REVIEW ARTICLE

# Tapinarof cream for atopic dermatitis in children and adults: an updated meta-analysis, and trial sequential analysis

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## ABSTRACT

**Background:** Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by pruritus and eczematous lesions. Conventional topical therapies, including corticosteroids and calcineurin inhibitors, are often associated with adverse effects, highlighting the need for safer long-term alternatives. Tapinarof, a novel aryl hydrocarbon receptor modulator, has emerged as a promising nonsteroidal topical agent for AD treatment. This systematic review and meta-analysis aimed to assess the efficacy and safety of tapinarof cream in patients with AD.

**Methods:** We systematically searched PubMed, Scopus, Embase, Cochrane, and Web of Science from inception to March 2025 to identify studies assessing the efficacy of tapinarof cream in AD. Randomized controlled trials (RCTs) reporting quantitative outcomes were included. Meta-analysis was performed using Review Manager V5.4, calculating relative risks and 95% confidence intervals (CIs) for primary and secondary outcomes.

**Results:** Five studies (six RCTs) involving 1,096 patients treated with tapinarof and 446 with vehicle were analyzed. At 8 weeks, tapinarof 1% cream significantly improved Investigator Global Assessment (IGA) success (RR: 3.21, 95% CI: 2.4-4.28, $p < 0.00001$) with low heterogeneity ($I^2 = 9\%$). Similarly, Eczema Area and Severity Index (EASI)-75 response rates were significantly higher at 8 weeks (RR: 2.86, 95% CI: 2.04-4.02, $p < 0.00001$). Adverse events, including folliculitis, headache, and nasopharyngitis, were more common with tapinarof, but serious adverse events were not significantly different between groups.

**Conclusion:** Tapinarof cream demonstrates significant efficacy in achieving IGA treatment success and EASI-75 response with a manageable safety profile. It represents a promising alternative for long-term management of AD, particularly for patients seeking nonsteroidal options.

**Keywords:** Atopic dermatitis, Tapinarof, Aryl hydrocarbon receptor, novel, review.

## Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin condition characterized by intense pruritus, xerosis, erythematous papules, and lichenification [1]. It significantly impacts patients' quality of life, leading to sleep disturbances, emotional distress, and social stigmatization [2]. AD affects approximately 10%-20% of children and 1%-3% of adults globally, making it a major dermatologic burden [3]. Despite advances in treatment, there remains an unmet need for effective, safe, and long-term topical therapies with minimal side effects.

Current topical treatment strategies include corticosteroids, calcineurin inhibitors, phosphodiesterase-4 (PDE4) inhibitors, and Janus kinase inhibitors. While effective, these therapies are often limited by adverse effects such as skin atrophy, burning, and systemic toxicity with long-term use [4]. Consequently, nonsteroidal topical agents with novel mechanisms of action are being explored as safer alternatives for sustained disease control [5].

Tapinarof is a novel, nonsteroidal topical agent that functions as an aryl hydrocarbon receptor (AhR)

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modulator [6]. By targeting AhR pathways, tapinarof reduces type 2 inflammation, enhances skin barrier integrity by upregulating structural proteins such as filaggrin and involucrin, and mitigates oxidative stress through nuclear factor erythroid 2-related factor 2 activation [7]. These mechanisms position tapinarof as a promising alternative for AD treatment, particularly for patients requiring long-term topical management without the risks associated with conventional therapies.

Recent clinical trials have demonstrated the efficacy and safety of tapinarof cream in AD, showing significant improvement in disease severity scores and patient-reported outcomes. However, data from observational studies, which provide real-world insights into the drug's effectiveness, remain scattered. To address this gap, this systematic review and meta-analysis aim to synthesize the available evidence to evaluate the efficacy of tapinarof in AD.

## Methods

This systematic review and meta-analysis were conducted according to the PRISMA checklist.

### *Source of data and the inclusion and exclusion criteria*

We collected data from five databases: PubMed, Scopus, Embase, Cochrane, and Web of Science from inception to March 2025 to identify all the studies that discuss the efficacy of tapinarof cream in patients with atopic dermatitis. A comprehensive search strategy was conducted using all the related keywords using the MeSH database, with suitable pollen operators. The full search strategy is available in Table S1.

The inclusion criteria were as follows: (1) Patients with atopic dermatitis. (2) Observational studies, like cohorts and case control studies, were included, and randomized controlled trials (RCTs). (3) All the included studies should report qualitative or quantitative results about the efficacy of tapinarof cream. However, case series, case reports, reviews, books, chapters, and editorials were excluded.

### *Data extraction*

After collecting the studies, we uploaded the data to an Excel sheet to remove the duplicates and to screen all the studies according to the inclusion criteria. Then, we extracted the characteristics of our study from an Excel sheet. Characteristics data such as the study ID, year, country, design, mean age, sex, aim, and conclusion. Also, numerical data for the efficacy of tapinarof cream in patients with atopic dermatitis were extracted.

### *Quality assessment*

The quality assessment of the included studies was conducted by two independent authors, and a third one was used to check and remove any errors. The risk of bias 2 tool was used to assess bias in all RCTs based on various domains. Each domain is rated as "low risk," "some concerns," or "high risk," and these ratings are used to determine the overall risk of bias for the study. Each study was rated as 1: high risk of bias, 2: some concerns of bias, or 3: low risk of bias.

### *Meta-analysis*

Review Manager V 5.4 was used for meta-analysis. Events and the total of each outcome were pooled. The data were presented using relative risks and 95% Confidence Intervals (CIs). A significance threshold of 0.05 was applied. Heterogeneity was assessed through the inconsistency index ($I^2$) and the chi-squared ($X^2$) test. The $I^2$ statistic measured the variation in study results, with values greater than 50% indicating substantial heterogeneity and values above 90% signifying major heterogeneity. For trial sequential analysis (TSA), we focused on quantifying effect sizes rather than binary significance testing. Analyses were conducted using TSA software version 0.9.5.10 Beta. We calculated the required sample size to ensure 80% power with a two-sided type I error rate of 5%, applying the O'Brien-Fleming α-spending function. In the superiority analysis, a definitive conclusion required the cumulative Z-curve to cross the predefined superiority boundary. We have performed TSA only for adverse event outcomes, as the incidence for the rest of the outcomes was low, and limited the applicability to conduct TSA.

## Results

### *Search results*

A comprehensive search across Medline (via PubMed), Web of Science, Scopus, Embase, and Cochrane databases initially identified 317 studies. After duplicate removal, 197 unique records remained for title and abstract screening, resulting in the exclusion of 190 studies. Subsequently, 7 full-text articles were independently evaluated, of which 5 met the eligibility criteria for inclusion [8-12]. The detailed search and selection process is illustrated in Figure 1.

### *Summary of the included studies*

Five studies, encompassing six randomized controlled trials, were included in our systematic review and meta-analysis [8-12]. 1,096 patients were treated with tapinarof, and 446 patients were treated with vehicle. The mean age of patients ranged from 7 years to 31 years. Two studies were conducted in Japan, or study in the USA, one study in Canada, and one study was multi-centers.

### *Quality assessment*

The ROB-2 tool was used to assess the quality of the included studies. Out of five studies, three were considered to have a low risk of bias, indicating high quality. However, two studies were considered to have moderate quality due to some concerns in the reported data Figure S1.

## *Meta-analysis*

### *Investigator global assessment (IGA) treatment success*

At 8 weeks of one daily tapinarof 1% dose, our results revealed that patients treated with tapinarof were associated with 3 folds higher IGA treatment success in comparison to vehicle (RR: 3.21, 95%CI (2.4, 4.28), $p$ value < 0.00001), with low heterogeneity ($I^2$ = 9%) Figure 2.

At 12 weeks of tapinarof 1%, our results revealed that patients treated with tapinarof were associated with 2-folds higher IGA treatment success in comparison to vehicle (RR: 2.02, 95%CI (1.49, 2.74), $p$ value < 0.00001), with zero heterogeneity ($I^2$ = 0%). Subgroup analysis according to the dose showed that both doses once daily (RR: 1.85, 95%CI (1.21, 2.85), $p$ value = 0.005) and twice daily (RR: 2.21, 95%CI (1.43, 3.41), $p$ value = 0.0004) were significantly associated with higher IGA success Figure 3.

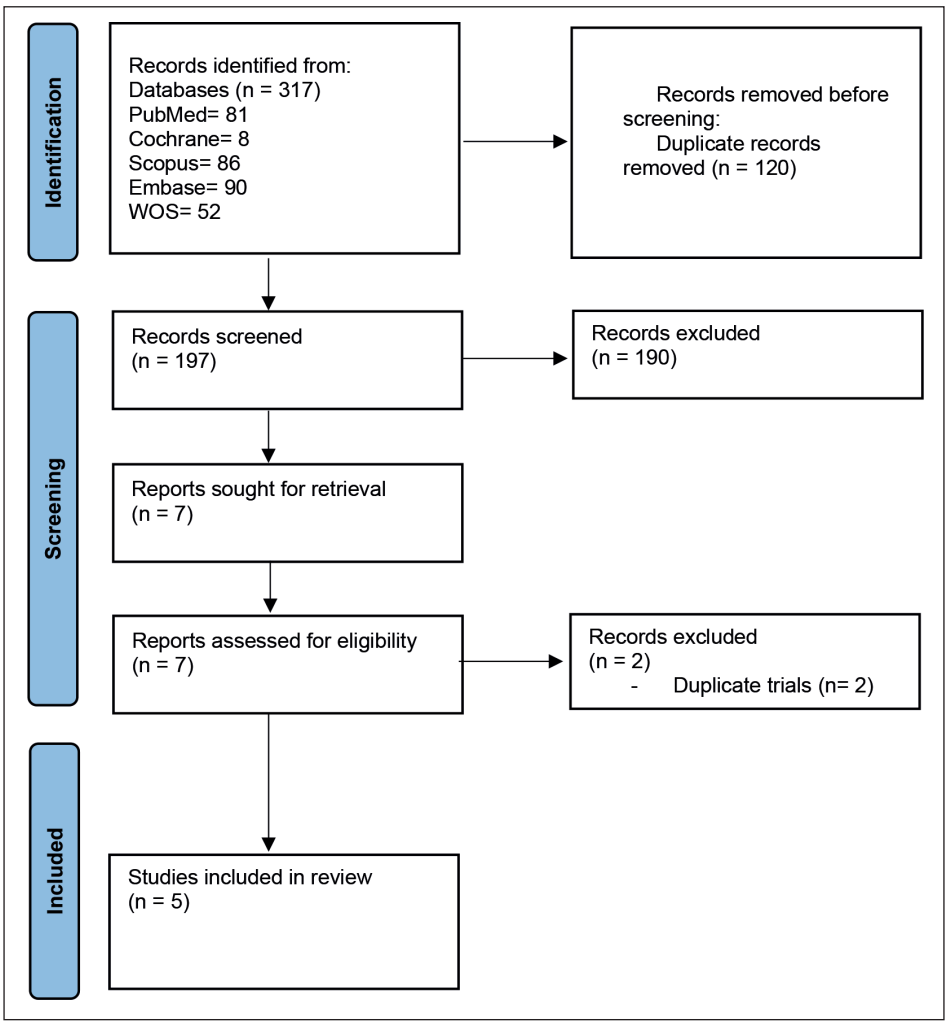


***Figure 1.*** *Flow chart of the selection process.*

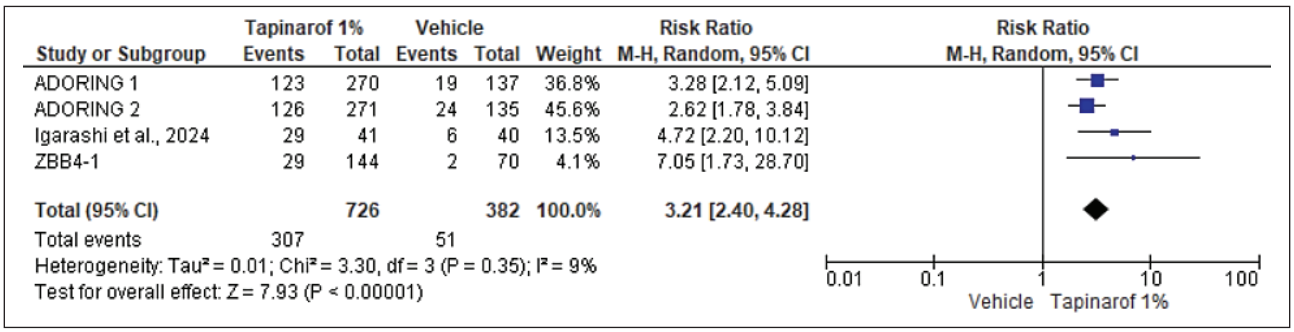


***Figure 2.*** *IGA treatment success at 8 weeks.*

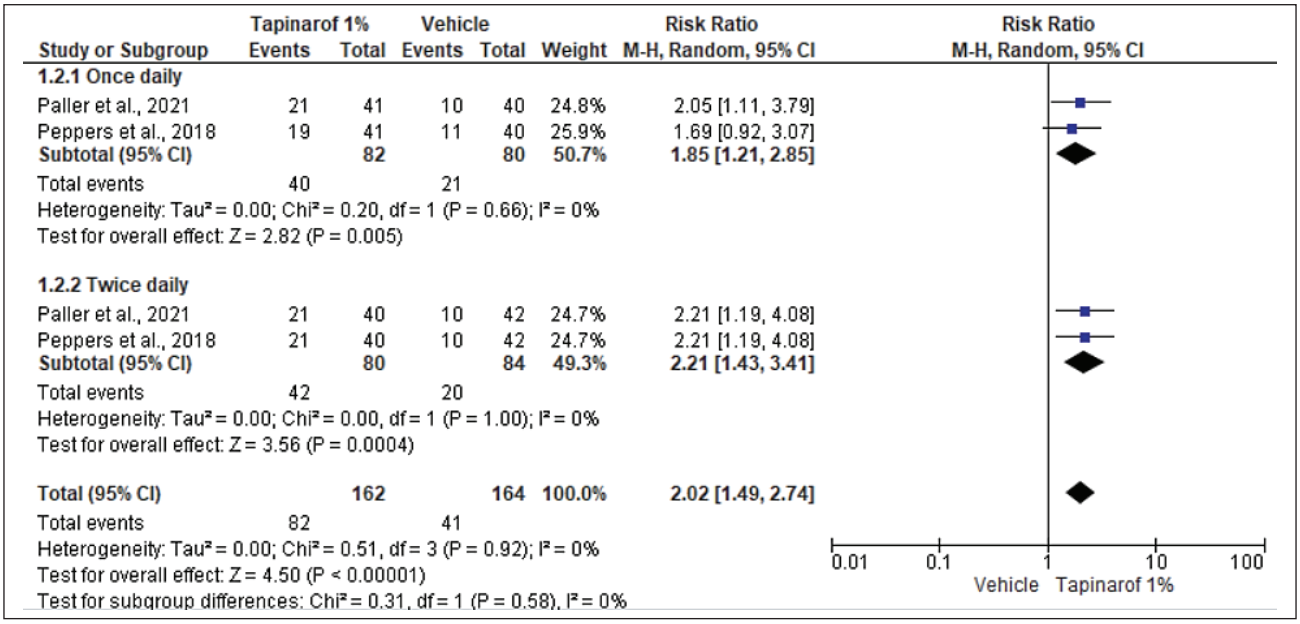


***Figure 3.*** *IGA treatment success at 12 weeks.*

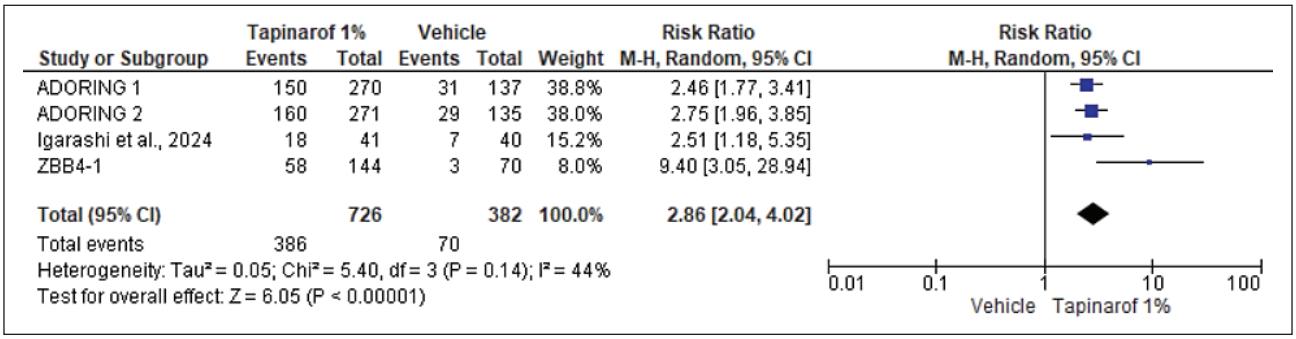


***Figure 4.*** *Eczema Area and Severity Index (EASI)-75 response rate at 8 weeks.*

### *Eczema area and severity index (EASI)-75 response rate*

At 8 weeks of one daily tapinarof 1% dose, our results revealed that patients treated with tapinarof were associated with 2.8 folds higher EASI-75 response rate in comparison to vehicle (RR: 2.86, 95%CI (2.04, 4.02), $p$ value < 0.00001), with low heterogeneity ($I^2$ = 44%) Figure 4. At 12 weeks of tapinarof 1% (twice daily), our results revealed that patients treated with tapinarof were associated with 2 folds higher EASI-75 response rate in comparison to vehicle (RR: 2.29, 95%CI (1.53, 3.42), $p$ value < 0.00001), with zero heterogeneity ($I^2$ = 0%) Figure S2.

### *Adverse events*

Our analysis showed that patients treated with one daily tapinarof 1% dose were associated with a higher risk of adverse events in comparison to vehicle (RR: 1.5, 95%CI (1.23, 1.83), $p$ value < 0.00001), with low heterogeneity ($I^2$ = 37%). For serious adverse events, no difference was reported between the groups Figure 5.

Our analysis showed that patients treated with one daily tapinarof 1% dose were associated with higher risk of folliculitis (RR: 6.9, 95%CI (2.5, 19.01), $p$ value = 0.0002), headache (RR: 3.28, 95%CI (1.39, 7.74), $p$ value = 0.007), and nasopharyngitis (RR: 2.44, 95%CI (1.09, 5.47), $p$ value = 0.03) Figure 6.

This TSA plot demonstrates that the cumulative Z-curve (blue line) has not crossed the conventional or TSA monitoring boundaries, and the required information size (TSA = 2465) has not been reached. This suggests that the current evidence is insufficient to draw a firm conclusion, and further studies are needed to confirm the findings Figure 7.

## Discussion

Atopic dermatitis is a chronic, relapsing inflammatory skin disorder that imposes a significant burden on patients' quality of life, particularly due to its hallmark symptom, pruritus, and associated sleep disturbances and emotional distress [1]. This systematic review and meta-analysis synthesizes evidence from multiple studies to evaluate the efficacy and safety of tapinarof cream in patients with AD. Our findings demonstrate robust

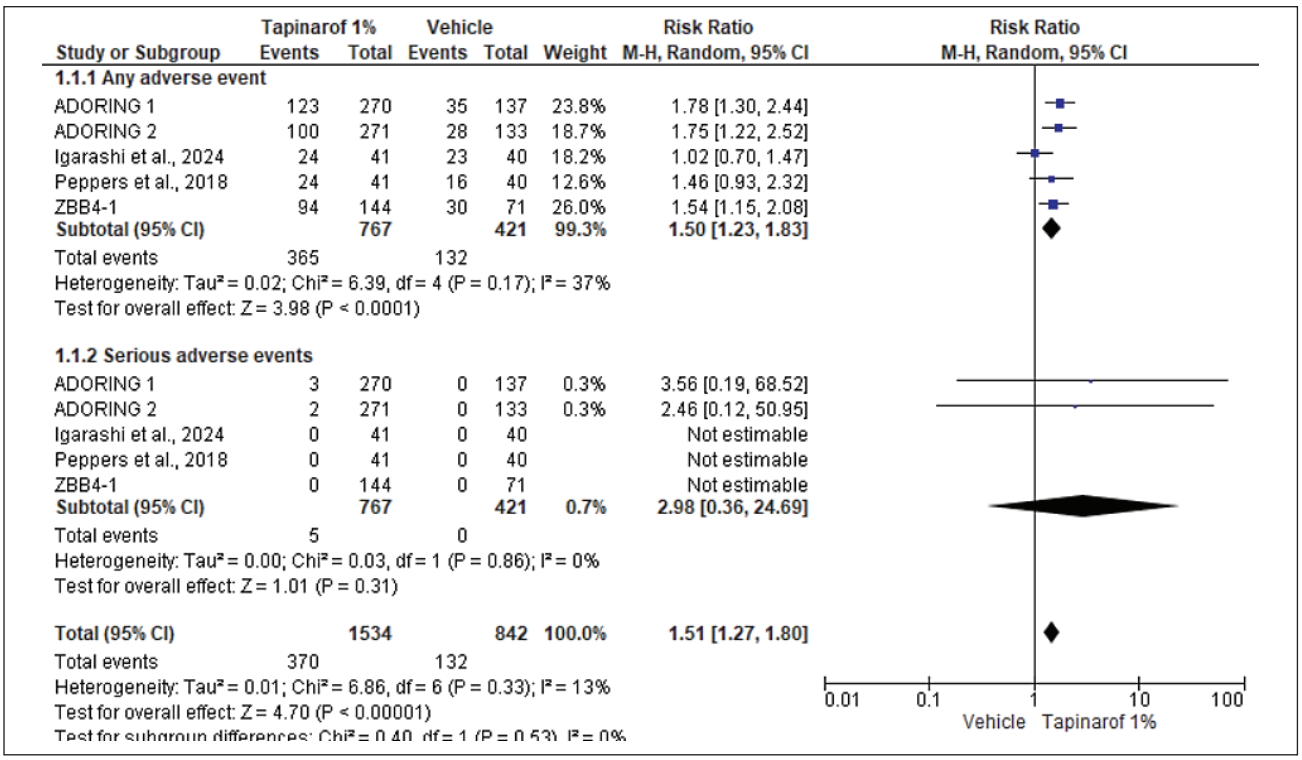


***Figure 5.*** *Risk of adverse events and serious adverse events.*

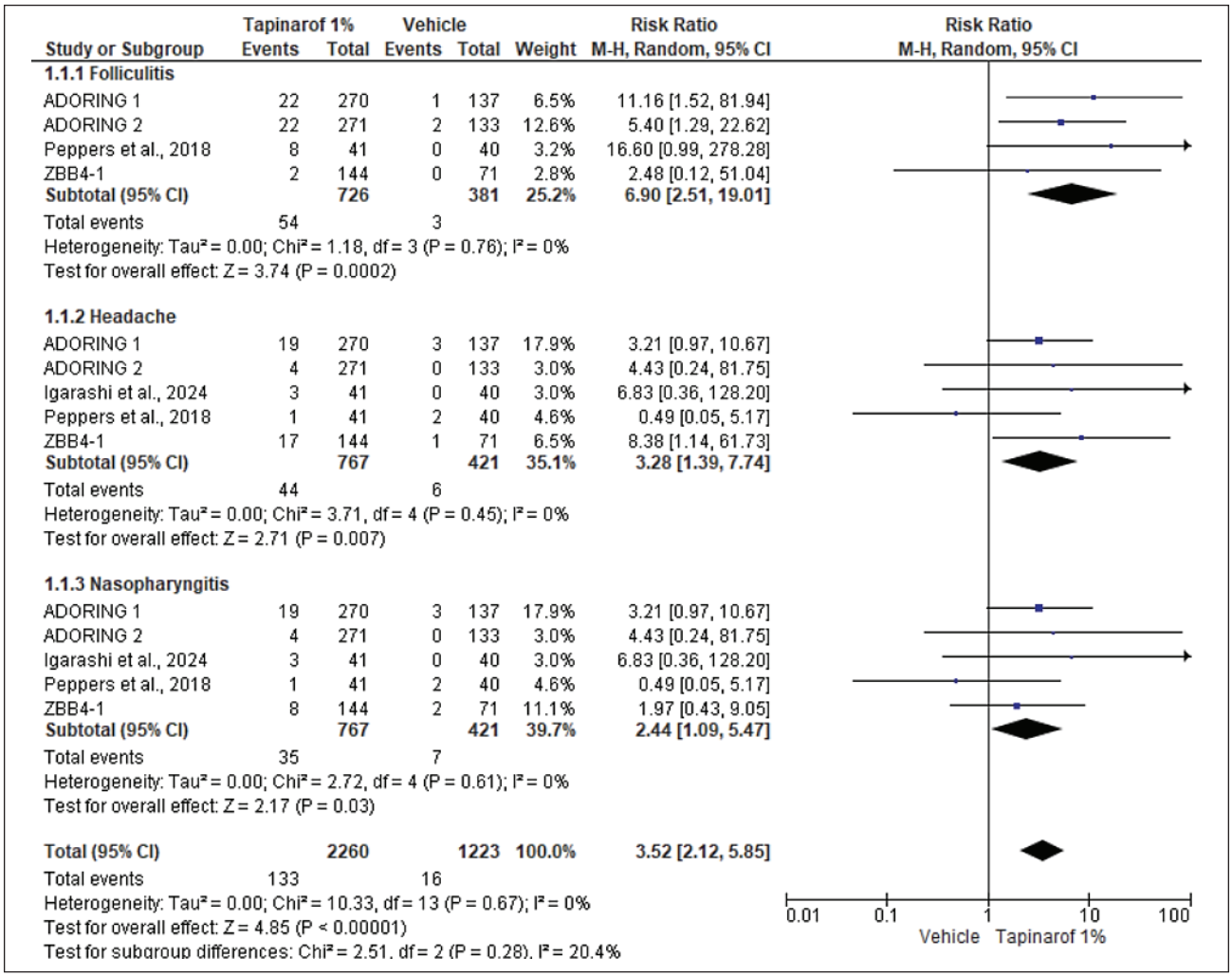


***Figure 6.*** *Risk of Nasopharyngitis, Headache, and Folliculitis.*

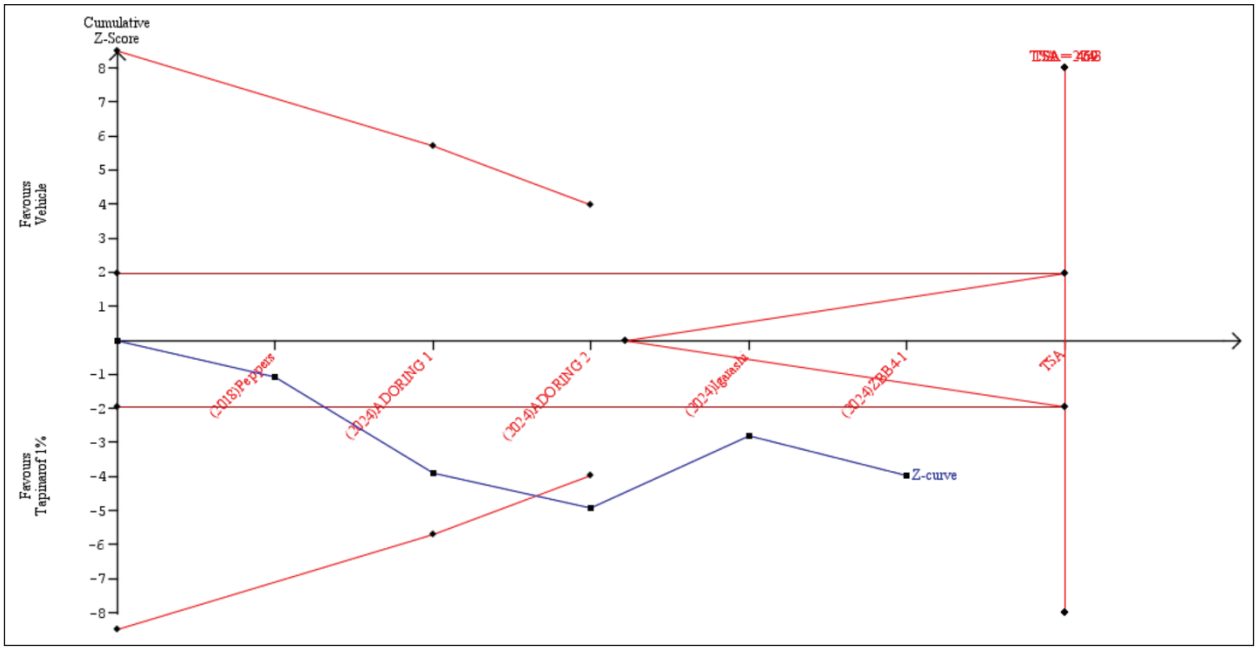


***Figure 7.*** *TSA analysis for the adverse events outcome.*

efficacy across key clinical endpoints, including IGA treatment success and EASI-75 response rates, while also highlighting a manageable safety profile. These results position tapinarof as a viable alternative to conventional therapies, particularly for patients requiring long-term management.

The primary outcome of this meta-analysis was IGA treatment success, defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline. Our results revealed that tapinarof 1% cream, administered once or twice daily, was significantly superior to vehicle in achieving IGA treatment success at both 8 and 12 weeks. At 8 weeks, tapinarof-treated patients were three times more likely to achieve IGA success compared to vehicle (RR: 3.21, 95% CI: 2.4-4.28, $p < 0.00001$), with low heterogeneity ($I^2 = 9\%$). By week 12, the effect remained strong, with a two-fold higher likelihood of success, and no heterogeneity ($I^2 = 0\%$). Subgroup analysis confirmed that both once-daily and twice-daily regimens were effective, though the twice-daily regimen showed a slightly higher response rate (RR: 2.21 *vs.* 1.85). These findings align with prior studies, which reported similar IGA success rates, further validating tapinarof's efficacy in diverse populations, including adolescents and adults [5,10].

The EASI-75 response rate, a secondary endpoint, also demonstrated significant improvements with tapinarof. At 8 weeks, patients treated with tapinarof 1% once daily were nearly three times more likely to achieve a 75% reduction in EASI score compared to vehicle (RR: 2.86, 95% CI: 2.04-4.02, $p < 0.00001$). By week 12, the response rate remained elevated. Notably, improvements in EASI scores were observed as early as week 1, underscoring tapinarof's rapid onset of action - a critical factor in enhancing patient adherence, particularly given the distressing nature of AD symptoms [13]. These results are consistent with earlier studies on tapinarof's mechanism of action, which involves upregulation of skin barrier proteins (e.g., filaggrin and involucrin) and suppression of type 2 inflammation via AhR modulation [7].

Current first-line topical treatments for AD include corticosteroids, calcineurin inhibitors, and PDE4 inhibitors [4]. While effective, these therapies are often limited by safety concerns, such as skin atrophy with prolonged corticosteroid use or burning sensations with calcineurin inhibitors [4]. Tapinarof offers a distinct advantage as a nonsteroidal agent with a novel mechanism of action, avoiding these pitfalls. In comparison to crisaborole, a PDE4 inhibitor, tapinarof demonstrates comparable or superior efficacy in achieving IGA success and EASI-75 responses, particularly in patients with moderate-to-severe AD [14]. Moreover, tapinarof's sustained efficacy beyond the treatment period - evidenced by maintained improvements for 4 weeks post-treatment - suggests potential remittive effects, a feature not commonly observed with existing topical therapies.

Tapinarof was generally well tolerated, with most adverse events (AEs) being mild to moderate in severity. The most common AEs included folliculitis (RR: 6.9, 95% CI: 2.5-19.01, $p = 0.0002$), headache (RR: 3.28, 95% CI: 1.39-7.74, $p = 0.007$), and nasopharyngitis (RR: 2.44, 95% CI: 1.09-5.47, $p = 0.03$). Folliculitis, though frequent, was typically noninfectious and resembled keratosis pilaris, resolving without intervention. Headache events were transient, with a median duration of 3 days, and showed no correlation with plasma tapinarof concentrations. Importantly, no significant difference in serious AEs was observed between tapinarof and vehicle groups, reinforcing its safety for long-term use.

The tolerability of tapinarof in pediatric populations is particularly noteworthy. In Japanese pediatric trials, tapinarof 0.5% and 1% creams were both effective and well tolerated, with no treatment-related serious

AEs reported. This is a critical finding, given the high prevalence of AD in children and the limited safe, long-term treatment options currently available.

This study has several important limitations that should be considered when interpreting the results. First, the analysis included a small number of studies, all of which were short-term (8-12 weeks), limiting insights into long-term efficacy and safety - a critical gap for a chronic condition like AD. Second, the lack of active comparator trials means tapinarof's efficacy relative to standard therapies (e.g., corticosteroids and calcineurin inhibitors) remains unclear, highlighting the need for future head-to-head studies. Third, most trials focused on mild-to-moderate AD, with limited representation of severe cases and diverse populations, potentially restricting generalizability. Finally, while the safety profile was favorable, longer-term data - especially in pediatric patients - are needed to fully assess risks with chronic use. Addressing these limitations in future research will better define tapinarof's role in AD management.

## Conclusion

This meta-analysis consolidates robust evidence supporting tapinarof as an effective and safe topical treatment for AD. Its unique mechanism of action, rapid clinical benefits, and sustained efficacy distinguish it from conventional therapies. While mild AEs such as folliculitis and headaches were observed, the overall risk-benefit profile remains highly favorable. Tapinarof represents a significant advancement in the AD therapeutic landscape, offering a much-needed nonsteroidal option for patients across all age groups. Future research should focus on long-term outcomes and comparative effectiveness to fully establish its place in clinical practice.

**Conflict of interest**
The authors declare that there is no conflict of interest regarding the publication of this article.

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*Supplementary content (If any) is available online.*

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