REVIEW

Expanding the Topical Therapeutic Landscape for Atopic Dermatitis: A Systematic Review

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BACKGROUND: Atopic dermatitis (AD) is a common chronic inflammatory disease. Despite its global prevalence, the current standard of care has remained unchanged for many years. Historically, first-line agents include topical corticosteroids (TCS) and topical calcineurin inhibitors (TCIs). However, these agents have significant limitations, including local and systemic adverse effects. In the last several years, novel topical therapeutic agents have been approved by the United States Food and Drug Administration (FDA) and more are being developed. **OBJECTIVE:** The present review aims to summarize these topical therapeutic advances and report their efficacy and safety relative to the existing armamentarium. **METHODS:** Three searches were conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the Agency for Healthcare Research and Quality Methods Guide for Effectiveness and Comparative Effectiveness Reviews guidelines. These included electronic searches of FDALabel (without date restriction) and PubMed and ClinicalTrials.gov (between April 8, 2020 and April 8, 2025). **RESULTS:** A total of 52 nongeneric, prescription topical therapeutic agents are currently approved by the FDA for AD, the majority of which are TCS (n=11; 52.4%) and TCIs (n=4; 19.0%). There have been several agents with novel mechanisms of action (n=3; 7.6%) approved by the FDA in recent years, including Janus kinase (JAK) inhibitors, nonsteroidal aryl hydrocarbon receptor (AhR) modulators, and phosphodiesterase 4 (PDE4) inhibitors. **CONCLUSION:** In the last 5 years, important innovations in the therapeutic landscape of AD have emerged. Treatments include novel JAK inhibitors, AhR modulators, and PDE4 inhibitors. Adopting these therapies as part of clinical care can improve patients' therapeutic outcomes and quality of life.
KEYWORDS: Atopic dermatitis, topical treatments, corticosteroids, nonsteroid, adverse effects, novel therapies

Atopic dermatitis (AD) is one of the most prevalent chronic inflammatory skin conditions worldwide, with millions of adults and children affected globally.[1] Historically, first-line therapy includes moisturizers and emollients to maintain skin hydration and barrier function, as well as topical corticosteroids (TCS).[2] In AD, low- to mid-level potency TCS are recommended as initial therapy, which can be raised to a higher potency in moderate-to-severe cases.[3] However, TCS are associated with many known cutaneous and systemic adverse effects (AE). Other historical topical therapies that do not contain corticosteroids include tacrolimus and pimecrolimus, topical calcineurin inhibitors (TCI), and crisaborole, a phosphodiesterase 4 (PDE4) inhibitor. These treatments have more favorable safety profiles and can be effective for anatomically sensitive areas (eg, face, eyelids).[4] Recent advancements in the therapeutic landscape have markedly transformed the management of AD, offering more targeted, effective, and personalized options than were previously available.

LIMITATIONS OF THE CURRENT STANDARD OF CARE

TCS are associated with numerous AEs, including skin atrophy, tachyphylaxis, permanent striae on the groin, inner thigh, and underarms, telangiectasias,[5] delayed wound healing,[6] perioral dermatitis, steroid acne, induction or exacerbation of rosacea, hypertrichosis, contact dermatitis, hypopigmentation, potential topical steroid withdrawal, and increased susceptibility to infections.[7] Systemic adverse effects can also arise due to suppression of the hypothalamic-pituitary-adrenal (HPA) axis, leading to hormonal dysregulation (caused by adrenal insufficiency), which can escalate to iatrogenic Cushing's disease.[7] Additionally, TCS can lead to hyperglycemia, particularly in individuals with pre-existing diabetes. Avascular necrosis has also been reported. Other rare systemic adverse effects include ocular defects (glaucoma, cataracts), electrolyte imbalances (edema, hypertension, hypocalcemia), and metabolic defects (osteopathy, decreased growth rate).[8] A recent expert consensus panel determined that the use of long-term TCS is associated with significant AEs as well as notable medicolegal risks for clinicians prescribing these medications.[8] While the adverse effects of TCI are milder than TCS, they also present with both local and systemic adverse effects. Local AEs include irritation (burning, itching, stinging),[9] erythema,[10] photosensitivity, and increased risk for skin infections and folliculitis.[11]

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TABLE 1. FDALabel search breakdown by category of topical approved for atopic dermatitis

COMPOUND	COUNT	%
Corticosteroid	11	52.4
Tricyclic antidepressant	2	9.5
Calcineurin inhibitor immunosuppressant	4	19.0
Phosphodiesterase 4 inhibitor	2	9.5
Janus kinase inhibitor; kinase inhibitor	1	4.8
Aryl hydrocarbon receptor agonist	1	4.8
Total	21	100

TABLE 2. FDA approvals for atopic dermatitis with novel mechanisms of action between 2020-2025

COMPOUND	BRAND NAME	PHASE III CLINICAL TRIALS	MECHANISM OF ACTION	FDA APPROVAL DATE
Ruxolitinib cream, 1.5%	Opzelura	NCT03745638, NCT03745651 (TRuE-AD1, TRuE-AD2)	Janus kinase inhibitor	09/21/21
Roflumilast cream, 0.15%	Zoryve	NCT04773587, NCT04773600 (INTEGUMENT1, INTEGUMENT2)	Enzyme phosphodiesterase 4 inhibition	07/09/24
Tapinarof cream, 1%	Vtama	NCT05014568, NCT05032859 (ADORING1, ADORING2)	Aryl hydrocarbon receptor modulation	12/16/24

FDA: United States Food and Drug Administration

The main theoretical systemic side effect of long-term TCI is lymphoma and skin cancers, for which there is a boxed warning.[12]

In the last decade, new insights into the mechanism of disease for AD have ignited research into finding new disease-specific therapeutic options for patients. As a result, several novel topical therapies have been approved by the United States (US) Food and Drug Administration (FDA) or are undergoing clinical trials. These advanced targeted topical therapies are reported to be safe and effective for treating AD.[8] Currently, limited literature critically analyzes these novel topical therapeutics relative to the existing armamentarium of topical therapies. The present review seeks to provide an overview of novel and upcoming topical therapies in the pipeline.

METHODS

FDALabel. A query was launched using the FDALabel website with the following criteria:

- Labeling Types: "HumanRX" and "Human OTC"
- Labeling Section: "Simple search" for "atopic dermatitis" within "1 indications and usage"
- Routes of Administration: "Topical"

This search generated 109 results. Results were filtered to include marketing categories New Drug Application (NDA) only (ie, excluding Abbreviated NDA, NDA Authorized Generic, OTC Monograph Final, and Unapproved drug other). This left 21 results, for which AD approval dates were manually confirmed using a public search engine. Missing drug classes were manually added.

PubMed. A literature review was conducted on PubMed. The review was based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[13] and Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews guidelines.[14] An electronic search of PubMed between April 8, 2020 and April 8, 2025 using the terms ("Atopic Dermatitis" AND "Topical") AND ("systematic review" OR "meta-analysis") was conducted.

Inclusion criteria. Studies published in English, between April 8, 2020 and April 8, 2025, and available in full text were included.

Exclusion criteria. Preprints and studies examining nontopical delivery mechanisms, probiotics, non-FDA–approved or over-the-counter (OTC) treatments/home remedies, indications other than AD, nonapproved drugs in the last 5 years, pediatric patients, or nonhuman participants were excluded.

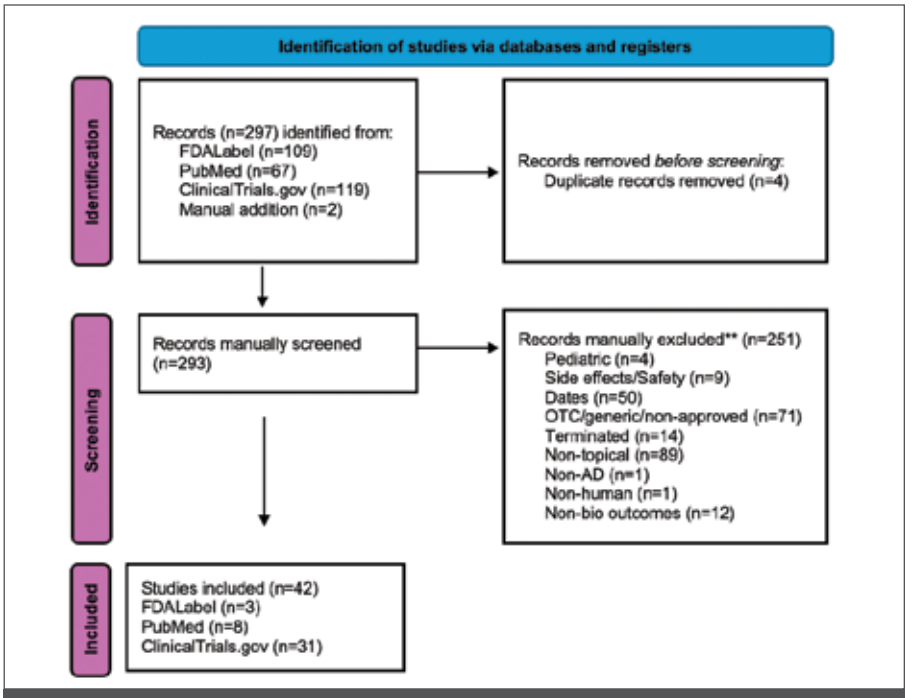

FIGURE 1. PubMed, FDALabel, and ClinicalTrials.gov searches
AD: atopic dermatitis; OTC: over-the-counter

ClinicalTrials.gov. A search on ClinicalTrials.gov was conducted to understand the volume and classes of compounds in the pipeline for future novel therapeutic applications. A search was launched using the following criteria: Atopic Dermatitis | Completed studies | Adult (18 - 64) | Interventional studies | Studies with results | Study completion from April 8, 2020 to April 8, 2025.

Inclusion criteria. Studies published in English, between April 8, 2020 and April 8, 2025, and available in full text were included.

Exclusion criteria. Preprints and studies examining nontopical delivery mechanisms, terminated trials, non-FDA–approved or OTC treatments/home remedies, indications other than AD, or pediatric participants were excluded.

RESULTS

FDALabel. TCS represented the largest share of the available 21 NDA approvals (n=11; 52.4%), followed by TCIs (n=4; 19.0%). Several agents with novel mechanisms of action were identified, including Janus kinase (JAK) inhibitors (4.8%), nonsteroidal aryl hydrocarbon receptor (AhR) modulators (4.8%), and PDE4 inhibitors (9.5%) (**Figure 1**; **Table 1**; **Table 2**). Three agents (7.6%) were approved by the FDA in the last 5 years (**Table 2**).

PubMed. Fifteen results matched the search criteria on PubMed and were filtered down to 8 (**Figure 1**; **Table 3**). Advanced targeted topical agents such as JAK inhibitors, AhR modulators, and PDE4 inhibitors were found to have efficacy for the treatment of AD with low rates of AEs.[15–18]

ClinicalTrials.gov. There were 119 results that were reduced to 31 trials upon secondary manual review (**Figure 1**; **Table 4**). Several novel JAK inhibitors were deemed safe and efficacious, including delgoticinib and ruxolitinib, while others failed to meet endpoints (ARQ-252).[19–26] Two phase 3 (crisaborole and roflumilast) and one phase 2 (difamilast) trials for PDE4 inhibitors demonstrated statistically significant results.[27–29] Other mechanisms of action were also examined with mixed findings and some AEs.[30–35] For example, a phase 2 clinical trial for an interleukin 1 receptor-associated kinase 4 (IRAK4) inhibitor did not demonstrate statistically significant improvement relative to vehicle, ending development for that compound.[36] Finally, 6 phase 3 trials were used to approve the agents tapinarof, roflumilast, and ruxolitinib (**Table 2**).[23,24,37–41]

Five studies (NCT04871711, NCT04872101, NCT05259722, NCT03683719, NCT04949841) examined delgoticinib, a JAK inhibitor, in phase 3 trials (DELTA1, DELTA2, and DELTA3) for the indication of chronic hand eczema (CHE).[20,25,26,42,43] Difamilast (PDE4 inhibitor) was another compound that was thoroughly investigated (NCT03961529).[44]

DISCUSSION

Nonsteroidal AhR modulator. The AHR/AHR-nuclear translocator (ARNT) system is a sensitive sensor for exogenous and endogenous small–molecule chemicals.[45] AhR expression has been shown to be increased in AD skin.[46] Once activated, the AhR/ARNT axis strengthens skin barrier function and accelerates epidermal terminal differentiation by upregulating filaggrin expression.[45] The FDA initially approved the first AhR modulator, tapinarof cream 1%, for plaque psoriasis in May 2022 and for AD in December 2024 in adults and children as young as 2 years. Two double-blind, randomized, vehicle-controlled phase 3 trials (NCT05014568, NCT05032859) were conducted.[37] A total of 407 and 406 patients were randomized in ADORING 1 and 2, respectively. A significantly higher proportion of patients treated with tapinarof achieved a Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score of 0 or 1 with at least a 2-grade improvement from baseline at Week 8 compared to those receiving the vehicle: 45.4% in the tapinarof arm compared with 13.9% with vehicle in ADORING 1 ($P<0.0001$) and 46.4% vs 18.0% in ADORING 2 ($P<0.0001$).[37] A greater proportion of patients treated with tapinarof achieved at least 75% improvement in the Eczema Area and Severity Index (EASI 75) at Week 8 compared to the vehicle group: 55.8% of tapinarof-treated patients vs 22.9% for vehicle in ADORING 1 ($P<0.0001$) and 59.1% vs 21.2% in ADORING 2 ($P<0.0001$).[37] Patients reported rapid and significant reductions in pruritus with tapinarof treatment compared to the vehicle.[37] Common AEs (occurring in ≥5% of patients) included folliculitis, headache, and nasopharyngitis.[37] Treatment-emergent adverse events (TEAEs) were reported in 70% of patients compared to 38% with vehicle, and these events were primarily mild or moderate in severity.[37] Notably, fewer patients discontinued treatment due to AEs in the tapinarof group compared to the vehicle group.[37]

Two recent Japanese phase 3 studies evaluating tapinarof cream, 1%, for AD shared similar efficacy endpoints. In the ZBB4-1 randomized, double-blind, vehicle-controlled trial, the primary endpoint was the proportion of patients who achieved an Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement at Week 8; this was reached by 20.24% of tapinarof-treated patients vs 2.24% on vehicle ($P=0.0007$).[47] EASI 75 was achieved by 40.3% in the tapinarof group vs 4.3% on vehicle ($P<0.0001$).[47] In the open-label, 52-week ZBB4-2 study, sustained efficacy was observed, with IGA success rates of 28.1% at Week 16, 32.3% at Week 24, and 41.3% at Week 52. EASI 75 response rates increased over time from 53.3% at Week 16 to 76.6% at Week 52.[47] Across both trials, most AEs were mild or moderate. Common AEs included folliculitis, acne, and headache, and no new safety concerns were identified over the 52-week treatment period.[47]

JAK inhibitors. The JAK/signal transducer and activator of transcription (STAT) pathway is a significant cell signaling pathway involved in cytokine production, well characterized for mediating the inflammatory immune response, among other functions.[48] It facilitates the production of inflammatory cytokines interleukin (IL) 4, IL-5, IL-13, and IL-31, which drive the activation of helper T-cell 2 cell-mediated immunity, a pathway crucial for the pathogenesis of AD.[49] Blocking this inflammatory pathway has been shown to alleviate symptoms of AD.[48,49] Regarding topical agents, research has indicated promise for both first-generation and second-generation JAK inhibitors for AD, including studies on delgocitinib (a pan-JAK inhibitor), ruxolitinib (a JAK1/JAK2 inhibitor), tofacitinib (a pan-JAK inhibitor), ifidancitinib (a JAK1/JAK3 inhibitor), upadacitinib (a JAK1 inhibitor), and brepocitinib (a TYK2/JAK1 inhibitor).[48,49]

Most recently, two phase 3 trials for ruxolitinib (TRuE-AD1 and TRuE-AD2) involving patients aged ≥12 years with mild-to-moderate AD found promising results.[40] At Week 8, 53.8% to 54.5% of patients using ruxolitinib cream, 1.5%, twice daily achieved Investigator's Global Assessment–Treatment Success (IGA–TS), defined as a score of 0 (clear) or 1 (almost clear) with ≥2-grade improvement from baseline, compared to 11.5% to 15.1% in the vehicle group.[40] Additionally, 61.8% to 62.0% achieved EASI 75 vs 24.6% to 29.6% with vehicle.[40] Treatment over 52 weeks resulted in 74.1% to 77.8% of patients achieving IGA 0 or 1.[41] AEs were mostly mild; the most common were nasopharyngitis and application site reactions.[40] After 1 year of treatment, only 7.4% experienced treatment-related AEs.[41]

Delgocitinib, a topical pan-JAK inhibitor, was approved in Japan in January 2020 for the treatment of AD in patients aged 16 years and older. In the US, delgocitinib received FDA approval for the treatment of moderate to severe CHE in adults in July 2025. In the European Union, delgocitinib cream received approval in September 2024 for the treatment of moderate to severe CHE in adults.

A phase 2B randomized, double-blind, vehicle-controlled study evaluated the efficacy and safety of brepocitinib, 1%, in adults with mild-to-moderate AD over 6 weeks.[50] Patients treated with brepocitinib 1% twice daily achieved a 75% reduction in EASI scores at Week 6, compared to a

TABLE 3. PubMed results

STUDY TITLE	INTERVENTIONS	# OF STUDIES	ENROLLMENT	RESULTS
Chu et al[15]	Pimecrolimus, low-dose tacrolimus, TCS, delgocitinib, ruxolitinib	219	43,123	Pimecrolimus: Demonstrated improvement in 6 of 7 assessed outcomes, ranking among the most effective for two outcomes. High-dose tacrolimus (0.1%): Showed improvement in five outcomes. Low-dose tacrolimus (0.03%): Improved five outcomes, ranking among the best for one. Moderate-potency TCS (Group 5): Improved six outcomes, being among the best for three. Delgocitinib and ruxolitinib: Improved for outcomes each, with delgocitinib among the best for two and ruxolitinib for one.
Dhar et al[4]	TCS, tacrolimus	4	101	Pooled data from two randomized controlled trials suggested that sequential therapy with TCS and tacrolimus was comparable to monotherapy or emollients. The overall effect was not significant (P=0.33), with high heterogeneity between studies (I^2=92%, P=0.0005)
Lax et al[51]	TCS, tacrolimus, JAK inhibitors, PDE4 inhibitors	291	45,846	Potent TCS, JAK inhibitors, and tacrolimus 0.1% were consistently ranked as among the most effective topical anti-inflammatory treatments for eczema, and PDE4 inhibitors as among the least effective. Mild TCS and tapinarof 1% were ranked amongst the least effective treatments in 3 of 5 efficacy networks. TCI and crisaborole 2% were ranked most likely to cause local application site reactions and TCS least likely. There was found no evidence for increased skin thinning with short-term TCS but an increase with longer-term use.
Chen et al[17]	Ruxolitinib	33	9,662	Ruxolitinib 1.5% twice daily was notably effective, with an RR of 4.14 for EASI 75.
Li et al[18]	JAK inhibitors	14	3,822	JAK inhibitors significantly improved both the IGA response and the EASI score compared to placebo. The most substantial improvements were observed by Week 4. Topical JAK inhibitors demonstrated higher efficacy than oral formulations.
Fahrbach et al[52]	Crisaborole 2%	9	1,522	Crisaborole ointment, 2%, demonstrated superior efficacy compared to vehicle and pimecrolimus cream, 1%, and was comparable to tacrolimus 0.1% and 0.03%. Patients using crisaborole were significantly more likely to achieve an ISGA score of clear (0) or almost clear (1) at 28–42 days. The hazard ratio for crisaborole vs vehicle was 2.07 (95% credible interval: 1.76–2.36), and vs pimecrolimus was 1.62 (95% credible interval: 1.04–2.48).
Gupta et al[16]	Ruxolitinib	40	6,482	Ruxolitinib cream, 1.5%, was ranked third in efficacy, following tacrolimus, 0.1%, and potent TCSs. The OR for ruxolitinib was 5.64 (95% CI: 1.26–25.25), indicating a significant improvement over vehicle treatments. Roflumilast cream, 0.15%, ranked lower in efficacy, with an OR of 2.43 (95% CI: 0.65–9.01), suggesting a less pronounced effect compared to ruxolitinib.
Thom et al[53]	Crisaborole, pimecrolimus, tacrolimus	2	938	Crisaborole ointment, 2%, was associated with higher odds of achieving an ISGA score of 0 or 1 (clear or almost clear) compared to both pimecrolimus 1% cream and tacrolimus 0.03% ointment. Crisaborole vs pimecrolimus: OR of 2.03 (95% CI: 1.45–2.85); ESS=627, reduced from 1,021; P<0.001). Crisaborole vs tacrolimus: OR of 1.50 (95% CI: 1.09–2.05; ESS = 311, reduced from 1,021; P=0.012).

EASI: Eczema Area and Severity Index; EASI 75: ≥ 75% improvement in EASI; ESS: effective sample size; IGA: Investigator Global Assessment; ISGA: Investigator Static Global Assessment; JAK: Janus kinase; OR: odds ratio; PDE4: phosphodiesterase 4; RR: relative risk; TCI: topical calcineurin inhibitor; TCS: topical corticosteroid

47.6% reduction in the vehicle group.[50] Once-daily applications of brepocitinib 1% and 3% resulted in EASI score reductions of 70.1% and 67.9%, respectively, vs 44.4% in the once-daily vehicle group.[50] A 90% reduction in EASI score (EASI 90) was observed in 27.0% to 41.7% of patients using brepocitinib, compared to 10.8% in the once-daily vehicle group and 8.3% with the twice-daily vehicle.[50] Topical brepocitinib was well tolerated, with no serious treatment-related AEs reported. The most common adverse effects were mild application site reactions.[50]

PDE4 inhibitors. Roflumilast cream, 0.15%, was approved by the FDA for AD in patients aged 6 years and older in 2024. Clinical trials showed a significantly greater proportion of patients treated with roflumilast cream achieved vIGA-AD success at Week 4 compared to those receiving the vehicle cream.[38,54] Of the patients treated with roflumilast, 42% achieved EASI 75 at Week 4, compared to 19.7% in the vehicle group (P<0.0001).[38,54] Those treated with roflumilast also had a higher rate of achieving IGA success (32.0% vs 15.2%, P<0.001).[38] Further, 30.2% of patients treated with roflumilast experienced a ≥4-point reduction in Worst Itch Numeric Rating Scale at Week 4 vs 12.4% in the vehicle group (P<0.01).[38,54] Roflumilast cream was well tolerated, with most TEAEs being mild-to-moderate in severity.[46,47] Serious AEs were experienced by 0.9% of patients, and 1.4% to 1.8% discontinued roflumilast due to any TEAE at 4 weeks.[38,54] The most common TEAEs included headache, nausea, vomiting, diarrhea, and upper respiratory tract infection.[38]

Difamilast is another PDE4 inhibitor approved in Japan for AD. A phase 3 randomized, double-blind, vehicle-controlled study assessed the efficacy of difamilast ointment, 1%, applied twice daily for 4 weeks in adult patients with mild-to-moderate AD.[44] At Week 4, 38.46% of patients achieved IGA 0 or 1 with a ≥2-grade improvement from baseline, compared to 12.64% in the vehicle group (P<0.0001).[44] The difamilast group had statistically significant improvements across EASI reductions, including 58.24% vs 25.82% achieving at least 50% improvement in EASI (P<0.001), 42.86% vs 13.19% for EASI 75 (P<0.0001), and 24.73% vs 5.49% for EASI 90 (P<0.0001), respectively.[44] Additionally, a significant mean percent change in overall EASI score from baseline was observed for the difamilast group compared

with vehicle at Week 1 (–32.6% vs –10.4%, respectively; $P<0.0001$) and was sustained until Week 4 (–49.1% vs –10.5%, respectively; $P<0.0001$).[44] TEAEs were mostly mild or moderate and occurred less frequently in the difamilast group than in the vehicle group.[44]

CONCLUSION

The therapeutic landscape for AD has been transformed through development of new, advanced targeted therapies. Short- and long-term use of TCS have substantial AEs, prompting a search for novel mechanisms of action to address this significant unmet need. Advanced agents have been introduced in the last five years using mechanisms such as JAK inhibition, PDE4 inhibition, and AhR modulation. Collectively, these advances mark a new era in the treatment of AD, offering more precise, effective, and safe options tailored to the disease's immunologic complexity. Incorporating these therapies into treatment protocols may substantially improve disease management and patient quality of life.

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TABLE 4. ClinicalTrials.gov results

STUDY TITLE (NCT NUMBER)	INTERVENTIONS	ENROLLMENT	PHASES	CONCLUSION
Dose ranging study to assess efficacy, safety, tolerability, and pharmacokinetics of PF-06700841 topical cream in participants with mild or moderate atopic dermatitis[22] (**NCT03903822**)	Brepocitinib, a TYK2/JAK1 inhibitor	292	2	**Efficacy:** The study met its primary endpoint, demonstrating that brepocitinib cream led to significant improvements in EASI scores compared to placebo. Notably, 42% of participants treated with the 3% once-daily formulation achieved at least EASI 90 by Week 6. **Safety:** The treatment was generally well tolerated. AEs were monitored, including changes in vital signs, laboratory values, and ECG parameters. No significant safety concerns were reported.
Study of TER-101 topical ointment in subjects with atopic dermatitis[30] (**NCT04753034**)	TER-101	63	2	**Efficacy:** Changes in pruritus severity were modest: the number of participants reporting no itch decreased slightly from 18 at baseline to 15 on Day 29, while those with moderate pruritus increased from 2 to 10, indicating limited or mixed improvement in itch relief. Erythema severity on Day 29 also remained present, with some cases of severe erythema noted, though exact numbers were not detailed. Clinical benefit in reducing symptoms, like itch and redness appear limited. **Safety:** TER-101 was generally well tolerated, and no serious safety concerns were highlighted.
Safety and efficacy study of EVO101 topical cream in atopic dermatitis[36] (**NCT05579899**)	IRAK4 inhibitor	119	2	**Efficacy:** The study did not demonstrate a statistically significant improvement in IGA scores for EVO101 compared to the vehicle cream. **Safety:** EVO101 was generally well tolerated, with no significant safety concerns reported during the 8-week treatment period.
Study of ATI-1777 in adult patients with moderate or severe atopic dermatitis[21] (**NCT04598269**)	JAK1/3 inhibitor	50	2	**Efficacy:** The study aimed to assess the preliminary clinical efficacy of ATI-1777 in reducing AD severity. Specific efficacy results, such as the magnitude of EASI score reduction or responder rates, were not provided in the available documents. **Safety:** Safety assessments included monitoring TEAEs, SAEs, laboratory parameters, vital signs, and ECGs. Detailed safety outcomes were not specified in the available documents. **Pharmacokinetics:** Plasma of ATI-1777 were measured to evaluate systemic exposure. These data were not shared.
Topical ruxolitinib evaluation in atopic dermatitis Study 1 (TRuE AD1) - an efficacy and safety study of ruxolitinib cream in adolescents and adults with atopic dermatitis[24] (**NCT03745638**)	Ruxolitinib cream	631	3	**Efficacy:** At Week 8, significantly more patients achieved IGA-TS with ruxolitinib cream compared to vehicle. (50.0% with ruxolitinib 0.75%, 53.8% with ruxolitinib 1.5%, and 15.1% with vehicle; $P<0.0001$ for both comparisons). Significant itch reductions were reported within 12 hours of the first application of 1.5% ruxolitinib cream compared to vehicle ($P<0.05$) . **Safety:** In the LTS period, patients continued treatment for up to 52 weeks. The percentage of patients who achieved IGA scores of 0 or 1 was sustained or further increased with 1.5% ruxolitinib cream. Mean affected body surface area remained low (<3%), and application site reactions occurred in 1.8% of adolescent patients, with no SAEs reported.
A study to evaluate long-term maintenance treatment with once daily crisaborole ointment 2% in pediatric and adult participants with mild-to-moderate atopic dermatitis[29] (**NCT04040192**)	Crisaborole 2%	620	3	**Efficacy:** Patients treated with once-daily crisaborole had a median time to first flare of 111 days, compared to 30 days for those on vehicle. This difference was statistically significant ($P<0.001$), indicating crisaborole significantly extended flare-free time. Over the 52-week maintenance period, 40.6% of patients on crisaborole experienced a flare vs 57.1% of patients on vehicle, a relative risk reduction of approximately 29% in flare occurrence with crisaborole. **Safety:** TEAEs in the maintenance phase were mild and included application site pain (reported in ≤4% of patients), URTIs, and nasopharyngitis (typical for this population). No serious AEs were attributed to crisaborole. Discontinuation due to AEs was rare (≤2%).
TRuE AD2 - an efficacy and safety study of ruxolitinib cream in adolescents and adults with atopic dermatitis[23] (**NCT03745651**)	Ruxolitinib cream	618	3	**Efficacy:** *Primary Endpoint (IGA-TS at Week 8):* • Ruxolitinib 0.75%: 39.0% of patients achieved IGA-TS • Ruxolitinib 1.5%: 51.3% achieved IGA-TS • Vehicle: 7.6% achieved IGA-TS Both ruxolitinib groups showed statistically significant improvements compared to vehicle ($P<0.0001$). *EASI 75 Response at Week 8:* • Ruxolitinib 0.75%: 51.5% of patients achieved EASI 75 • Ruxolitinib 1.5%: 61.8% achieved EASI 75 • Vehicle: 14.4% achieved EASI 75 Both ruxolitinib groups demonstrated significant improvements over vehicle ($P<0.0001$). *Itch Reduction (NRS4) at Week 8:* A significantly higher proportion of patients in both ruxolitinib groups achieved a ≥4-point improvement in itch severity compared to vehicle. **Safety:** TEAEs were comparable across groups, occurring in 29.4%, 26.3%, and 33.6% of patients treated with ruxolitinb 0.75%, ruxolitinib 1.5%, and vehicle, respectively. SAEs occurred in 0.8%, 0.6%, and 0.8%, respectively. No new safety signals were observed.

TABLE 4 CONTINUED. ClinicalTrials.gov results

STUDY TITLE	INTERVENTIONS	ENROLLMENT	PHASES	CONCLUSION
Topically applied AMTX-100 CF for adult patients with mild-to-moderate atopic dermatitis[31] (**NCT04313400**)	NTCI, which targets two nuclear transport shuttles, importin α5 and importin β1	91	1, 2	**Efficacy:** While specific numerical results from the trial have not been publicly disclosed, preclinical studies demonstrated that NTCI effectively reduced the expression of pro-inflammatory cytokines and chemokines such as TSLP, IL-4, IL-6, IL-13, and IL-33, which are implicated in the pathogenesis of AD. NTCI also suppressed skin infiltration by inflammatory cells, including eosinophils, macrophages, and CD4+ T lymphocytes, and reduced epidermal hyperplasia. **Safety:** The treatment was well tolerated in preclinical models, with no significant adverse effects reported. The Phase 1 portion of the clinical trial aimed to confirm these findings in human subjects.
Dose-ranging trial to evaluate delgocitinib cream 1, 3, 8, and 20 mg/g compared to delgocitinib cream vehicle over an 8-week treatment period in adult subjects with atopic dermatitis[55] (**NCT03725722**)	Delgocitinib cream	251	2	**Efficacy:** The 20 mg/g delgocitinib group showed a mean EASI score reduction of 7.6 points at Week 8, compared to a 1.9-point reduction in the vehicle group ($P<0.05$). All delgocitinib doses demonstrated significant separation from the vehicle group by week 1, with the highest dose showing the greatest efficacy. EASI 75 response rates and DLQI scores improved significantly in the delgocitinib groups, particularly at higher doses. Baseline itch scores averaged 6.1. By week 8, itch scores decreased by 4.6 points in the 20 mg/g group, compared to a 1.0-point reduction in the vehicle group ($P<0.05$). Significant itch relief was observed as early as Day 2 in all but the lowest dose group. **Safety:** The safety profile of delgocitinib was comparable to that of the vehicle cream, with no significant differences in adverse events reported.
Trial of PDE4 inhibition with roflumilast for the management of atopic dermatitis (INTEGUMENT-II)[28] (**NCT04773600**)	Roflumilast cream	683	3	**Efficacy:** A significantly greater proportion of patients treated with roflumilast cream achieved vIGA-AD success at week 4 compared to those receiving the vehicle cream. Of patients receiving roflumilast, 42% achieved EASI 75 at Week 4, compared to 19.7% in the vehicle group ($P<0.0001$); 30.2% of patients treated with roflumilast cream experienced a ≥4-point reduction in WI-NRS at Week 4 vs 12.4% in the vehicle group ($P<0.01$). **Safety:** Roflumilast cream was well tolerated, with most TEAEs being mild to moderate in severity. The most common TEAEs included headache, nausea, vomiting, diarrhea, and URTI.
Phase 2a study of the safety, tolerability, and pharmacokinetics of topically administered PRN473 (SAR444727) in patients with mild-to-moderate atopic dermatitis[35] (**NCT04992546**)	Atuzabrutinib: Covalent BTK inhibitor	39	2	**Efficacy:** At Week 4, the mean reduction in EASI score from baseline was –24.8% with twice-daily atuzabrutinib vs –23.1% with placebo. The difference was not statistically significant, indicating no meaningful efficacy over placebo. The proportion of patients achieving IGA score of 0/1 with ≥2-grade improvement at Week 4 was 15.5% with twice-daily atuzabrutinib 0.5% vs 17.2% with placebo. The average reduction in pruritus NRS at Week 4 was comparable across all groups, with no statistical superiority for the atuzabrutinib arms. **Safety:** Topical atuzabrutinib was generally well tolerated. Most common adverse events were mild application site reactions (eg, erythema, itching), with similar incidence across all groups. No treatment-related SAEs reported.
A 24 week trial to compare the efficacy and safety of delgocitinib cream 20 mg/g twice-daily with alitretinoin capsules once-daily in adult participants with severe chronic hand eczema[26] (**NCT05259722**)	Delgocitinib cream	513	3	**Efficacy:** At week 12, the delgocitinib group showed a significantly greater reduction in HECSI scores compared to the alitretinoin group (LSM change: –67.6 vs –51.5; difference –16.1; 95% CI: –23.3 to –8.9; $P<0.0001$). Delgocitinib cream also demonstrated superiority over alitretinoin in all key secondary endpoints, including IGA-CHE treatment success and HRQoL improvements. **Safety:** Fewer patients reported adverse events in the delgocitinib group (49%) compared to the alitretinoin group (76%). Common adverse events included headache (4% in delgocitinib vs 32% in alitretinoin), nasopharyngitis (12% vs 14%), and nausea (<1% vs 6%).
Efficacy and safety of delgocitinib cream in adults with moderate-to-severe chronic hand eczema[25] (**NCT04871711**)	Delgocitinib cream	487	3	**Efficacy:** At Week 16, 20% of patients in the delgocitinib group achieved treatment success, defined as an IGA-CHE score of 0 (clear) or 1 (almost clear) with at least a two-step improvement from baseline. In contrast, 10% of patients in the vehicle group achieved this outcome ($p \leq 0.0055$). Delgocitinib-treated patients also demonstrated significant improvements in secondary endpoints, including reductions in HECSI scores and improvements in quality-of-life measures. **Safety:** The incidence of TEAEs was similar between the delgocitinib (45%) and vehicle (51%) groups. The most common adverse events were COVID-19 and nasopharyngitis, occurring in at least 2% of patients in both groups.

TABLE 4 CONTINUED. ClinicalTrials.gov results

STUDY TITLE	INTERVENTIONS	ENROLLMENT	PHASES	CONCLUSION
Efficacy and safety of delgocitinib cream in adults with moderate-to-severe chronic hand eczema (DELTA 2)[20] (**NCT04872101**)	Delgocitinib cream	473	3	**Efficacy:** At Week 16, 29% of patients in the delgocitinib group achieved IGA-CHE treatment success, defined as an IGA-CHE score of 0 (clear) or 1 (almost clear) with at least a two-step improvement from baseline. In contrast, 7% of patients in the vehicle group achieved this outcome ($P<0.0001$). Delgocitinib-treated patients also demonstrated significant improvements in secondary endpoints, including reductions in HECSI scores and improvements in quality-of-life measures. **Safety:** The incidence of TEAEs was similar between the delgocitinib (46%) and vehicle (45%) groups. The most common adverse events were COVID-19, nasopharyngitis, and headache, occurring in at least 2% of patients in both groups.
Study to assess efficacy, safety, tolerability and pharmacokinetics of PF-07038124 ointment in participants with atopic dermatitis or plaque psoriasis[27] (**NCT04664153**)	PDE4 inhibitor	104	2	**Efficacy:** In AD patients, the LSM percent change in EASI score from baseline to Week 6 was −74.9% for PF-07038124 vs −35.5% for the vehicle, with a treatment difference of −39.4% ($P<0.001$). In plaque psoriasis patients, the LSM percent change in PASI score was −4.8 for PF-07038124 vs 0.1 for the vehicle, with a treatment difference of −4.9 ($P<0.001$). Of patients with AD receiving PF-07038124, 41.2% achieved ≥4-point improvement in PP-NRS, compared to 13.8% on vehicle. A significantly greater proportion of AD patients on PF-07038124 achieved IGA treatment success (IGA score of 0 or 1 with ≥2-point improvement) compared to those on vehicle ($P=0.0004$). **Safety:** The incidence of TEAEs was similar between groups: 25% with PF-07038124 and 26.5% with vehicle for AD patients, and 17.6% vs 35.3%, respectively, for plaque psoriasis patients. No application site reactions were reported with PF-07038124. The most common adverse events included COVID-19 and nasopharyngitis, each occurring in at least 2% of participants in both groups.
Phase 2b dose-ranging trial to evaluate delgocitinib cream 1, 3, 8, and 20 mg/g compared to delgocitinib cream vehicle over a 16-week treatment period in adult subjects with chronic hand eczema[19] (**NCT03683719**)	Delgocitinib cream	258	2	**Efficacy:** The 20 mg/g concentration of delgocitinib cream demonstrated the most significant improvement in the primary endpoint, the IGA-CHE, compared to the vehicle. Secondary endpoints, including reductions in HECSI and improvements in patient-reported outcomes such as itch and pain, also favored the 20 mg/g concentration. **Safety:** The safety profile of delgocitinib cream was consistent across all concentrations, with no new safety concerns identified. The most common adverse events were mild and included application site reactions.
Ruxolitinib cream in participants with facial and/or neck atopic dermatitis involvement[56] (**NCT05127421**)	Ruxolitinib cream	77	2	**Efficacy:** For the primary endpoint (Week 4 head/neck EASI 75), 37.0% of ruxolitinib users achieved ≥75% improvement vs 17.4% in the vehicle group ($P=0.091$), a nonsignificant trend favoring ruxolitinib. **Safety:** Ruxolitinib cream was well tolerated, including on face and neck. Application site reactions occurred in 1.9% of ruxolitinib patients (vs 8.7% with vehicle) with mostly mild irritations or burning. TEAEs occurred in ~21.7% in the ruxolitinib group; none led to discontinuation, and no serious TEAEs were reported.
The purpose of the study is to evaluate the effect of ruxolitinib cream on itch in participants with atopic dermatitis[57] (**NCT04839380**)	Ruxolitinib cream	49	2	**Efficacy:** Patients reported a 3.4-point drop on PP-NRS score by Day 2 that increased to −5.7 points by Day 29, reflecting rapid and sustained itch relief. Notably, patients experienced significant relief as early as 15 minutes post-application, reaching −4.2 points by 4 hours on Day 1. Secondary outcomes also showed strong clinical responses: EASI 75 was achieved by 84.4% by Day 15 and 95.5% by Day 29, while IGA treatment success (IGA 0/1 with a ≥2-grade improvement) reached 45.5% at Day 8, rising to 77.3% by Day 29. **Safety:** TEAEs were reported in 30.6% of participants, all Grade 1 or 2, with no serious events (COVID-19, back pain, headache, nasopharyngitis, URTI; each in ≥4% of patients). There was 1 treatment-related event of mild acne at the application site. No discontinuations or serious AEs were reported.
Long-term trial of OPA-15406 ointment in adult and pediatric patients with atopic dermatitis[58] (**NCT03961529**)	Difamilast	366	3	**Efficacy:** Among adults using 1% ointment, EASI 75 response rates improved from 9.6% at Week 4 to 55.4% at Week 52. Pediatric patients treated with either 0.3% or 1% difamilast showed even stronger responses, with EASI 75 rates rising from 32.0% at Week 4 to 73.5% by Week 52. Investigator's Global Assessment (IGA) success rates also improved steadily over time: in adults, from 3.6% at Week 4 to 34.9% at Week 52, and in pediatric patients, from 15.5% to 52.5% over the same period. **Safety:** TEAEs occurred in 72.3% of adults and 89.0% of pediatric patients, and the majority were mild to moderate. Discontinuations due to TEAEs were 7.8% in adults and 3.5% in children. The most common TEAEs included mild cases of AD flare, acne, and pigmentation disorders. A small number of infections such as folliculitis and Kaposi varicelliform eruption were reported, with only one considered to be treatment related. Notably, no systemic or gastrointestinal adverse effects occurred, and no pediatric patients reported stinging or burning sensations.

TABLE 4 CONTINUED. ClinicalTrials.gov results

STUDY TITLE	INTERVENTIONS	ENROLLMENT	PHASES	CONCLUSION
Efficacy and safety of SHR0302, a highly selective Janus kinase 1 inhibitor, in patients with moderate-to-severe atopic dermatitis: a phase II randomized clinical trial[59] (**NCT04162899**)	Oral SHR0302, a selective JAK1 inhibitor	105	2	**Efficacy:** After 12 weeks of treatment, 54.3% of patients receiving 8 mg and 25.7% receiving 4 mg achieved IGA 0/1 with ≥2-grade improvement, compared to only 5.7% on placebo. Corresponding EASI 75 response rates were 74.3% (8 mg) and 51.4% (4 mg) vs 22.9% for placebo. Additionally, itch reduction of ≥3 points on the NRS was reported in 74.3% (8 mg) and 65.7% (4 mg), compared to 22.9% in the placebo group. **Safety:** TEAEs occurred in 60% to 69% of treated patients, mostly mild in severity. Three SAEs, all AD flares, were reported.
Efficacy and safety of IDP-124 lotion for the treatment of moderate-to-severe atopic dermatitis in pediatric and adult subjects[60] (**NCT03058783**)	Difamilast	328	3	**Efficacy:** By Week 8, 20.3% of patients using IDP-124 achieved ≥2-point improvement in IGA vs 7.7% with vehicle. Mean EASI reduction was 44.3% for IDP-124 compared to 21.4% with vehicle, with notable gains in EASI 50, EASI 75, and EASI 90 responder rates. **Safety:** No serious treatment-related adverse events or systemic safety concerns were reported.
Efficacy and safety of IDP-124 lotion for the treatment of moderate-to-severe atopic dermatitis in pediatric and adult Subjects (301)[61] (**NCT03002571**)	Unknown	338	3	Trial was unsuccessful and development was discontinued.
Trial of PDE4 inhibition with roflumilast for the management of atopic dermatitis[28] (**NCT04773587**)	Roflumilast cream	654	3	**Efficacy:** 32.0% of patients treated with roflumilast cream achieved vIGA-AD success at Week 4 compared to 15.2% with vehicle ($P<0.001$). **Safety:** TEAEs were reported in about 21% to 23% of roflumilast-treated patients, slightly higher than in vehicle groups (13% to 16%). Most adverse events were mild and localized, with application-site irritation being minimal, with over 95% of patients reported no signs of irritation and more than 90% experienced no or only mild sensations at the application site. Treatment-related AEs occurred in approximately 6% of patients. SAEs were rare (<1%) and included conditions such as atopic dermatitis worsening and staphylococcal scalded skin syndrome, which were deemed unlikely related to the treatment.
A study to evaluate the anti-pruritic effectiveness of ASN008 in adults with mild-to-moderate atopic dermatitis[62] (**NCT05870865**)	ASN008, a permanently charged sodium-channel blocker	144	2	Results not published.
A study to learn about the study medicine (PF-07038124) in patients with mild-to-moderate atopic dermatitis or mild-to-severe plaque psoriasis[63] (**NCT05375955**)	Topical PDE4 inhibitor	263	2	**Efficacy:** Neither the 0.01% nor 0.03% doses met the primary endpoint (IGA 0/1 plus ≥2 point improvement vs vehicle) at Week 12. Response rates were 23.8% (0.01%) and 21.4% (0.03%) vs 11.4% with vehicle improvements that were not statistically significant. **Safety:** PF-07038124 was well tolerated. No deaths occurred, and only three SAEs, unrelated to treatment, were reported. No treatment-related AEs were reported in the psoriasis cohort, and there were no treatment-related contact dermatitis, acne, or folliculitis cases in the AD groups.
Safety and efficacy of ARQ-252 cream in subjects with chronic hand eczema[64] (**NCT04378569**)	Topical JAK1 inhibitor	230	1, 2	**Efficacy:** The trial did not meet its primary endpoint. None of the ARQ-252 dose groups (which included 0.1% and 0.3%) achieved a statistically significant improvement over vehicle in clearing or almost clearing hand eczema (IGA-CHE success) by Week 12/16. **Safety:** ARQ-252 cream was well tolerated, with no unexpected safety concerns. No treatment-related systemic adverse effects were reported, and tolerability was similar to vehicle.
Open-label multisite extension trial in subjects who completed the DELTA 1 or DELTA 2 trials[65] (**NCT04949841**)	Delgocitinib cream	801	3	**Efficacy:** Patients who initially achieved IGA-CHE 0/1 maintained these clear/almost-clear outcomes, with rates holding steady from 24.6% at DELTA 3 baseline to 30.0% by Week 36. Likewise, HECSI-75/90 responses remained high. The baseline to Week 36 HECSI 75 rose from 51.8% to 58.6% and HECSI 90 from 31.8% to 36.6%. **Safety:** The most common adverse events were mild to moderate nasopharyngitis (16.0%) and COVID-19 (16.7%). Approximately 17% of participants discontinued (mostly due to inefficacy or withdrawal), while 3.6% used rescue treatment. No increase in AE rates compared to parent studies was observed.

TABLE 4 CONTINUED. ClinicalTrials.gov results

STUDY TITLE	INTERVENTIONS	ENROLLMENT	PHASES	CONCLUSION
Safety and efficacy of a topical scalp treatment for dry scalp conditions in children and adult[66] (**NCT03830177**)	Crisaborole	77	1, 2	**Efficacy:** Crisaborole twice daily for 28 days led to significantly greater improvements in ISGA: 32.1% of treated patients achieved clear or almost clear skin with a ≥2-point improvement vs 21.8% in the vehicle group ($P<0.001$). **Safety:** TEAEs were primarily mild to moderate in severity, occurring at similar rates between groups. Application-site pain (burning/stinging) was the most common AE, affecting approximately 4% to 6% of crisaborole users vs 1% to 2% with vehicle. SAEs and discontinuations due to AEs were rare (<1% in both groups), with no treatment-related serious AEs reported.
Crisaborole for Chinese and Japanese Subjects (≥2 Years of Age) with mild-to-moderate atopic dermatitis[67] (**NCT04360187**)	Crisaborole	391	3	**Efficacy:** At Day 29, crisaborole-treated patients showed a significantly greater mean reduction in EASI score (−66.3% vs −50.2% with vehicle; LS mean difference ≈ −16.2%; $P=0.0002$). ISGA improvement (≥1 grade) occurred in 43.2% vs 33.4%, and ISGA success (0/1 with ≥2-grade improvement) in 31.7% vs 21.5% ($P=0.0124$ and $P=0.0078$, respectively). A greater itch reduction was also observed at Week 4 (PP-NRS LSM change −1.98 vs −1.08; $P=0.0009$). **Safety:** Treatment-related AEs occurred in ~27.4% of crisaborole patients vs ~22.5% of vehicle-treated individuals. The most common AE was application-site pain (17.8%). No serious treatment-related AEs were reported, and there were no new safety signals, including no significant lab, vital sign, or systemic abnormalities.
Tapinarof for the treatment of atopic dermatitis in children and adults (DMVT-505-3102)[68] (**NCT05032859**)	Tapinarof	406	3	**Efficacy:** At Week 8, 46.4% of tapinarof-treated patients achieved a vIGA-AD score of clear (0) or almost clear (1) with at least a 2-grade improvement from baseline, compared to 18% on vehicle ($P<0.0001$). Additionally, 59.1% achieved a ≥75% improvement in the EASI 75, and 52.8% of patients aged ≥12 years with a baseline PP-NRS score ≥4 achieved a ≥4-point reduction in pruritus ($P=0.0015$). **Safety:** Adverse events primarily mild-to-moderate. The study had a low discontinuation rate due to adverse events (1.5% for tapinarof vs 3.0% for vehicle). Notable adverse events included contact dermatitis (1.1% tapinarof vs 1.5% vehicle) and follicular events (8.9% tapinarof vs 1.5% vehicle).
Long term extension study of tapinarof cream, 1% for subjects with atopic dermatitis[69] (**NCT05142774**)	Tapinarof	728	3	**Efficacy:** 51.2% of patients achieved complete disease clearance, defined as a vIGA-AD score of 0. Additionally, in an integrated analysis of all ADORING studies, 73% of patients achieved a vIGA-AD score of 0 or 1 with at ≥2-grade improvement from baseline. Furthermore, 80.7% of patients achieved EASI 75. Among patients aged 12 years and older with a baseline PP-NRS score ≥4, 77.9% achieved a ≥4-point reduction in pruritus. **Safety:** The most common adverse events included folliculitis and contact dermatitis.

AD: atopic dermatitis; AE: adverse event; BTK: Bruton tyrosine kinase; CD: clusters of differentiation; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; EASI 75: at least a 75% improvement in EASI score; EASI 90: at least a 90% improvement in EASI score; ECG: electrocardiogram; HECSI: Hand Eczema Severity Index; HECSI 75: at least a 75% improvement in HESCI score; HECSI 90: at least a 90% improvement in HESCI score; HRQoL: health-related quality of life; IGA: Investigator Global Assessment; IGA-CHE: IGA of Chronic Hand Eczema; IGA-TS: IGA-Treatment Success; IL: interleukin; IRAK4: interleukin 1 receptor-associated kinase 4; ISGA: Investigator Static Global Assessment; JAK: Janus kinase; LSM: least squares mean; NRS: numeric rating scale; NTCI: nuclear transport checkpoint inhibitor; PASI: Psoriasis Area and Severity Index; PP-NRS: Peak Pruritus NRS; SAE: serious adverse event; TEAE: treatment-emergent adverse event; TSLP: thymic stromal lymphopoietin; TYK2: tyrosine kinase 2; URTI: upper respiratory tract infection; vIGA-AD: Validated Global Assessment for Atopic Dermatitis; WI-NRS: Worst Itch NRS

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