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Tapinarof 1% Cream in Plaque Psoriasis: Mechanism of Action, Pharmacology, Clinical Efficacy, and Emerging Therapeutic Horizons — A Systematic Review

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Abstract

Background. Psoriasis is a chronic, immune-mediated inflammatory dermatosis characterized by the hyperproliferation of keratinocytes and the formation of erythematous, scaly plaques. Traditional topical therapies, primarily corticosteroids and vitamin D analogs, are often limited by long-term safety concerns, such as skin atrophy. Tapinarof, a first-in-class, non-steroidal,

small-molecule therapeutic agent that modulates the aryl hydrocarbon receptor (AhR), has recently emerged as a novel topical intervention.

Aim. This paper evaluates the clinical efficacy, safety profile, and unique mechanism of action of tapinarof cream, 1%, for the treatment of plaque psoriasis in adults.

Materials and Methods. A comprehensive review of the PSOARING 1 and PSOARING 2 Phase III clinical trials was conducted. Data were synthesized to assess primary endpoints, specifically the Physician's Global Assessment (PGA) success—defined as a score of "clear" (0) or "almost clear" (1) with a minimum 2-grade improvement from baseline.

Results. Clinical data demonstrate that tapinarof 1% cream, administered once daily, significantly improves Psoriasis Area and Severity Index (PASI) scores and PGA success compared to vehicle controls. Notably, tapinarof exhibits a unique "remittive effect," maintaining clinical response for a median of four months post-discontinuation. While generally well-tolerated, the most frequently reported adverse events include localized folliculitis and contact dermatitis, which were typically mild to moderate in severity.

Conclusions Tapinarof 1% cream represents a significant shift in the topical management of psoriasis, offering a potent, non-steroidal alternative with a durable off-treatment effect. Its ability to modulate the AhR pathway addresses both the inflammatory cascade and skin barrier dysfunction, positioning it as a foundational therapy for patients seeking long-term disease control without the risks associated with chronic corticosteroid use.

Keywords: Tapinarof; Psoriasis Vulgaris; Aryl Hydrocarbon Receptor (AhR); PSOARING Trials; Topical Therapeutics

Introduction

Plaque psoriasis, also known as psoriasis vulgaris, is recognized as the most common type of psoriasis. Its etiology is multifactorial, involving genetic, immunologic, and environmental factors [1,2]. It affects roughly 125 million people worldwide. The frequency of occurrence appears to be equal in both sexes; males may be more likely to be exposed to a more severe form of the disease [3]. It shows a lower prevalence in Asian and African countries and an increased incidence in the Caucasian and Scandinavian population [4]. Psoriasis vulgaris clinical manifestation usually consists of sharply circumscribed, oval plaques. The initial

clinical presentation of psoriasis typically manifests as discrete erythematous macules or papules. Primary lesions demonstrate a propensity for peripheral extension, subsequently undergoing coalescence to form expansive, well-demarcated plaques exceeding several centimeters in diameter [5]. The pathogenesis of psoriasis is characterized by a dysregulated interplay between innate and adaptive immunity, specifically dominated by the IL-23/Th17 signaling cascade [4]. Inflammation can occur in predisposed individuals due to injury, sun exposure, infection, or stress. Pattern recognition receptors (PRRs) play a huge role in response to those triggers [6]. Primary effector functions are mediated by T-lymphocytes, which secrete IL-17, IL-21, IL-22, and IFN-gamma, alongside dendritic cells (DCs) that produce TNF-alpha, IL-6, IL-20, IL-23, and nitric oxide (NO) [6]. Keratinocytes (KCs) further propagate this environment by expressing antimicrobial peptides (AMPs), IL-20, and chemotactic cytokines [6]. The coalescence of these populations establishes a critical pathogenic feedback loop, defined by a functional triad: IL-23-secreting dendritic cells, IL-17-producing Th17 cells, and activated keratinocytes [6]. This reciprocal signaling axis drives the chronic inflammation and epidermal hyperplasia characteristic of the disease.

The IL-23/IL-17A pathway has been a focus of biological therapies, which have been highly successful in treatment [7]. Systemic treatment is not necessary in most cases because many patients present with mild disease and require topical therapy rather than systemic therapy. Topical corticosteroids remain the most commonly used treatment for plaque psoriasis [8]. Limitations of prolonged corticosteroid therapy include skin thinning, potential adverse effects, and loss of efficacy [9]. Other topical treatment options include retinoids and vitamin D derivatives [10]. Although complete remission remains elusive, effective management of flare-ups and symptoms can significantly improve patients' quality of life, thereby encouraging clinicians to explore promising options such as Tapinarof.

Tapinarof cream 1% (VTAMA®) is an aryl hydrocarbon receptor (AhR) agonist [11] that targets key drivers of inflammation, empowering clinicians with a novel approach to disrupt the disease's self-sustaining cycle and promote skin health. Tapinarof simultaneously targets the immune and structural components of the disease. Specifically, it suppresses IL-23 production by dendritic cells and inhibits IL-17A/F secretion by Th17 cells [7,9], thereby neutralizing the primary drivers of inflammation. Concurrently, tapinarof acts directly on activated keratinocytes to upregulate essential barrier proteins and induce terminal differentiation [9], effectively breaking the self-sustaining inflammatory loop and promoting long-term skin homeostasis.

2. Mechanism of action

2.1 Aryl Hydrocarbon Receptor (AhR) Modulation

The Aryl Hydrocarbon Receptor (AhR) is a ligand-activated transcription factor expressed in epidermal keratinocytes [12]. As a ligand-dependent transcription factor, the AhR is susceptible to activation by a heterogeneous group of small molecules. Anthropogenic pollutants such as dioxins and combustion byproducts, along with naturally occurring nutritional metabolites and plant-derived phytochemicals, act as potent agonists that initiate AhR-mediated signaling pathways [12]. Extensive investigation has established the Aryl Hydrocarbon Receptor (AhR) as a fundamental mediator of systemic homeostasis, characterized by domain structures and regulatory functions that remain highly conserved across the phylogeny of multicellular organisms. Upon agonism by a specific ligand, the cytosolic AhR undergoes nuclear translocation to facilitate heterodimerization with the AhR Nuclear Translocator (ARNT) [13]. This activated transcriptional complex targets xenobiotic-responsive elements (XREs), thereby inducing the expression of the cytochrome P450 (CYP) enzymatic suite, specifically CYP1A1, CYP1A2, and CYP1B1 [13]. Unlike other members of the basic helix-loop-helix/Per-Arnt-Sim (bHLH/PAS) superfamily, AhR serves as the primary sensor for naturally occurring xenobiotics [12,13]. Consequently, genetic polymorphisms or dysregulation within the AhR signaling axis are implicated in diverse pathologies, typically manifesting through aberrant metabolic processing, disrupted gene transcription, and compromised immunological integrity [13].

Tapinarof is a high-affinity exogenous ligand for the Aryl Hydrocarbon Receptor (AhR) [11]. Upon ligation, the tapinarof-AhR complex undergoes nuclear translocation and heterodimerization with the AhR Nuclear Translocator (ARNT) [14]. This complex subsequently orchestrates a specific transcriptional program by binding to Xenobiotic Response Elements (XREs), leading to the dual-action attenuation of the IL-23/Th17 axis and the upregulation of essential epidermal barrier proteins, including filaggrin and loricrin [11]. This selective modulation distinguishes tapinarof from traditional AhR agonists, favoring therapeutic resolution over xenobiotic toxicity.

2.2 Downregulation of Pro-inflammatory Cytokines:

Investigations into the Aryl Hydrocarbon Receptor (AhR) have demonstrated its pivotal role in modulating immune transcriptional regulation, particularly in the lineage commitment of Th17 and regulatory T cells (Tregs) [15]. Given that the clinical neutralization of IL-17A

significantly ameliorates plaque psoriasis [15], the AhR-mediated downregulation of IL-17 is a primary mechanism underlying tapinarof's therapeutic efficacy. To evaluate these effects, a skin-resident immune cell activation (sRICA) model was utilized—a liquid-air interface culture of ex vivo human skin designed to simulate in situ immunocompetent cell activation [15]. This model effectively replicates the cytokine milieu characteristic of inflammatory dermatoses, specifically the Type 17/Type 22 profile (IL-17A, IL-17F, and IL-22) (Table 1) [16]. Under these experimental conditions, tapinarof treatment resulted in an approximate 50% reduction in IL-17A mRNA expression (Table 1). Conversely, robust induction of IL-22 levels was observed—a divergent cytokine response pattern consistent with previously documented effects of AhR agonism (Table 1) [17].

Table 1. Summary of Tapinarof's effects on cytokines and its clinical significance [16,17]

Cytokine	*Change with Tapinarof*	*Clinical Signifcance*
IL-17A	~50% Reduction	Attenuation of neutrophil recruitment and epidermal scaling
IL-17F	Downregulation	Reduction in synergistic inflammatory signaling
IL-22	Increase	Suggests a distinct Aryl Hydrocarbon Receptor mediated differentiation pathway

2.3 Antioxidant activity

In addition to its established role in direct immunomodulation, tapinarof acts via AhR-Nrf2 signaling crosstalk to significantly augment the skin's endogenous antioxidant capacity. The chronic inflammatory milieu of a psoriatic plaque is characterized by an accumulation of

reactive oxygen species (ROS) and reactive nitrogen species, which act as second messengers, amplifying pro-inflammatory cytokine production and exacerbating tissue damage [16]. Tapinarof serves as a molecular catalyst for the induction of Phase II detoxifying enzymes, effectively neutralizing this localized oxidative burden and disrupting the oxidative-stress-driven "feed-forward" inflammatory cycle [12]. The pharmacological activation of the Nuclear factor erythroid 2-related factor 2 (Nrf2) pathway by tapinarof facilitates the stabilization and nuclear translocation of this master antioxidant transcription factor [18]. Once situated within the nucleus, Nrf2 orchestrates a comprehensive cytoprotective program by binding to Antioxidant Response Elements (ARE) [15]. This transcriptional event leads to the robust upregulation of essential enzymes, including heme oxygenase-1 (HO-1), NAD(P)H: quinone oxidoreductase 1 (NQO1), and superoxide dismutase (SOD) [15,19]. By bolstering these enzymatic defenses, tapinarof not only safeguards keratinocytes against ROS-induced apoptosis and DNA damage but also effectively restores cellular redox homeostasis [12]. This transition from an oxidative to a balanced, homeostatic state is critical, as it modulates the triggers underlying innate immune activation, thereby providing a stable physiological environment that supports long-term clinical remission. Consequently, the antioxidant activity of tapinarof is a vital, multidimensional component of its efficacy, bridging the gap between immunosuppression and structural epidermal repair.

3. Pharmacokinetics and pharmacodynamics

The clinical utility of Tapinarof 1% is rooted in its selective modulation of the aryl hydrocarbon receptor (AhR). As a member of the bHLH/PAS protein family, AhR functions as a molecular sensor; in the quiescent state, it remains localized to the cytosol, chaperoned by a multi-protein assembly including heat shock protein 90 (HSP90), until ligand activation occurs [19]. Upon tapinarof binding, the anti-inflammatory effects are mediated by AhR activation across multiple cell types, including keratinocytes, fibroblasts, and immune cells in the target tissue—human skin [15]. Upon ligand ligation, the Aryl Hydrocarbon Receptor (AhR) undergoes nuclear translocation and subsequent heterodimerization with the AhR nuclear translocator (ARNT). This activated ligand–AhR–ARNT complex, in association with the p300 transcriptional coactivator, binds specifically to xenobiotic response elements (XREs) within the genomic promoter regions. This molecular recruitment orchestrates the transcriptional upregulation of a diverse suite of target genes essential for both metabolic homeostasis and epidermal integrity, notably including the cytochrome P450 enzyme CYP1A1, the transcription factor OVOL1, and

critical cornified envelope proteins such as filaggrin (FLG), loricrin (LOR), and involucrin (IVL) [16]. The pharmacodynamic consequences of this signaling cascade act through three principal, interconnected mechanisms.

The first mechanism is immunomodulation. Upon ligation, tapinarof-mediated AhR signaling orchestrates a multifaceted modulation of the cutaneous immune network, effectively recalibrating the activity of pathogenic lymphocyte subsets. In the context of atopic dermatitis, tapinarof attenuates the Th2-polarized response, thereby reducing the production of type 2 cytokines [14]. In relation to plaque psoriasis, the agent targets the IL-23/Th17 axis by suppressing Th17 cell activation and notably inhibiting the formation, persistence, and cytokine secretion of tissue-resident memory (TRM) cells [14]. More specifically, tapinarof downregulates pro-inflammatory Th2 cytokines — including IL-4, IL-5, and IL-13, implicated in atopic dermatitis — as well as Th17 cytokines IL-17A and IL-17F, implicated in plaque psoriasis [20]. Using the imiquimod-induced psoriasiform murine model, research has shown that topical tapinarof significantly mitigates erythema, epidermal hyperplasia, and the local inflammatory cytokine burden in AhR-competent subjects [15]. Conversely, these therapeutic benefits were entirely abrogated in AhR-deficient cohorts [15]. These divergent outcomes provide definitive evidence that the pharmacological efficacy of tapinarof is strictly contingent on functional Aryl Hydrocarbon Receptor (AhR) signaling, thereby confirming AhR as the primary molecular target for its anti-psoriatic activity [15].

The secondary mechanism of action pertains to the restoration of epidermal barrier homeostasis. Upon ligation, the AhR-mediated signaling cascade activates the downstream transcription factor OVOL1. This molecular event subsequently orchestrates the upregulation of loricrin and filaggrin, foundational structural proteins indispensable for reinforcing the cornified envelope and ensuring the functional integrity of the cutaneous permeability barrier [21]. Following its nuclear translocation, OVOL1 functions as a pivotal transcriptional regulator, facilitating the upregulation of FLG and LOR expression. However, the modulation of IVL remains independent of this specific signaling axis, suggesting that the induction of involucrin is governed by distinct, parallel regulatory mechanisms within the AhR framework [16].

Furthermore, pharmacological agonism of the AhR by tapinarof has been shown to augment the synthesis of ceramide-based barrier lipids and to induce the expression of essential structural proteins, specifically hornerin and involucrin [14]. This coordinated molecular response facilitates comprehensive reinforcement of the lipid matrix and cornified envelope, thereby further promoting the restoration of epidermal barrier function and cutaneous homeostasis [14]. This barrier-normalizing effect provides a mechanistic rationale for the remittive activity

observed clinically, in which disease control persists beyond the period of active drug administration.

The tertiary mechanism of action encompasses a dual-faceted antioxidant response. Tapinarof facilitates activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling axis, which subsequently orchestrates the induction of an endogenous battery of cytoprotective enzymes [21]. This molecular recruitment mitigates localized oxidative stress and safeguards cellular components from the deleterious effects of reactive oxygen species (ROS) [21]. The Nrf2 transcription factor orchestrates the transcriptional upregulation of a robust suite of cytoprotective enzymes, most notably heme oxygenase 1 (HMOX1) and NAD(P)H dehydrogenase quinone 1 (NQO1) [19]. These biocatalysts function synergistically to quench reactive oxygen species (ROS), thereby neutralizing oxidative stress and insulating the cutaneous microenvironment from inflammatory damage [19]. Complementing this transcriptional response, tapinarof also leads to marked reductions in chemically induced ROS levels through direct scavenging, an activity distinct from the classical AhR ligand mechanism [15]. This dual antioxidant profile—characterized by the transcriptional induction of endogenous cytoprotective systems alongside direct radical scavenging is especially pertinent in the pathogenesis of atopic dermatitis. In this condition, the Th2-type cytokines IL-4 and IL-13 drive the accumulation of reactive oxygen species (ROS), which subsequently amplify STAT6 phosphorylation and perpetuate the inflammatory cascade [16]. As a dual AhR/Nrf2 agonist, tapinarof facilitates the upregulation of essential antioxidative enzymes, such as NQO1 and HMOX1. These enzymes effectively quench IL-4/IL-13-induced ROS, thereby restoring the functional activity of protein-tyrosine phosphatase non-receptor type 1 (PTPN1) [16]. This restoration leads to the subsequent dephosphorylation of STAT6, thereby dampening the feed-forward inflammatory signaling inherent in the disease [16].

The pharmacokinetic profile of tapinarof 1% cream is characterized by a high degree of cutaneous sequestration coupled with negligible systemic bioavailability. Under maximal-use conditions, the topical administration of a once-daily regimen resulted in plasma concentrations falling below the lower limit of quantification (LLoQ: 50 pg/mL) in approximately 68% of analyzed pharmacokinetic samples. This localized disposition underscores the drug's targeted efficacy within the epidermal and dermal compartments while minimizing the potential for systemic exposure [11]. Initial pharmacokinetic assessments on Day 1 revealed a mean peak plasma concentration (*Cmax*) of 0.9 ng/mL and a mean area under the curve (*AUC0-last*) of 4.1 ng·h/mL [11]. These exposure metrics were observed following administration of a mean daily dose of 5.23 g, with a mean affected body surface area (BSA) of 27.2%, and a time to maximum

concentration (*Tmax*) of 2-5 hours post-application [11]. By Day 29 of the treatment period, both the mean and median *Cmax* values had declined markedly to 0.116 ng/mL and 0.059 ng/mL, respectively [20]. This temporal decline in systemic bioavailability was further evidenced by a geometric mean *AUC0-las*t of 0.321 ng·h/mL, indicating a significant reduction in total drug exposure with repeated topical administration [20]. In terms of distribution, *in vitro* investigations have corroborated that tapinarof exhibits extensive plasma protein binding, estimated at approximately 99% [22]. This high affinity for circulating proteins significantly restricts the free, pharmacologically active fraction of the drug within the systemic compartment [22]. Concerning its metabolic profile, tapinarof undergoes extensive hepatic biotransformation, mediated primarily by oxidative pathways, sulfation, and glucuronidation [22]. Notably, the molecule does not appear to modulate the activity of cytochrome P450 enzymes or membrane transporters [22]. This lack of metabolic interference has been corroborated clinically; both *in vitro* drug interaction assessments and pharmacokinetic evaluations in patients with psoriasis have failed to identify any clinically significant drug–drug interactions involving tapinarof [22]. Consistent with a pharmacological profile characterized by negligible systemic bioavailability, topical administration of tapinarof has demonstrated no discernible impact on renal or hepatic physiological parameters [14]. This absence of organ-specific toxicity was consistent across a wide range of therapeutic doses and dosing intervals, further validating the safety margin afforded by its highly localized disposition [14]. At the approved recommended dosage, tapinarof does not prolong the QTc interval to any clinically relevant extent [11]. Collectively, these data illustrate that tapinarof 1% cream possesses a favorable pharmacokinetic profile characterized by high-fidelity sequestration at the site of administration [14]. By prioritizing cutaneous bioavailability over systemic circulation, the formulation successfully circumvents the common pitfalls of systemic therapies, including off-target metabolic effects, potential drug-drug interactions, and generalized safety concerns [14].

4. Clinical Trials

Phase 1: Clinical Trial

The formal clinical evaluation of tapinarof cream for inflammatory dermatoses commenced with an open-label, two-cohort sequential Phase 1 study (Study 201851; NCT02466152), the findings of which were detailed by Bissonnette et al. (2018) in *Clinical Pharmacology in Drug Development* [23]. This foundational trial was structured to evaluate the systemic pharmacokinetics, safety profile, and preliminary efficacy of tapinarof in an adult

population presenting with moderate-to-severe atopic dermatitis [23]. The study enrolled 11 participants, who were stratified into two treatment arms: five received the 2% formulation, and six received the 1% cream [23]. Both cohorts used a twice-daily dosing regimen across all affected cutaneous areas—except the scalp and periorbital regions—for 20 days, concluding with a final application on Day 21 [23]. To capture peak and trough systemic exposure, participants underwent comprehensive pharmacokinetic blood sampling during on-site stays on Days 1 and 21. Serial clinical and laboratory assessments were performed throughout the study at Days 2, 3, 4, 7, 14, and 22 to monitor for adverse events and therapeutic response [23]. Pharmacokinetic analysis revealed that tapinarof was systemically absorbed, with quantifiable plasma concentrations observed across both treatment cohorts [23]. Exposure metrics were generally proportional to the concentration, with the 2% formulation yielding higher plasma levels than the 1% cream [23]. Notably, systemic concentrations declined between Day 1 and Day 21, suggesting a lack of drug accumulation with repeated administration. The median time to maximum plasma concentration (*Tmax*) was within a 1- to 4-hour window for both groups [23]. While preliminary efficacy data appeared comparable between the two concentrations, the 1% formulation demonstrated a superior safety profile.

In contrast, the 2% cohort experienced a higher rate of attrition, with three participants discontinuing the study due to systemic adverse events (AEs) [23]. These findings underscored the 1% cream as the optimal balance of therapeutic activity and clinical tolerability. Based on these collective findings, the 1% concentration was prioritized for subsequent clinical development. This decision was informed by the 2% formulation's comparable therapeutic efficacy, coupled with a markedly lower incidence of adverse events (AEs) [23]. Although this Phase 1 investigation was conducted in an atopic dermatitis cohort, it established the foundational pharmacokinetic framework for the broader tapinarof program, demonstrating that the 1% cream facilitates potent localized activity while maintaining an optimal systemic safety margin [23]. The most frequently reported adverse events included headache, folliculitis, diarrhea, nausea, and vomiting [23]. Notably, these reactions were transient and typically resolved within 24 hours of treatment cessation. Clinically, the 1% formulation exhibited superior tolerability, with side effects significantly more prevalent among participants using the 2% cream [23].

Phase 2: Clinical Trial

The Phase 2b dose-finding study, conducted by Robbins et al. (2019), represented a critical transition from early safety evaluations to the optimization of tapinarof for the treatment of plaque psoriasis [24]. This multicenter, randomized, double-anonymized, vehicle-controlled

trial utilized a robust six-arm design to evaluate the comparative efficacy and safety of different concentrations and dosing frequencies [24]. Spanning 40 sites across the United States, Canada, and Japan between November 2015 and October 2016, the study recruited a diverse cohort of adults aged 18 to 65 [24]. Eligible participants were required to present with stable disease involving 1% to 15% of their body surface area and a baseline Physician Global Assessment (PGA) score of 2 or higher, thereby providing a standardized clinical baseline to assess the dose-response relationship 23 rigorously. Participants were stratified into six distinct treatment arms to evaluate a range of potencies and frequencies: tapinarof 1% (once or twice daily), tapinarof 0.5% (once or twice daily), and corresponding vehicle control groups (once or twice daily) [24]. Secondary outcomes centered on the Psoriasis Area and Severity Index (PASI), specifically measuring the percentage of patients attaining significant reductions in total disease burden. The study's longitudinal structure comprised a 4-week screening period, a 12-week active intervention phase, and a concluding 4-week follow-up to monitor post-treatment safety and response durability [24]. Of the 290 patients originally screened, 227 were randomized, and 175 completed the 12-week treatment phase. The primary efficacy endpoint was a PGA score of 0 (clear) or 1 (almost clear) with a minimum 2-grade improvement from baseline at Week 12 and [24]. Treatment success defined by PGA 0 or 1 and a 2-grade improvement at Week 12 was statistically significantly higher in all tapinarof groups compared to vehicle: 65% (1% twice daily), 56% (1% once daily), 46% (0.5% twice daily), and 36% (0.5% once daily), versus 11% (vehicle twice daily) and 5% (vehicle once daily) [24]. Secondary efficacy measures mirrored these results, with tapinarof cohorts exhibiting a markedly higher incidence of PASI 75 (75% improvement in the Psoriasis Area and Severity Index); specifically, 65% and 56% of patients in the 1% BID and QD groups, respectively, reached this threshold [24]. The therapeutic onset was rapid, becoming evident by Week 2, and clinical benefits persisted for 4 weeks post-treatment, indicating a sustained remissive effect [24]. Furthermore, tapinarof treatment led to a significant reduction in affected body surface area (BSA), with decreases ranging from 3.6% to 4.9%, compared to a negligible 1% to 1.6% in the vehicle cohorts [24]. The most prevalent treatment-emergent adverse events (TEAEs) observed across the tapinarof cohorts included folliculitis (10%) and contact dermatitis (3%). Other less frequent reactions reported by participants were localized skin irritation, allergic dermatitis, and headache (1%) [24].

Secondary efficacy outcomes, detailed by Stein Gold and colleagues in a 2021 companion paper in the *Journal of the American Academy of Dermatology*, further substantiated the robust clinical signal of tapinarof [25]. By the end of the 12-week treatment period, all tapinarof cohorts demonstrated significant superiority over vehicle controls across a

wide spectrum of clinical assessments. These improvements were not limited to Physician Global Assessment (PGA) success; they also included marked reductions in total target lesion grading scores, reflecting specific improvements in erythema, induration, and scaling. Furthermore, tapinarof treatment resulted in high-level skin clearance, with significantly higher proportions of patients achieving the stringent therapeutic thresholds of PASI 50, PASI 75, and PASI 90 compared with the vehicle group, confirming the drug's ability to achieve substantial and clinically meaningful disease resolution [25]. Specifically, tapinarof treatment yielded substantial, dose-dependent clearance, with PASI 50 achieved by 71%–92% of patients, compared with only 10%–32% in the vehicle cohorts. More rigorous thresholds also showed dramatic separation: PASI 75 was reached by 46%–65% of tapinarof-treated subjects (vs. 5%–16% for vehicle), and PASI 90—representing near-total clearance—was achieved by 18%–40% of patients, whereas no vehicle-treated patients reached this milestone [25]. The therapeutic onset was remarkably rapid, with clinical separation apparent by Week 2 and statistically significant by Week 8. Notably, these gains were durable, remaining stable through Week 16, a full month after the final dose. While efficacious, tapinarof was associated with a higher incidence of treatment-emergent adverse events (TEAEs) than vehicle (56% vs. 25%, respectively), though the vast majority were mild to moderate [25]. The safety profile was characterized primarily by folliculitis, contact dermatitis, and headache. The observation of contact dermatitis-led discontinuations—first noted in three patients within the Phase 1 2% cohort and recurring in the Phase 2 study—prompted investigators to identify this as a key tolerability signal requiring close monitoring in subsequent pivotal trials [25]. Crucially, the epigenetic discovery that tapinarof induces increased methylation of the IL-17A promoter provides a molecular rationale for the sustained therapeutic durability observed in the Phase 2b trial. Clinical improvements persisted for 4 weeks after cessation of treatment, suggesting that this epigenetic modification may be a primary driver of the off-therapy remission effect [18]. By functionally "silencing" a key pro-inflammatory driver of psoriasis at the genomic level, tapinarof achieves a stabilization of the skin environment that outlasts the presence of the drug itself [18]. Based on the totality of the Phase 2b data, the 1% once-daily (QD) regimen was selected as the optimal dose for Phase 3 development. This concentration and frequency offered the most favorable clinical profile, striking a precise balance between high-level efficacy, manageable tolerability, and enhanced patient convenience.

Phase 3: Clinical Trial

PSOARING 1 and PSOARING 2

The definitive evidence supporting the efficacy and safety of tapinarof in plaque psoriasis was established through two identically designed, pivotal Phase 3 trials: PSOARING 1 (NCT03956355) and PSOARING 2 (NCT03983980). Sponsored by Dermavant Sciences, Inc., the results were published by Lebwohl et al. in the *New England Journal of Medicine* in December 2021 [26]. These multicenter, randomized, double-blind, vehicle-controlled trials were conducted across 97 sites in the United States and Canada, enrolling adults (ages 18–75) with stable plaque psoriasis. Eligible participants were required to have a baseline Physician Global Assessment (PGA) score of 2, 3, or 4 (mild to severe) and a body surface area (BSA) involvement of 3% to 20% [26]. Patients were randomized in a 2:1 ratio to receive either tapinarof 1% cream or a matching vehicle, with stratification based on baseline PGA scores to ensure balanced cohorts. The treatment protocol required a once-daily (QD) application to all affected areas, including new lesions and sites of resolved lesions. To ensure an unbiased assessment of tapinarof's monotherapy potential, a 4-week washout period was mandated for systemic agents, such as methotrexate, and topical corticosteroids [26]. Patient-reported outcomes were a focal point of the Phase 3 clinical program, with data captured through the Peak Pruritus Numeric Rating Scale (PP-NRS), the Dermatology Life Quality Index (DLQI) total score, and the Psoriasis Symptom Diary (PSD). These metrics provided a direct assessment of the drug's impact on quality of life and symptomatic relief. Comprehensive safety profiles were simultaneously established via clinical interviews, physical examinations, and serial laboratory evaluations. Conducted between March 2019 and May 2020, the trials achieved high enrollment across North America. In PSOARING 1, 674 patients were screened, resulting in 510 randomized participants; 340 received tapinarof. PSOARING 2 saw similar volume, with 515 of the 692 screened patients randomized and 343 allocated to the tapinarof arm [26]. Patients were predominantly white (approximately 85%) and male (57%), with a median age of 51 years. The primary efficacy results demonstrated a stark, statistically significant separation from the vehicle. In PSOARING 1, the proportion of patients achieving the primary PGA success endpoint was 35.4% in the tapinarof group and 6.0% in the vehicle group. These results were replicated and slightly exceeded in PSOARING 2, where 40.2% of tapinarof-treated patients reached the target PGA score, compared with 6.3% in the vehicle control arm [26]. A defining characteristic of these results was the consistency of response across diverse patient demographics and clinical profiles. Tapinarof efficacy remained stable regardless of baseline disease severity, with response rates of approximately 20% in the mild, 40% in the moderate,

and 36% in the severe psoriasis cohorts. Furthermore, therapeutic outcomes were independent of disease burden and duration; patients with body surface area (BSA) involvement above or below 10% both showed response rates exceeding 35%, and those who had lived with psoriasis for less than five years or more than a decade achieved nearly identical rates of clearance (35%–39%) [26]. Patient-reported outcomes further validated the clinical efficacy of tapinarof, with treated patients achieving statistically significant improvements over vehicle across all subjective measures. The Psoriasis Symptom Diary (PSD)—a comprehensive 16-item tool evaluating symptoms such as pruritus, stinging, burning, pain, cracking, scaling, and skin discoloration—revealed consistent superiority for the tapinarof cohorts as early as Week 2 [5,26]. These symptomatic gains translated into broader psychosocial benefits, as evidenced by clinically meaningful improvements in Dermatology Life Quality Index (DLQI) scores [27]. Furthermore, rapid and sustained relief from itch was confirmed by the Peak Pruritus Numeric Rating Scale (PP-NRS) score of [28], providing a holistic picture of therapeutic success that extended beyond physical clearance to encompass significant improvements in patient-perceived health-related quality of life [26]. The safety profile observed in the PSOARING 1 and 2 trials was characterized primarily by localized, mild-to-moderate cutaneous events at the application site. The most prevalent adverse events (AEs) included folliculitis, nasopharyngitis, and contact dermatitis, with a discontinuation rate for tapinarof-treated patients remaining remarkably low at < 5.8% [26]. Notably, no drug-related serious adverse events (SAEs) were reported in either pivotal study. Folliculitis, the most frequently observed reaction, was typically self-limiting and is increasingly categorized as an on-target pharmacodynamic effect rather than a traditional adverse reaction [26]. This phenomenon is likely a result of tapinarof-induced upregulation of skin barrier proteins within the follicular epithelium, reflecting the drug's role in modulating keratinocyte differentiation. Clinical monitoring revealed no detrimental effects on cardiac conduction (specifically, no QTc interval prolongation), laboratory parameters, or vital signs. The absence of systemic liabilities is particularly significant when contrasted with the established risks of conventional topical therapies, such as skin atrophy and HPA-axis suppression associated with chronic corticosteroid use, or the anatomical restrictions associated with topical calcineurin inhibitors [8,26,29]. A defining characteristic of tapinarof's clinical performance in the Phase 3 program was its rapid onset of action. Statistically significant improvements in Physician Global Assessment (PGA) scores were observed as early as Week 2, reinforcing the accelerated therapeutic trajectory first identified in the Phase 2b dose-finding studies [26]. The quality of the clinical response was equally significant. Among the cohort that met the primary endpoint at Week 12, a substantial

proportion achieved deep skin clearance: approximately 40.9% reached a PGA score of 0 (Complete Clearance). Furthermore, roughly 58% of these responders met the dual criteria of achieving "clear" or "almost clear" skin and the mandatory minimum 2-grade improvement from their baseline severity [26]. Evidence from the four-week post-treatment follow-up period in PSOARING 1 and 2 further corroborated the drug's unique remittive effect, as a significant number of patients maintained clinical improvements well after their final dose. This capacity for sustained benefit was the primary focus of the PSOARING 3 long-term extension (LTE) trial, which enrolled 91.6% of eligible participants from the pivotal studies. The LTE results: 40.9% of the total cohort achieved complete skin clearance (PGA 0), while 58.2% of patients who entered the study with a baseline PGA score >2 reached a "clear" or "almost clear" status (PGA 0/1). Most notably, for patients who achieved total clearance (PGA 0), the mean duration of the off-therapy remittive effect was 130.1 days [30]. This nearly four-month period of disease control without active medication suggests a fundamental shift in the skin's inflammatory environment. Importantly, no new safety signals emerged during this extended observation period, confirming that tapinarof 1% cream remains a well-tolerated option for long-term disease management [30]. The comprehensive data from the PSOARING 1 and 2 trials served as the foundation for the New Drug Application (NDA) submitted to the U.S. Food and Drug Administration. This regulatory pathway culminated in the FDA approval of tapinarof cream 1% (VTAMA®) on May 23, 2022, for the treatment of plaque psoriasis in adults [11]. This landmark approval established tapinarof as the first topical aryl hydrocarbon receptor (AhR) agonist authorized for any dermatological indication, introducing a novel, non-steroidal mechanism of action to the therapeutic landscape [11].

5. Safety and tolerability profile

Throughout the comprehensive clinical development program—spanning Phase 1 through Phase 3 trials and including more than 2,200 patients across 18 studies—tapinarof 1% cream has maintained a consistently well-characterized and manageable safety profile [26]. Whether evaluated for plaque psoriasis or atopic dermatitis, the therapy has proven to be generally well tolerated [31]. The vast majority of treatment-emergent adverse events (TEAEs) were categorized as mild to moderate in severity, with no evidence of cumulative toxicity or unexpected systemic liabilities [32]. This extensive dataset reinforces tapinarof's reliability as a versatile, nonsteroidal option for chronic inflammatory skin conditions. The adverse events most closely associated with tapinarof use are folliculitis, contact dermatitis, and headache, all

of which were prospectively designated as adverse events of special interest across the pivotal trials, based on observations from earlier-phase studies [31]. Folliculitis was the most frequently reported adverse event, occurring in 23.5% of tapinarof-treated patients in PSOARING 1 (vs. 1.2% in vehicle) and in 17.8% of tapinarof-treated patients in PSOARING 2 (vs. 0.6% in vehicle; Table 2) [26]. Contact dermatitis showed a similar trend, reported at 5.0% and 5.8% in the tapinarof groups in the respective trials, compared with negligible rates in the vehicle arms (0.6% and 0%). Regarding systemic effects, headache was noted in 3.8% of tapinarof-treated patients across both studies, whereas vehicle rates were lower at 2.4% and 0.6%, respectively (Table 2) [26]. While these events occurred more frequently with the active drug, most were mild to moderate in intensity and did not significantly affect the overall discontinuation rate.

Table 2. Demonstrates a summary of adverse effects documented in PSOARING 1 and PSOARING 2 trials [26]

Adverse Event	*PSOARING 1 (Tapinarof vs. Vehicle)*	*PSOARING 2 (Tapinarof vs. Vehicle)*
Folliculitis	23.5% vs. 1.2%	17.8% vs. 0.6%
Contact Dermatitis	5.0% vs. 0.6%	5.8% vs. 0%
Headache	3.8% vs. 2.4%	3.8% vs. 0.6%

Critically, across the two Phase 3 trials, only one severe adverse event of folliculitis and one severe adverse event of contact dermatitis were reported, and no drug-related serious adverse events occurred in either study. Folliculitis led to trial discontinuation in 1.8% of tapinarof-treated patients in PSOARING 1 and 0.9% in PSOARING 2, while contact dermatitis

led to discontinuation in 1.5% and 2.0%, respectively [26].

Specific investigations into the nature of tapinarof-associated folliculitis suggest that the condition is an on-target pharmacodynamic effect rather than a traditional adverse reaction. This localized event is believed to be directly linked to the drug's primary mechanism of action: activation of the aryl hydrocarbon receptor (AhR) [14]. By stimulating this pathway, tapinarof induces the upregulation of key structural proteins within the stratum corneum and follicular epithelium. This process promotes keratinocyte differentiation and strengthens the skin barrier, but it can also manifest clinically as mild folliculitis as the follicular structure responds to these localized architectural changes [14]. At a molecular level, tapinarof-mediated AhR activation triggers the expression of CYP1A1 within the pilosebaceous unit [33]. Research in cultured sebocytes suggests that this increased CYP1A1 activity acts as a biological switch, redirecting LRIG1-positive stem cells toward a keratinocyte-like differentiation pathway. This shift alters the standard keratinization process within the hair follicle, providing a clear mechanistic explanation for the development of the follicular events observed in clinical trials [33]. Crucially, sebaceous gland atrophy—a pathological hallmark of dioxin-induced chloracne—is absent from the tapinarof safety profile [34]. Preclinical *in vivo* studies have consistently demonstrated that tapinarof does not induce these atrophic changes, regardless of the route of administration or the duration of exposure [34]. Clinically, folliculitis in the Phase 3 psoriasis trials was mostly mild, with a low discontinuation rate of less than 1.8%, localized to the hair follicle, and not associated with a higher frequency in acne-prone areas [26,34]. Consistent with these findings, discontinuation rates due to follicular events and contact dermatitis remained remarkably low throughout the PSOARING and ADORING trial programs [32]. Most patients were able to maintain their treatment regimen without the need for dose modifications or interruptions. Generally, these adverse events are mild and self-limiting, only rarely posing a significant barrier to continued therapy [32]. Notably, PSOARING 3 also confirmed the absence of tachyphylaxis — demonstrating that tapinarof remains effective without loss of efficacy with extended use, a property that distinguishes it from topical corticosteroids [35]. A few cases of asymptomatic aminotransferase elevations were reported; however, these events were transient and did not necessitate discontinuation of treatment [35].

A particularly important aspect of tapinarof's tolerability profile is the absence of the safety concerns traditionally associated with long-term use of topical corticosteroids [36]. In contrast to corticosteroids, tapinarof lacks the associated risks of skin atrophy, striae, or hypothalamic-pituitary-adrenal (HPA) axis suppression [37], making it a safer profile for long-term use. Furthermore, unlike topical calcineurin inhibitors and JAK inhibitors, tapinarof is not

subject to black box warnings or restrictive limitations on application sites or treatment duration [38,39]. Tapinarof cream demonstrated excellent tolerability even on sensitive skin areas, and no correlation was found between systemic exposure and the extent of affected body surface area, even in applications over large areas of up to 90% BSA [40]. By mitigating the long-term safety risks inherent to topical corticosteroids, tapinarof addresses a critical therapeutic gap in psoriasis management. Its favorable tolerability profile makes it an ideal alternative for patients experiencing "steroid phobia" or those who have historically demonstrated an inadequate response to standard-of-care topicals. As a non-steroidal option, it provides clinicians with a versatile tool that can be used continuously, ensuring that patients who are either ineligible for or wary of hormonal therapies can still achieve high-level disease clearance [35]. The systemic safety of tapinarof is further supported by the absence of drug-drug interactions and clinically relevant cardiac effects, with no prolongation of the QTc interval at the approved once-daily dose demonstrated across pharmacokinetic and safety studies [26].

6. Clinical Application, Positioning, and Dosage

VTAMA® (tapinarof) cream, 1%, is indicated for the topical treatment of plaque psoriasis in adults and has received subsequent FDA approval for the treatment of atopic dermatitis (AD) in both adults and pediatric patients aged 2 years and older. The therapeutic regimen is designed for simplicity and ease of use: a thin layer is applied once daily to all affected areas of skin [41]. The once-daily dosing of tapinarof represents a significant clinical and practical advantage over existing nonsteroidal topicals [31]. Competing therapies—including crisaborole (PDE4 inhibitor), tacrolimus and pimecrolimus (calcineurin inhibitors), and ruxolitinib (JAK inhibitor)—all require twice-daily application [5,8,31]. This more demanding schedule increases the overall treatment burden, which often erodes patient adherence, particularly in pediatric populations, where adherence can be more challenging for caregivers. By simplifying the regimen to a single daily application, tapinarof removes a common barrier to compliance, potentially leading to more consistent disease control than therapies that require more frequent dosing. Tapinarof is approved for use in plaque psoriasis in adults without restrictions on duration, extent, or sites of use, including intertriginous and sensitive skin areas across the spectrum of disease severity [14]. The prescribing flexibility of tapinarof stands in stark contrast to the stringent limitations governing other topical therapies. While topical corticosteroids require cautious application to avoid sensitive sites and prolonged use, and calcineurin inhibitors (tacrolimus and pimecrolimus) are often restricted to second-line, short-

term therapy, tapinarof offers a more versatile profile. Furthermore, it avoids the age and surface area constraints seen with ruxolitinib, which is limited to patients aged 12 years and older with body surface area (BSA) involvement of less than 20% [39,42,43]. Exceptional longitudinal data support this favorable clinical positioning. In clinical trials, patient adherence to the tapinarof regimen remained high, reaching approximately 90% over 40 weeks. This was mirrored by subjective feedback in the PSOARING 3 long-term extension, where investigator- and patient-reported tolerability scores were consistently positive for 86%–92% of participants, confirming that the treatment is both easy to follow and well tolerated over extended durations [44]. These data establish tapinarof as a primary nonsteroidal alternative for patients requiring chronic therapy, offering the unique advantage of continuous use without mandatory treatment intervals or application-site rotation. Within the psoriasis treatment paradigm, tapinarof is most appropriately positioned as a first-line nonsteroidal topical agent for adults. Its versatility allows for use as a potent monotherapy across the full spectrum of disease severity—from mild to severe—and as an effective combination partner with systemic or biologic agents for patients with more extensive involvement. By providing an efficacious, well-tolerated, and convenient once-daily regimen, tapinarof addresses critical gaps in traditional psoriasis management. Furthermore, its ability to delay or potentially avoid progression to oral or biologic systemic therapies offers significant advantages, including improved patient convenience and substantial cost savings for the healthcare system [44].

7. Discussion and Future Investigations

Tapinarof 1% cream marks one of the most significant clinical breakthroughs in topical dermatology in over twenty years. As the first-in-class aryl hydrocarbon receptor (AhR) agonist, it introduces an entirely novel mechanism of action to the field [11]. Several key aspects of tapinarof's clinical pharmacology continue to drive scientific inquiry and clinical discussion, especially its remittive effect: the observation that patients achieving complete clearance in the PSOARING 3 trial maintained disease control for a mean of 130 days after discontinuing the medication [9,26]. This capacity for sustained clinical benefit following treatment withdrawal remains the most scientifically compelling discovery of the clinical program. The mechanism underlying this sustained remittive effect appears to be rooted in AhR-driven epigenetic modifications of the *FoxP3* and *IL-17* gene promoters [30]. By modulating these pathways, tapinarof promotes the preferential differentiation of regulatory T cells (Tregs) while simultaneously inhibiting Th17 cells. Furthermore, AhR activation leads to a significant

reduction in the activity of tissue-resident memory T cells [45]. These specialized cells are believed to be the primary drivers of chronicity and rapid relapse in both psoriasis and atopic dermatitis [30]. The most pressing unmet need in the clinical literature is the absence of direct head-to-head comparative trials between tapinarof and established therapies. As the authors of PSOARING 1 and 2 themselves concluded, larger and longer trials are needed to evaluate the efficacy and safety of tapinarof cream as compared with existing treatments for psoriasis [26]. In the absence of such clinical trials, the relative positioning of tapinarof against established therapies—such as high-potency corticosteroids, roflumilast, or ruxolitinib—must be inferred through indirect comparisons and network meta-analyses. However, these methods are often hampered by significant methodological limitations, including heterogeneity in study populations, varying clinical endpoints, and diverse comparator arms. To fully delineate tapinarof's role in the standard of care, pragmatic comparative effectiveness studies and robust real-world evidence registries will be essential. The clinical landscape for tapinarof is rapidly expanding, with ongoing research aimed at broadening its therapeutic reach and deepening our understanding of its long-term benefits. Currently, a dedicated clinical trial (NCT05172726) is investigating the safety and efficacy of tapinarof cream, 1% once daily, for pediatric psoriasis patients as young as 2 years old [44]. Simultaneously, the ADORING 3 long-term extension trial is underway to evaluate the treatment's durability and potential remittive effect specifically within the atopic dermatitis (AD) population [31,46]. This study mirrors the successful design of the PSOARING 3 psoriasis trials, seeking to confirm if the unique "off-therapy" disease control observed in psoriasis patients can be replicated for those suffering from AD. An additional Japanese Phase 3 trial is slated to evaluate a 0.5% tapinarof cream formulation in pediatric patients aged 2 to 11 years. This shift to a lower concentration follows a Japanese Phase 2 trial, where the 0.5% once-daily dose surprisingly outperformed the 1% concentration, demonstrating both numerically higher efficacy and a superior safety profile with fewer adverse events. These findings highlight that the optimal pediatric dose is not yet definitive and requires further clinical validation to balance potency with the unique physiological needs of younger patients [35]. The therapeutic potential of Aryl hydrocarbon Receptor (AhR) agonism extends far beyond dermatology. Given the clinical success of tapinarof in treating inflammatory skin conditions, the AhR pathway represents a compelling target for a diverse range of systemic diseases characterized by epithelial barrier dysfunction and immune dysregulation [14]. Research is increasingly focusing on conditions with shared pathogenic features, including asthma, inflammatory bowel disease (IBD), eosinophilic esophagitis, and various ophthalmic and neurological disorders [14]. In the field of dermatology, the impairment of aryl hydrocarbon

receptor (AhR) signaling has been linked to several conditions, including vitiligo, acne, and hidradenitis suppurativa [47,48]. In cases of vitiligo, a reduction in AhR expression within both the skin and CD4+ T cells is closely tied to increased disease volatility and clinical severity [47]. Early-stage research indicates that stimulating the AhR pathway may provide a significant therapeutic advantage by bolstering the antioxidant defenses of melanocytes while simultaneously dampening the localized autoimmune attacks that lead to their destruction. By triggering these protective pathways and promoting the expression of genes involved in melanogenesis, AhR activation can shield pigment-producing cells from oxidative injury, halt the spread of depigmentation, and encourage the repigmentation of existing lesions—positioning it as a promising new frontier in the treatment of vitiligo [47,49]. In the context of hidradenitis suppurativa (HS), recent research has identified a link between the condition and impaired tryptophan catabolism by skin-surface bacteria, which results in diminished AhR signaling. To address this deficit, a novel topical AhR agonist, AT193, is currently undergoing evaluation in a Phase 1b clinical trial. This targeted approach aims to restore AhR activation to mitigate the characteristic inflammation and follicular dysfunction seen in HS patients [48]. Tapinarof itself has not yet been formally studied in hidradenitis suppurativa, representing a potential investigational opportunity.

Significant ambiguity remains regarding the most effective integration of tapinarof into combination therapy protocols. While pivotal trials focused on monotherapy, real-world clinical observations from experts indicate that tapinarof can be successfully paired with topical corticosteroids. This "hybrid" approach—such as staggering applications throughout the day—may be particularly useful for managing disease flares or mitigating localized side effects like folliculitis, thereby extending the drug's utility in complex clinical scenarios [32,46]. Despite these practical insights, there is a distinct lack of formal clinical data. To date, no controlled studies have specifically defined the efficacy, safety, or complex pharmacodynamic interactions that occur when tapinarof is used concurrently with other topicals, phototherapy, or systemic biologic agents. The existing analyses currently lack the depth of stratified data necessary to conduct comprehensive subgroup evaluations. As a result, critical assessments based on patient age, disease severity, anatomical location, and treatment duration remain unavailable [35]. This limitation underscores a vital requirement for more granular data reporting in upcoming clinical trials to better understand how these variables influence therapeutic outcomes.

Conclusions

The successful discovery and clinical validation of tapinarof have solidified the Aryl hydrocarbon Receptor (AhR) as a legitimate and powerful therapeutic target within the field of immune-mediated dermatology [13,15]. This breakthrough carries significant implications that likely extend well beyond its initial regulatory approvals. By modulating the AhR pathway, tapinarof simultaneously targets the inflammatory cascade and restores skin barrier integrity. This dual-action mechanism establishes it as a cornerstone therapy for patients requiring sustained disease management while avoiding the complications typically linked to long-term corticosteroid application. As the clinical trial landscape matures and real-world evidence continues to grow, tapinarof is positioned to play an increasingly vital role in the long-term management of diverse inflammatory skin conditions.

Disclosure:

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