Efficacy and patient-reported outcomes from a phase 2b, randomized clinical trial of tapinarof cream for the treatment of adolescents and adults with atopic dermatitis

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Background: Tapinarof is a topical therapeutic aryl hydrocarbon receptor modulating agent under investigation for atopic dermatitis (AD) and psoriasis treatment.

Methods: A phase 2b, double-blind, vehicle-controlled study randomly assigned adolescents and adults with AD to receive tapinarof cream 0.5%, 1%, or vehicle, once or twice daily, for 12 weeks with a 4-week follow-up. Outcomes included Investigator Global Assessment (IGA), Eczema Area and Severity Index (EASI), body surface area affected, pruritus numeric rating scale scores, patients' impressions of AD and pruritus symptom severity, and Patient-Oriented Eczema Measure (POEM) scores.

Results: Overall, 191 of 247 randomized patients completed the study. Week 12 IGA responses were higher in the tapinarof groups versus the vehicle group, reaching statistical significance with tapinarof 1% twice daily, ≥75%/90% improvement in EASI from baseline were significantly higher in the tapinarof groups (except 0.5% once daily and 0.5% twice daily), EASI scores were significantly improved in all tapinarof groups, and body surface area affected was significantly reduced in the tapinarof groups (except 0.5% twice daily). More patients reported AD and pruritus symptom severity as very/moderately improved in tapinarof groups, and POEM improvements were observed in all groups. Most adverse events were mild or moderate.

Limitations: Larger prospective studies are required to confirm the reported analyses.

Conclusions: Tapinarof is a potential important advance in topical medicine development for AD. (J Am Acad Dermatol 2021;84:632-8.)

Key words: atopic dermatitis; patient-reported outcomes; tapinarof; therapeutic aryl hydrocarbon receptor (AhR) modulating agent (TAMA); topical therapy.

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Atopic dermatitis (AD) is a chronic, relapsing, and remitting skin disease characterized by pruritus, burning and stinging, xerosis, erythematous papules and plaques, exudation, crusting, and lichenification.[1,2] Patients with AD have reported an impact on their sleep, quality of life, and psychosocial domains (social, academic, and occupational) due to the persistent, intense pruritus and the stigma associated with having visibly affected skin.[1,3,4] Globally, approximately 1% to 3% of adults and 15% to 20% of children are affected by AD.[5]

Currently, there is no curative therapy for AD. Stabilizing the disease and reducing the number and severity of flares are primary treatment goals. Topical treatment directed at skin inflammation is a key part of disease management to provide symptomatic relief from the core symptoms of AD, such as pruritus.[6,7] Although there are several topical options available for the treatment of AD, there remains a need for efficacious topical therapies that can be used without restrictions on body surface area (BSA) or treatment duration.

The cause of AD is multifactorial and comprises genetic and environmental factors, skin barrier defects, and immune dysregulation.[8-10] Inflammation in AD is mediated primarily by type 2 inflammation; although in chronic lesions, the cellular infiltrate is expanded.[11]

Tapinarof is a therapeutic aryl hydrocarbon receptor—modulating agent that is under investigation for the treatment of AD and psoriasis. The efficacy of tapinarof in AD is attributed to activation of aryl hydrocarbon receptor signaling pathways, resulting in decreased proinflammatory type 2 cytokine expression, reduced oxidative stress via activation of the antioxidant Nrf2 pathway, increased skin barrier protein expression, and re-established skin homeostasis.[12-14]

The primary analysis of this phase 2b study showed that tapinarof cream was efficacious and well tolerated in adolescents and adults with AD, and it may represent an effective topical treatment option.[1] This report describes additional efficacy, safety, and patient-reported outcomes (PROs) of tapinarof cream in adolescent and adult patients with AD.

CAPSULE SUMMARY

- Tapinarof, a topical therapeutic aryl hydrocarbon receptor—modulating agent, was efficacious and well tolerated in adolescents and adults with atopic dermatitis (AD).
- Tapinarof cream has the potential to provide a novel and clinically meaningful therapeutic option for AD with a unique mechanism of action distinct from currently available AD therapies.

METHODS

Study design

In this multicenter, phase 2b, double-blind, vehicle-controlled, randomized study, adolescents and adults with AD were randomized 1:1:1:1:1:1 to receive tapinarof cream 0.5% or 1% either once or twice daily or vehicle once or twice daily for 12 weeks. The detailed study design, baseline characteristics of patients, and primary study endpoints have been reported previously.[1] The study consisted of 3 evaluation periods: up to 4 weeks of screening, 12 weeks of double-blind treatment, and 4 weeks of treatment-free follow-up. Study visits occurred at screening; baseline; and weeks 1, 2, 4, 8, and 12 during the treatment period; and at 2 and 4 weeks after the last application of the study treatment (weeks 14 and 16). Use of treatments that could significantly influence responses to tapinarof cream were prohibited for appropriate washout periods before the baseline visit and during the study, including biologic agents and systemic or topical immunosuppressive and immunomodulating agents.

The study was conducted in compliance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. Approval was obtained from the local ethics committee or institutional review board at each study center. All patients provided written informed consent.

Participants

Patients were male or female aged 12 to 65 years with a clinical diagnosis of AD. The required severity of AD was BSA involvement of ≥5% to 35% (excluding the scalp) at screening and baseline and Investigator Global Assessment (IGA) score ≥3 at baseline. Key exclusion criteria were unstable AD (either spontaneously improving or rapidly deteriorating) and concurrent or a history of serious illness, including being

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Abbreviations used:

AD:	atopic dermatitis
AE:	adverse event
BSA:	body surface area
IGA:	Investigator Global Assessment
EASI:	Eczema Area and Severity Index
EASI75:	≥75% improvement in Eczema Area and Severity Index from baseline
EASI90:	≥90% improvement in Eczema Area and Severity Index from baseline
ITT:	intent-to-treat
NRS:	numeric rating scale
POEM:	Patient-Oriented Eczema Measure
PRO:	patient-reported outcome

immunocompromised, having infections requiring treatment, and having other skin disorders.

Outcome measures and statistical analysis

The previously reported primary endpoint was the proportion of patients with an IGA score of clear (0) or almost clear (1) and ≥2-grade improvement in IGA score from baseline to week 12.[1] Secondary endpoints included the proportion of patients with ≥75% improvement in Eczema Area and Severity Index (EASI) from baseline (EASI75) to each study visit, mean percent change in EASI score, mean change in weekly average of daily pruritus assessed by numeric rating scale (NRS) score based on the Daily Signs and Symptoms Severity Diary, proportion of patients who achieved a ≥3-point improvement in the weekly average of pruritus NRS score at each study visit, and mean change in percentage of BSA affected. The proportion of patients with a ≥90% improvement in EASI from baseline (EASI90) to each study visit was calculated post hoc.

Additional PROs included patients' impression of severity of AD symptoms, assessed on a scale ranging from 1 (mild) to 4 (very severe); overall change in severity of AD symptoms—response options ranged from 1 (very improved) to 7 (very worse); and overall change in severity of pruritus symptoms from baseline to week 12. The expanded Patient-Oriented Eczema Measure (POEM) was used to assess pruritus, sleep disturbance, skin bleeding, skin weeping/oozing, cracked skin, flaking skin, and dry/rough skin.[15,16] The Daily Signs and Symptoms Severity Diary (based on the POEM) was used to score the following 11 disease-related symptoms: skin that is itchy, discolored, bleeding, oozing, cracked, scaly, flaky, dry/rough, painful, burning, or stinging.

The primary safety assessments have been previously reported, including the incidence, frequency, and severity of adverse events (AEs), treatment-emergent AEs, and serious AEs.[1] Application-site tolerability of tapinarof cream was assessed by investigators and patients. Investigators assessed application-site tolerability by the presence and overall degree of irritation using a scale from 0 (no irritation) to 4 (very severe/strong reaction) at each study visit to week 12 and 2 weeks after the last application of the study treatment (week 14). A score of 3 or 4 was reported as an AE; study treatment was discontinued if a score of 4 was noted. Participant-reported application-site tolerability was assessed using a 5-point scale from 0 (no discomfort) to 4 (definite continuous discomfort that interferes with normal daily activities) to evaluate the presence and degree of burning/stinging and itching within approximately 2 hours after application of the study treatment.

The intent-to-treat (ITT) population, which included all randomized patients, was used for the primary and secondary efficacy analyses. To adjust for higher dropout rates in the vehicle groups, a nonresponder imputation method was used to impute missing data, where any missing values were treated as a nonresponse for the following endpoints at week 12: IGA response (an IGA score of 0 or 1 and ≥2-grade improvement from baseline), EASI75, EASI90, proportion of patients with a ≥3-point improvement in pruritus NRS score from baseline, and proportion of patients who rated their overall AD and pruritus symptoms as very or moderately improved. For patients' impressions of change in severity of AD and pruritus symptoms, worst-case imputation was used to impute missing data. *P* values for differences between tapinarof cream groups and the corresponding vehicle group for IGA, EASI75, EASI90, and NRS response rates at weeks 12 and 16, as well as patients' impressions of the overall change in severity of AD and pruritus symptoms at week 12 were calculated post hoc using Barnard's and Fisher's exact tests. *P* values for mean percent change in EASI and BSA scores at weeks 12 and 16 were based on a post hoc analysis of covariance with the main effect of treatment and covariates of baseline score, age group, and pooled country, and missing data were imputed using the last observation carried forward.

RESULTS

Patient disposition

Of 363 patients screened, 247 were randomized from 53 sites in the United States, Canada, and Japan (ITT and safety population: tapinarof 1% twice daily, n = 40; tapinarof 1% once daily, n = 41; tapinarof 0.5% twice daily, n = 43; tapinarof 0.5% once daily, n = 41; vehicle twice daily, n = 42; and vehicle once daily, n = 40). A total of 191 (77%) randomized patients completed the study, including the week

16 follow-up visit (Supplemental Fig 1; available via Mendeley at http://dx.doi.org/10.17632/zrmp3sk953.2). Overall, baseline demographic and disease characteristics were comparable across treatment groups (Supplemental Table I; available via Mendeley at http://dx.doi.org/10.17632/zrmp3sk953.2). Most patients (91%) had a baseline IGA score of 3 (moderate). The baseline mean EASI score was 11.3 (standard deviation, 6.0). Thirty percent (n = 73) of randomized patients were adolescents; however, this phase 2b study was not statistically powered to detect differences between the adolescent and adult populations.

Primary efficacy endpoint

The proportion of patients achieving an IGA response was numerically higher for the tapinarof cream groups than for the vehicle groups at all visits beyond week 2.[1] At week 12, IGA response rates were 53% (1% twice daily; $P = .008$), 46% (1% once daily; $P = .084$), 37% (0.5% twice daily; $P = .240$), and 34% (0.5% once daily; $P = .535$) versus 24% (vehicle twice daily) and 28% (vehicle once daily). This improvement was maintained for 4 weeks after the end of the study treatment. Overall, patients treated with tapinarof cream 1% showed higher rates of response than the 0.5% groups.

EASI

EASI75 was significantly higher in the tapinarof groups, except the 0.5% once daily group, than in the vehicle groups at week 12: 60% (1% twice daily; $P = .002$), 51% (1% once daily; $P = .016$), 51% (0.5% twice daily; $P = .018$), and 39% (0.5% once daily; $P = .240$) versus 26% (vehicle twice daily) and 25% (vehicle once daily). Improvement in the tapinarof groups was maintained for 4 weeks after the last application of the study treatment.

EASI90 was significantly higher in the tapinarof groups, except the 0.5% twice daily group, than in the vehicle groups at week 12: 43% (1% twice daily; $P = .005$), 27% (1% once daily; $P = .007$), 28% (0.5% twice daily; $P = .134$), and 22% (0.5% once daily; $P = .027$) versus 14% (vehicle twice daily) and 5% (vehicle once daily).

Greater improvements in mean percent change in EASI scores from baseline were apparent in all tapinarof groups compared with vehicle from week 1. At week 12, the mean percent change in EASI was significantly higher in all tapinarof groups than in vehicle groups: −73% (1% twice daily; $P < .001$), −62% (1% once daily; $P = .002$), −66% (0.5% twice daily; $P = .004$), and −66% (0.5% once daily; $P < .001$) versus −38% (vehicle twice daily) and −28% (vehicle once daily) (Fig 1). These statistically

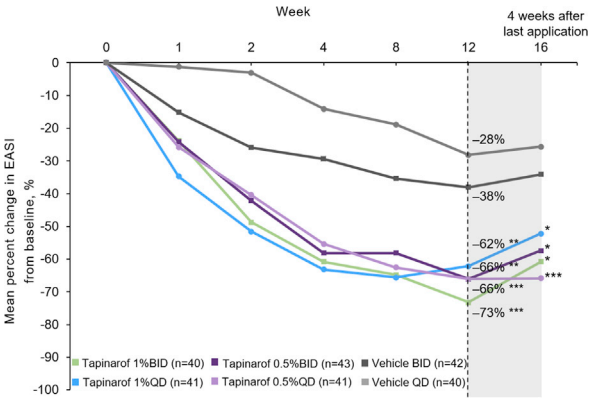

Fig 1. Mean percent change in EASI scores from baseline to the primary endpoint (week 12) and 4 weeks after the last application of the study treatment (week 16) (ITT population; last observation carried forward). The difference versus vehicle was statistically significant at $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$. The dotted vertical line represents the primary endpoint (week 12). *BID*, Twice daily; *EASI*, Eczema Area and Severity Index; *ITT*, intent-to-treat; *QD*, once daily.

significant differences in mean EASI scores at week 12 in the tapinarof groups versus vehicle groups were observed at week 16, indicating a maintenance of beneficial effect for at least 4 weeks after the last application of the study treatment: −61% (1% twice daily; $P = .012$), −52% (1% once daily; $P = .017$), −57% (0.5% twice daily; $P = .034$), and −66% (0.5% once daily; $P < .001$) versus −34% (vehicle twice daily) and −26% (vehicle once daily).

Pruritus NRS

More patients in the tapinarof groups achieved a ≥3-point improvement in pruritus NRS from week 2 onward than in the vehicle groups.[1] At week 12, the proportion of patients who achieved a ≥3-point improvement in pruritus NRS was 30% (1% twice daily; $P = .003$), 32% (1% once daily; $P = .081$), 33% (0.5% twice daily; $P = .001$), and 29% (0.5% once daily; $P = .131$) versus 5% (vehicle twice daily) and 15% (vehicle once daily).

BSA

There were significantly greater reductions from baseline in the mean percent change in BSA in the tapinarof groups, except the 0.5% twice daily group, than in the vehicle groups at week 12: −68% (1% twice daily; $P = .002$), −48% (1% once daily; $P = .006$), −43% (0.5% twice daily; $P = .194$), and −56% (0.5% once daily; $P < .001$) versus −23% (vehicle twice daily) and −5% (vehicle once daily). Similarly, these significant differences between the tapinarof groups and vehicle were maintained for 4 weeks after the last

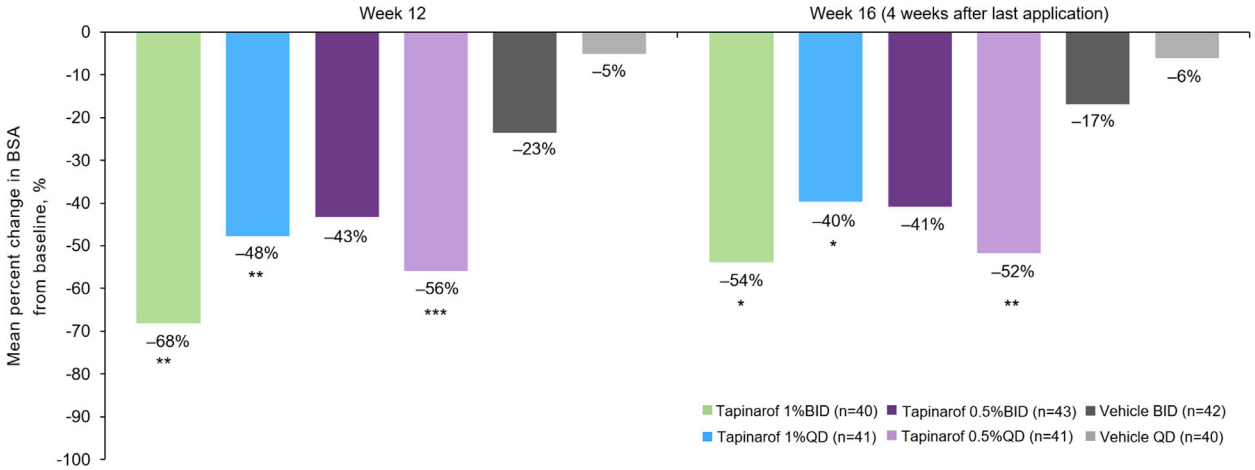

Fig 2. Mean percent change in BSA affected from baseline to the primary endpoint (week 12) and 4 weeks after the last application of the study treatment (week 16) (ITT population; last observation carried forward). The difference versus vehicle was statistically significant at $^{*}P < .05$; $^{**}P < .01$; $^{***}P < .001$. *BID*, Twice daily; *BSA*, body surface area; *ITT*, intent-to-treat; *QD*, once daily.

application of the study treatment: −54% (1% twice daily; $P = .012$), −40% (1% once daily; $P = .038$), −41% (0.5% twice daily; $P = .145$), and −52% (0.5% once daily; $P = .003$) versus −17% (vehicle twice daily) and −6% (vehicle once daily) at week 16 (Fig 2).

Patient-reported outcomes

Overall, the proportion of patients who rated their AD symptoms as mild, moderate, or severe at baseline was 7.0% (17/242), 50.8% (123/242), and 34.7% (84/242), respectively. A significantly greater proportion of patients in the tapinarof groups rated the overall severity of their AD symptoms as very or moderately improved compared with the vehicle groups at week 12: 73% (1% twice daily; $P = .006$), 80% (1% once daily; $P < .001$), 67% (0.5% twice daily; $P = .026$), and 71% (0.5% once daily; $P = .012$) versus 43% (vehicle twice daily) and 43% (vehicle once daily) (Supplemental Fig 2; available via Mendeley at http://dx.doi.org/10.17632/zrmp3sk953.2). When asked to rate the overall severity of their pruritus symptoms at week 12, significantly more patients in the tapinarof groups rated their symptoms as very or moderately improved compared with the vehicle groups: 70% (1% twice daily; $P < .001$), 78% (1% once daily; $P < .001$), 60% (0.5% twice daily; $P = .007$), and 68% (0.5% once daily; $P = .013$) versus 31% (vehicle twice daily) and 40% (vehicle once daily) (Fig 3).

At week 12, improvements were observed in all groups treated with tapinarof cream or vehicle for all 7 core POEM items, except for item 4 (weeping or oozing) for the tapinarof 1% twice daily group in which there was no change. The 3 additional sleep-related items (items 8-10) in the expanded POEM showed that overall sleep quality improved across all groups. For item 9, the proportion of patients finding it not at all difficult to fall asleep at baseline was 20% to 39% across all groups and increased to more than 50% at week 12 in the tapinarof groups only: 55% (1% twice daily), 51% (1% once daily), 51% (0.5% twice daily), and 51% (0.5% once daily) versus 31% (vehicle twice daily) and 25% (vehicle once daily) (Supplemental Table II; available via Mendeley at http://dx.doi.org/10.17632/zrmp3sk953.2).

The highest mean baseline scores across all treatment groups were seen for dry or rough skin (range, 6.2-6.9), red or discolored skin (range, 4.8-6.0), and flaky skin (range, 4.2-5.8), as measured by the Daily Signs and Symptoms Severity Diary scores. Overall, there was an improvement in dry or rough, red or discolored, and flaky skin in all treatment groups, with the magnitude of improvement being consistently smaller, numerically, for the vehicle twice daily group compared with the tapinarof groups for all items.

Safety and tolerability

AEs were mostly mild to moderate in severity and were previously reported in detail.[1] Most patients had little to no investigator-assessed application-site irritation or self-reported application-site burning/stinging and itching throughout the study period, with no apparent differences between the tapinarof cream and vehicle groups. The mean investigator-assessed application-site tolerability scores were between 0 (no irritation) and 1 (mild) in all groups at week 1 (range, 0.3-0.7) and were maintained

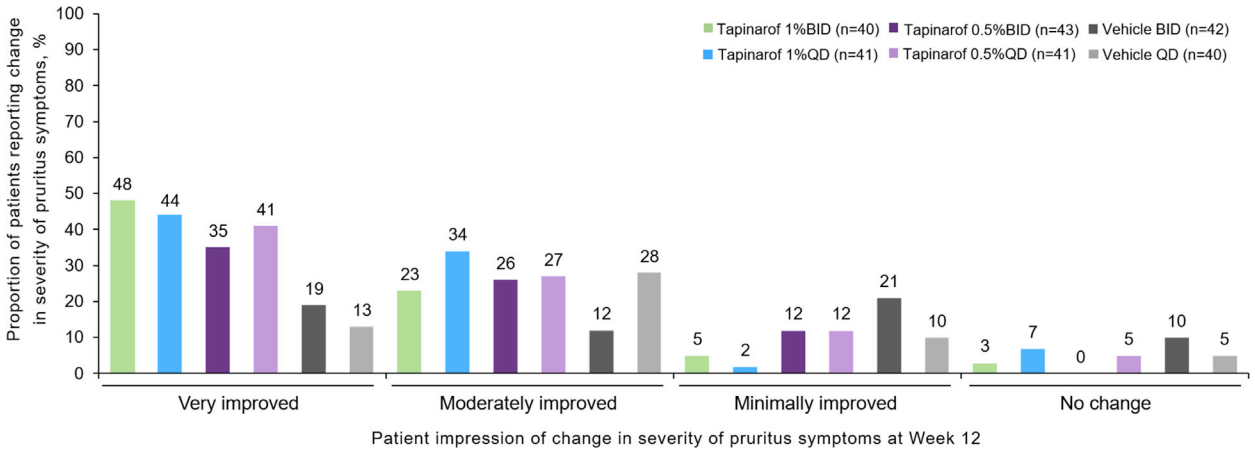

Fig 3. Patient impression of change in the severity of pruritus symptoms at week 12 (ITT population; worst-case imputation). Statistical significance was shown for patients who considered an overall change in the severity of pruritus as very improved or moderately improved in the tapinarof groups from baseline to week 12, compared with a matched vehicle control: 70% (1% twice daily; $P < .001$), 78% (1% once daily; $P < .001$), 60% (0.5% twice daily; $P = .007$), and 68% (0.5% once daily; $P = .013$) versus 31% (vehicle twice daily) and 40% (vehicle once daily). *AD*, Atopic dermatitis; *BID*, twice daily; *ITT*, intent-to-treat; *QD*, once daily.

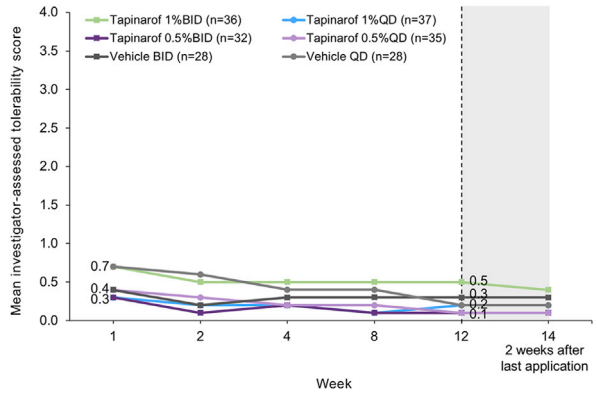

Fig 4. Mean investigator-assessed application-site tolerability scores from baseline to the primary endpoint (week 12) and 2 weeks after the last application of the study treatment (week 14) (safety population). Investigator-assessed irritation scores used a scale of 0 (no irritation) to 4 (very severe/strong reaction) to assess the presence and overall degree of irritation at the application sites. A score of 3 or 4 was reported to be an adverse event; study treatment was discontinued if a score of 4 was noted. The dotted vertical line represents the primary endpoint (week 12); *n* designates the number of patients with results available at week 12. *BID,* Twice daily; *QD*, once daily.

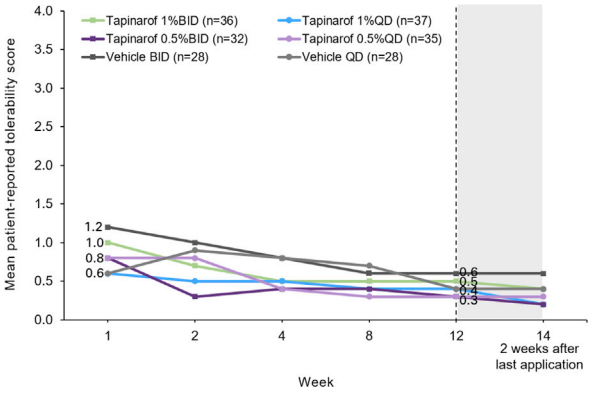

Fig 5. Mean patient-reported application-site tolerability scores from baseline to the primary endpoint (week 12) and 2 weeks after the last application of the study treatment (week 14) (safety population). Patient-reported tolerability used a 5-point tolerability scale of 0 (none) to 4 (strong/severe) to assess the presence and degree of burning/stinging and itching after application of the study treatment. The dotted vertical line represents the primary endpoint (week 12); *n* designates the number of patients with results available at week 12. *BID,* Twice daily; *QD*, once daily.

through week 12 (range, 0.1-0.5) and 2 weeks after the last application of the study treatment (week 14) (Fig 4). The mean patient-reported application-site tolerability scores were between 0 (none) and 2 (mild) in all groups at week 1 (range, 0.6-1.2) and between 0 (none) and 1 (slight) in all groups at week 12 (range, 0.3-0.6) and 2 weeks after the last application of the study treatment (week 14) (Fig 5).

No apparent patterns were observed between investigator-assessed or patient-reported tolerability scores and severity of AD, week of onset of reported tolerability, or the occurrence of AD AEs.

DISCUSSION

These results support the primary analysis that tapinarof cream was efficacious and well tolerated in adolescents and adults with AD. As previously

reported, tapinarof cream was more efficacious than vehicle in achieving an IGA response at week 12, and improvements were maintained for 4 weeks after the last application of the study treatment.[1]

Treatment with tapinarof cream 1% consistently led to statistically significant and clinically meaningful improvements in other efficacy analyses, including the proportion of patients achieving EASI75 and EASI90 and the overall improvements in EASI scores and BSA affected. Improvements were apparent as early as week 1 and were maintained for 4 weeks after the last application of the study treatment.

A significantly greater proportion of patients treated with tapinarof cream (≥67%) rated the severity of their AD symptoms as very or moderately improved compared with those treated with vehicle (43%). Similarly, ≥60% of patients treated with tapinarof cream rated the severity of their pruritus as very or moderately improved compared with vehicle (≤40%).

Overall, tapinarof cream was well tolerated, with most AEs reported as mild or moderate. Investigator- and self-reported application-site irritation scores were low and no different from vehicle in the tapinarof cream groups across the duration of the study.

Although this phase 2b study was not powered to detect differences between the adolescent and adult populations and the number of adolescents in each arm was small, to our knowledge, this was the first clinical trial of tapinarof cream in an adolescent population. As previously reported in the primary analysis, no apparent differences were observed in the efficacy, safety, or tolerability outcomes in the 30% of patients who were adolescents.[1]

The primary analysis of this phase 2b study showed that tapinarof cream was efficacious and well tolerated in adolescents and adults with AD and may represent an effective topical treatment option.

The results also show that tapinarof cream had beneficial effects on secondary efficacy and PROs in adolescents and adults with AD. These findings support the hypothesis that tapinarof cream represents an important advance in the development of topical medicines for AD and warrants further study in phase 3 clinical trials.

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