Pediatr Dermatol* (2005) 22(3):192–9. doi: 10.1111/j.1525-1470.2005.22303.x

7. Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. *Int J Clin Pract* (2006) 60(8):984–92. doi: 10.1111/j.1742-1241.2006.01047.x

8. Weidinger S, Simpson EL, Silverberg JI, Barbarot S, Eckert L, Mina-Osorio P, et al. Burden of atopic dermatitis in paediatric patients: an international cross-sectional study. *Br J Dermatol* (2024) 190(6):846–57. doi: 10.1093/bjd/ljad449

9. Smith SH, Jayawickreme C, Rickard DJ, Nicodeme E, Bui T, Simmons C, et al. Tapinarof is a natural AhR agonist that resolves skin inflammation in mice and humans. *J Invest Dermatol* (2017) 137(10):2110–9. doi: 10.1016/j.jid.2017.05.004

10. Urashima T, Katsuda Y, Yoshiuchi H, Ebihara S, Shinozaki Y, Kato T, et al. Tapinarof, a novel topical therapeutic Aryl Hydrocarbon receptor agonist, suppresses atopic dermatitis-like skin inflammation in mice. *BPB Rep* (2024) 7(4):123–31. doi: 10.1248/bpbreports.7.4_123

11. Igarashi A, Tsuji G, Murata R, Fukasawa S, Yamane S. Improvement effects of tapinarof on the skin barrier function in Japanese patients with atopic dermatitis. *J Cutan Immunol Allergy* (2024) 7:13418. doi: 10.3389/jcia.2024.13418

12. Furue M, Hashimoto-Hachiya A, Tsuji G. Aryl hydrocarbon receptor in atopic dermatitis and psoriasis. *Int J Mol Sci* (2019) 20(21):5424. doi: 10.3390/ijms20215424

13. U.S. Food and Drug Administration. VTAMA® (tapinarof) cream, 1%: US prescribing information (2024). Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/215272s002lbl.pdf (Accessed July 1, 2026).

14. Organon. Emirates drug establishment approves Tapinarof Cream 1%, a new treatment for plaque psoriasis in adults and atopic dermatitis in adults and children 2 years of age and older (2025). Available online at: https://www.organon.com/meta-en/news/emirates-drug-establishment-approves-tapinarof-cream-1-a-new-treatment-for-plaque-psoriasis-in-adults-and-atopic-dermatitis-in-adults-and-children-2-years-of-age-and-older/ (Accessed July 1, 2026).

15. Japan Tobacco Inc. JT receives manufacturing and marketing approval of VTAMA® cream 1% for the treatment of atopic dermatitis and plaque psoriasis in Japan (2024). Available online at: https://www.jt.com/media/news/2024/pdf/20240624_E01.pdf (Accessed July 1, 2026).

16. Igarashi A, Tsuji G, Murata R, Fukasawa S, Yamane S. A phase 2, randomized, double-blind, vehicle-controlled trial of tapinarof cream in Japanese pediatric patients with atopic dermatitis. *J Dermatol* (2025) 52(2):247–55. doi: 10.1111/1346-8138.17587

17. Rehal B, Armstrong AW. Health outcome measures in atopic dermatitis: a systematic review of trends in disease severity and quality-of-life instruments 1985-2010. *PLoS One* (2011) 6(4):e17520. doi: 10.1371/journal.pone.0017520

18. Hill MK, Kheirandish Pishkenari A, Braunberger TL, Armstrong AW, Dunnick CA. Recent trends in disease severity and quality of life instruments for patients with atopic dermatitis: a systematic review. *J Am Acad Dermatol* (2016) 75(5):906–17. doi: 10.1016/j.jaad.2016.07.002

19. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. *EASI Evaluator Group Exp Dermatol* (2001) 10(1):11–8. doi: 10.1034/j.1600-0625.2001.100102.x

20. Schmitt J, Spuls PI, Thomas KS, Simpson E, Furue M, Deckert S, et al. The harmonising outcome measures for eczema (HOME) statement to assess clinical signs of atopic eczema in trials. *J Allergy Clin Immunol* (2014) 134(4):800–7. doi: 10.1016/j.jaci.2014.07.043

21. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Arch Dermatol* (2004) 140(12):1513–9. doi: 10.1001/archderm.140.12.1513

22. Spuls PI, Gerbens LAA, Simpson E, Apfelbacher CJ, Chalmers JR, Thomas KS, et al. Patient-oriented eczema measure (POEM), a core instrument to measure symptoms in clinical trials: a harmonising outcome measures for eczema (HOME) statement. *Br J Dermatol* (2017) 176(4):979–84. doi: 10.1111/bjd.15179

23. Kawashima M, Harada S, Tango T. Evaluation of itch based on a new rating scale using patient diary. *Jpn J Clin Dermatol* (2002) 56(9):692–7. doi: 10.11477/mf.1412904049

24. Sato T, Greenland S, Robins JM. On the variance estimator for the mantel-haenszel risk difference. *Biometrics* (1989) 45(4):1323–4. doi: 10.2307/2531784

25. Igarashi A, Tsuji G, Fukasawa S, Murata R, Yamane S. Tapinarof cream for the treatment of atopic dermatitis: efficacy and safety results from two Japanese phase 3 trials. *J Dermatol* (2024) 51(11):1404–13. doi: 10.1111/1346-8138.17451

26. Desai SR, Stein Gold L, Cameron MC, Golant A, Lewitt GM, Bruno MJ, et al. Tapinarof cream 1% once daily for the treatment of plaque psoriasis: case photography of clinical outcomes from three phase 3 trials. *Dermatol Ther (Heidelb)* (2023) 13(10): 2443–60. doi: 10.1007/s13555-023-01008-9

27. Gold LS, Bruno MJ, Lewitt GM, Hebert AA. Characteristics and management of follicular events and contact dermatitis in patients using tapinarof cream for the treatment of atopic dermatitis or plaque psoriasis. *J Dermatolog Treat* (2025) 36(1): 2517388. doi: 10.1080/09546634.2025.2517388