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ADISINSIGHT REPORT

Tapinarof Cream 1%: First Approval

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Abstract
Tapinarof cream 1% (VTAMA®) is an aryl hydrocarbon receptor (AhR) agonist that is being developed by Dermavant Sciences Inc. (a subsidiary of Roivant Sciences Inc.) as a once-daily topical treatment for plaque psoriasis and atopic dermatitis. AhR is a ligand-dependent transcription factor that has a role in immune-mediated skin responses. In May 2022, tapinarof cream 1% was approved in the USA for the topical treatment of plaque psoriasis in adults. Tapinarof cream 1% is also being investigated for the treatment of atopic dermatitis. This article summarizes the milestones in the development of tapinarof cream 1% leading to this first approval for the topical treatment of plaque psoriasis.

Digital Features for this AdisInsight Report can be found at https://doi.org/10.6084/m9.figshare.20224350.

Tapinarof cream 1% (VTAMA®): Key points

An aryl hydrocarbon receptor agonist that is being developed by Dermavant Sciences Inc. (a subsidiary of Roivant Sciences Inc.) as a topical treatment for plaque psoriasis and atopic dermatitis

Received its first approval on 23 May 2022 in the USA

Approved for the topical treatment of plaque psoriasis in adults

1 Introduction

The skin is a physical barrier, protecting the body against pathogens and exogenous and environmental threats [1, 2]. To maintain skin homeostasis, skin cells (including keratinocytes) express environmental sensors such as the aryl hydrocarbon receptor (AhR), a ligand-dependent transcription factor that has a role in immune-mediated skin responses (including the regulation of cytokine expression), skin barrier protein expression and antioxidant activity [1, 2]. Deregulation of immune cells, plus alterations in keratinocyte differentiation and proliferation and skin barrier disruption are evident in chronic inflammatory skin disorders such as psoriasis [an immune-mediated disease characterized by upregulation of tumour necrosis factor-α (TNF-α)/interleukin (IL)-23/IL-17 and thought to be associated with increased AhR expression] [1–4] and atopic dermatitis [characterized by increased IgE production and T helper (Th)2-deviated skin inflammation, barrier disruption and chronic pruritus] [2, 5]. For several decades, the most common topical agents used to treat mild-to-moderate psoriasis have been corticosteroids and vitamin D analogues [3, 4]; the predominant topical treatments for mild-to-moderate atopic dermatitis are corticosteroids and calcineurin inhibitors [6]. While these agents show efficacy in psoriasis and atopic dermatitis, adverse effects limit their long-term use. New topical agents that target cutaneous pathological processes are currently being developed [4, 6].

Tapinarof is a small molecule AhR agonist that binds specifically to and activates AhR [3, 7]. Based on evidence from in vitro and animal studies, AhR activation by tapinarof induces gene expression that leads to decreased skin inflammation (by downregulation of Th17 cytokines implicated in plaque psoriasis, including IL-17A and IL-17F, and Th2 cytokines implicated in atopic dermatitis, including IL-4, IL-5 and IL-13), skin barrier normalization (through

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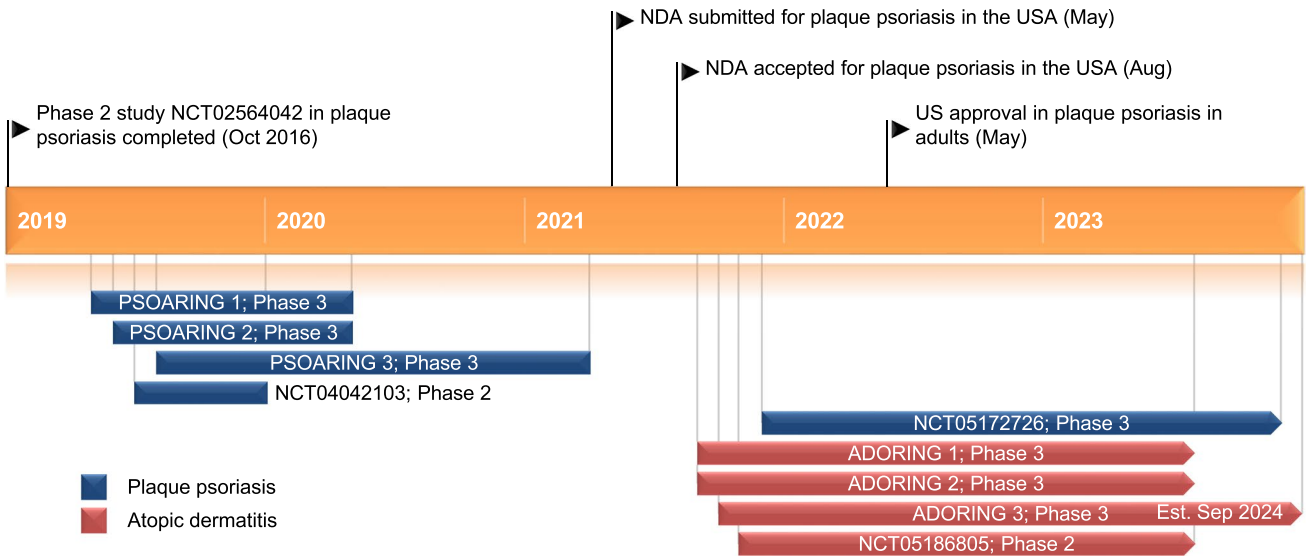


Key milestones in the development of tapinarof cream 1% for the topical treatment of plaque psoriasis and atopic dermatitis. *NDA* New Drug Application

increased expression of skin barrier proteins associated with keratinocyte differentiation, including filaggrin, loricrin and involucrin), and reduced oxidative stress (via increased antioxidant response through the Nrf2 pathway, as well as direct scavenging of reactive oxygen species by tapinarof) [3, 5]. Tapinarof cream 1% (VTAMA®) was approved in May 2022 in the USA for the topical treatment of plaque psoriasis in adults [7, 8]. When using tapinarof cream 1%, a thin layer should be applied to affected areas of the skin once daily; the cream is not for oral, ophthalmic or intravaginal use [7]. Tapinarof cream 1% is also under investigation for use in pediatric patients (aged 2–17 years) with psoriasis and in patients aged ≥2 years with moderate to severe atopic dermatitis [9].

Although tapinarof cream 1% has the same active pharmaceutical component (i.e., 3,5-dihydroxy-4-isopropyl-*trans*-stilbene) as benvitimod cream 1% (WBI-1001), a twice-daily topical oil-in-water cream formulation that has been developed in China and was approved for use in China in 2019 in patients with mild-to-moderate plaque psoriasis [10–12], it differs from benvitimod cream 1% in terms of excipients and frequency of administration (once vs twice daily) and has been developed and approved via a separate, larger clinical trial program that evaluated patients with the full spectrum of disease severity (mild to severe plaque psoriasis) [11].

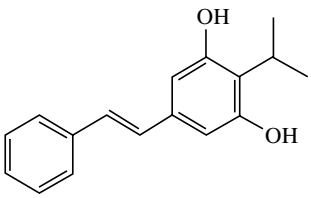
1.1 Company Agreements

In January 2020, Dermavant Sciences (a subsidiary of Roivant Sciences) entered into an exclusive license agreement with Japan Tobacco, giving Japan Tobacco exclusive rights to develop, register and market tapinarof in Japan for the treatment of psoriasis and atopic dermatitis [13]. In January 2020, Japan Tobacco and Torii Pharmaceutical entered into an exclusive license agreement for co-development and commercialization of tapinarof in Japan [14]. In August 2018, Dermavant Sciences completed the purchase of all global rights to tapinarof (except in China) with GlaxoSmithKline (GSK). This included global rights to tapinarof (GSK2894512) for the treatment of psoriasis and atopic dermatitis and the preclinical back-up programmes [15, 16]. In 2012, Stiefel, a GSK company, had completed the acquisition of development and commercialization rights to GSK2894512 outside China from Welichem [17, 18].

2 Scientific Summary

2.1 Pharmacodynamics

In vitro and ex vivo studies have shown that tapinarof directly binds to and activates AhR in multiple cell types, including $CD4^+$ T cells, HaCaT cells and human skin explants [5]. Tapinarof promoted CYP1A1 expression in peripheral blood $CD4^+$ T cells and human skin explants and induced nuclear



Chemical structure of tapinarof (molecular weight 254 g/mol)

translocation of AhR in HaCaT cells. In human keratinocytes, tapinarof induced CYP1A1 expression without marked cell death and significantly induced mRNA expression of the barrier genes filaggrin, hornerin and involucrin, which are associated with epidermal differentiation. In vitro studies also suggest that the antioxidant activity of tapinarof is likely to result from a combination of intrinsic capabilities (it is a stilbene derivative) and the partial induction of Nrf2 pathway genes. Tapinarof inhibited IL-17A message expression and increased IL-22 levels in ex vivo SRICA cultures and dose-dependently reduced IL-17A levels in $CD4^+$ cells [5].

Topical treatment with tapinarof significantly improved imiquimod-induced psoriasiform lesions in mouse models of psoriasis [5]. Tapinarof reduced skin erythema and epidermal thickening and dose-dependently decreased tissue cytokine expression (IL-17A, IL-17F, IL-19, IL-22, IL-23A and IL-1B) in a mouse model of psoriasis; similar responses to topical tapinarof were seen in imiquimod-treated AhR-sufficient mice, but not in those that were AhR-deficient [5]. The specific pharmacodynamics of tapinarof cream 1% and the mechanisms by which tapinarof cream 1% exerts its specific effects in patients with psoriasis are unknown [7].

Consistent with its pharmacokinetic profile and minimal systemic exposure (Sect. 2.2), no evidence of clinically relevant QTc interval prolongation has been observed either when tapinarof cream 1% is used at the approved recommended dosage [7] or under maximal use conditions in adults with a body surface area (BSA) involvement ≥ 20% [19].

2.2 Pharmacokinetics

Following topical application of tapinarof cream 1%, tapinarof is absorbed into the skin; however after once-daily applications, the plasma concentration of tapinarof was below the quantifiable limits in 68% of pharmacokinetic samples in a sensitive assay (lower limit of quantification of the assay was 50 pg/mL) in a maximal use trial [7, 19]. The tapinarof mean C_{max} was 0.9 ng/mL and mean $AUC_{0–last}$ was 4.1 ng·h/mL on day 1 after application of a mean daily dose of 5.23 g to a mean BSA involvement of 27.2% (range 20.5–46.0%) in patients ($n=21$) with extensive plaque psoriasis. T_{max} occurred 2–5 h after application [7, 19]. No accumulation was evident after repeated topical application; on day 29 the mean C_{max} was 0.12 ng/mL and $AUC_{0–last}$ was 0.61 ng·h/mL [7, 19]. These results indicate minimal systemic exposure to tapinarof following topical application under conditions of maximal use. Tapinarof is highly bound (≈99%) to human plasma protein in vitro [7].

In vitro studies indicate that tapinarof is metabolized in the liver via multiple pathways (including oxidation, glucuronidation and sulfation). In vitro, tapinarof does not inhibit CYP2B6, CYP2C8, CYP2C9, CYP2C19, CRP2D6 or CYP3A4/5 or induce CYP1A2, CYP2B6 or CYP3A4. Tapinarof does not inhibit the transporter systems BCRP, MATE1, MATE-2K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2 or P-gp and is not a substrate for BCRP, OATP1B1, OATP1B3 or P-gp [7].

Features and properties of tapinarof cream 1%

Alternative names	DMVT 505; VTAMA; GSK2894512
Class	Anti-inflammatories; Antipsoriatics; Nonsteroidal anti-inflammatories; Skin disorder therapies; Small molecules; Stilbenes
Mechanism of action	Aryl hydrocarbon receptor agonists
Route of administration and formulation	Topical cream
Pharmacodynamics	Directly binds to and activates AhR in multiple cell types in vitro and ex vivo, including $CD4^+$ T cells, HaCaT cells and human skin explants. Significantly improved imiquimod-induced psoriasiform lesions in mouse models of psoriasis
Pharmacokinetics	After once daily applications plasma concentration of tapinarof was below the quantifiable limits in 68% of patients; mean C_{max} 0.9 ng/mL, mean AUC_{last} 4.1 ng·h/mL on day 1; no accumulation after repeated topical application
Adverse events	
Most frequent TEAEs (incidence ≥ 1%)	Folliculitis, nasopharyngitis, contact dermatitis, headache, pruritus and influenza
Occasional	Urticaria
ATC codes	
WHO ATC code	D05A (Antipsoriatics for topical use), D11-A-H (Agents for atopic dermatitis, excluding corticosteroids)
EphMRA ATC code	D11A (Other Dermatological Preparations), D5A (Topical antipsoriasis products)
Chemical name	(E)-2-isopropyl-5-styrylbenzene-1,3-diol

2.3 Therapeutic Trials

2.3.1 Plaque Psoriasis

2.3.1.1 Phase 3 Trials Once-daily topical administration of tapinarof cream 1% to affected areas significantly reduced the severity of plaque psoriasis in two identical 12-week, phase 3 randomized trials, PSOARING 1 (NCT03956355) [$n=510$] and PSOARING 2 (NCT03983980) [$n=515$] [20]. Eligible patients in PSOARING 1 and PSOARING 2 were aged 18–75 years and had a baseline Physician's Global Assessment (PGA) score of 2 (mild), 3 (moderate) or 4 (severe) and a percent of total BSA affected (excluding scalp, palms, soles, fingernails and toenails) of 3–20%. At baseline, most patients (79.2% of patients in PSOARING 1 and 83.9% of those in PSOARING 2) had a PGA score of 3, 11.8% and 8.3% had a PGA score of 2, and 9.0% and 7.8% had a PGA score of 4; the mean PASI score in the respective trials was 8.9 and 9.1 and the extent of disease involvement (mean BSA affected) was 7.9% and 7.6%. At baseline across all arms in both trials, the Peak Pruritus Numeric Rating Scale (PP-NRS) score was 5.7–6.1, Dermatology Life Quality Index (DLQI) total score was 8.2–8.7 and the Psoriasis Symptom Diary total score was 73.1–76.0 [20].

Treatment success [PGA response; PGA score of 0 (clear) or 1 (almost clear) and ≥2-point improvement from baseline on the 5-point PGA scale] at 12 weeks (primary endpoint) was seen in significantly more tapinarof cream 1% than vehicle cream recipients in both PSOARING 1 [35.4% vs 6.0%; relative rate vs vehicle (RR) 5.8; $p<0.001$] and PSOARING 2 (40.2% vs 6.3%; RR 6.1; $p<0.001$). By week 4, treatment success was seen in 14.0% and 13.7% of tapinarof cream 1% recipients in PSOARING 1 and PSOARING 2, compared with 1.3% and 3.1% of vehicle recipients; by week 8, treatment success had risen to 28.1% and 30.5% of tapinarof cream 1% recipients compared with 2.2% and 4.5% of patients in the vehicle cream arms, respectively [20]. After 12 weeks of treatment, complete disease clearance (PGA 0) and withdrawal of tapinarof cream 1% occurred in 74 of 508 patients in the tapinarof cream 1% arms of PSOARING 1 and PSOARING 2 who subsequently enrolled in the phase 3 PSOARING 3 (NCT04053387) long-term extension trial; 5 of 255 vehicle cream recipients enrolled in PSOARING 3 also achieved complete disease clearance (PGA 0) at 12 weeks [21].

At week 12, a significantly higher percentage of tapinarof cream 1% recipients had a reduction of at least 75% in the Psoriasis Area and Severity Index (PASI) score (PASI 75) compared with those receiving vehicle cream in both PSOARING 1 (36.1% vs 10.2%; RR 2.8; $p<0.001$) and PSOARING 2 (47.6% vs 6.9%; RR 6.5; $p<0.001$). In both trials, significantly more tapinarof cream 1% than vehicle cream recipients also had a PGA score of 0 or 1 at week 12 (37.8% vs 9.9%; RR 2.7; $p<0.001$ in PSOARING 1 and 43.6% vs 8.1%; RR 4.6; $p<0.001$ in PSOARING 2) and a greater reduction in the extent of disease involvement [mean change in % of total BSA affected from baseline] (−3.5% vs −0.2%; $p<0.001$ in PSOARING 1 and −4.2% vs +0.1%; $p<0.001$ in PSOARING 2). At week 12, significantly more patients in the tapinarof cream 1% arms than in the vehicle arms in both trials achieved PASI 90 (18.8% vs 1.6%; RR 8.5; $p<0.001$ in PSOARING 1 and 20.9% vs 2.5%; RR 7.2; $p<0.001$ in PSOARING 2) [20].

In terms of patient-reported outcomes [20], the mean change in the total PP-NRS score from baseline to week 12 in the tapinarof cream 1% and vehicle arms was −3.6 and −2.7 in PSOARING 1 and −3.0 and −1.4 in PSOARING 2. In patients with a baseline score of ≥4 points in the PP-NRS score, a decrease of ≥4 points at week 12 was seen in 60.7% of tapinarof cream 1% recipients and 43.2% of vehicle cream recipients in PSOARING 1; corresponding percentages in PSOARING 2 were 56.9% and 29.6%. The mean change in the DLQI total score from baseline to week 12 in the tapinarof cream 1% and vehicle arms was −4.6 and −2.8 in PSOARING 1 and −4.4 and −1.1 in PSOARING 2, and the mean change from baseline in the Psoriasis Symptom Diary score at week 12 in the tapinarof cream 1% and vehicle arms was −48.5 and −34.0 in PSOARING 1 and −42.9 and −18.8 in PSOARING 2 [20].

Patients enrolled in PSOARING 3 (508 from the tapinarof cream 1% arms and 255 from the vehicle arms of PSOARING 1 and PSOARING 2) were treated with tapinarof cream 1% according to PGA score for 40 weeks [21]. Those who entered with or achieved a PGA score of 0 discontinued treatment and were observed for remittive effect (maintenance of a PGA score of 0 or 1 while off therapy). Those who entered with a PGA score ≥1 were treated with tapinarof cream 1% once daily until complete disease clearance (PGA 0) at which time treatment was discontinued. If disease worsening (PGA ≥2) occurred in those who were off treatment, tapinarof cream 1% once daily was started and continued until PGA 0 was achieved [21].

With long-term intermittent use, tapinarof cream 1% provided additional and sustained efficacy beyond 12 weeks in the PSOARING 3 trial [21]. Complete disease clearance (PGA 0) was achieved in 40.9% (312/763) of patients at least once during the 40-week treatment phase and 58.2% (302/519) of patients with a PGA ≥2 at study entry achieved PGA 0 or PGA 1 at least once during the trial. In the 79 patients who entered the study with a PGA of 0, the median duration of remittive effect (maintenance of PGA 0 or 1 while off therapy) was 115 days. The response to intermittent treatment with tapinarof cream 1% (PGA score of 0 or 1 at least once during the study) was durable (i.e. no loss of response while on therapy) for up to 52 weeks [21].

2.3.1.2 Phase 2 Trials Tapinarof cream 1% applied to affected skin once daily significantly reduced the severity of plaque psoriasis in a 29-day phase 2a maximal use trial (NCT04042103) in patients with extensive plaque psoriasis (mean BSA affected at baseline was 27.2%) [19]. At baseline, 12 of the 19 patients who completed the study had a PGA score of 3 and the remaining 7 patients had a PGA score of 4; by day 29 of treatment, only 5 patients had a PGA score of 3 and 1 patient had a PGA score of 4. At day 29, 9 patients had improved to PGA 2 and 4 patients had improved to PGA 1. The mean change from baseline in PGA score at the end of the study was −1.2 ($p < 0.0001$ vs baseline). Four patients achieved treatment success (PGA score 0 or 1 and a ≥2-grade improvement from baseline) by day 29 [19].

Tapinarof cream was significantly more effective than vehicle cream in terms of achieving treatment success in a 12-week, double-blind, randomized phase 2b trial (NCT02564042) that was designed to identify the optimal tapinarof cream concentration and dosing frequency in adults with plaque psoriasis [22]. Eligible patients were aged 18–65 years and had chronic stable plaque psoriasis with BSA involvement of 1–15% and a PGA score ≥2; at baseline, 80% of patients had a PGA score of 3 and mean PASI score was 8.8. Patients were randomized to receive tapinarof cream 1% once or twice daily, tapinarof cream 0.5% once or twice daily or vehicle cream once or twice daily [22].

In the phase 2b trial, PGA response rates at week 12 were significantly higher ($p < 0.05$ for all comparisons) in the tapinarof cream treatment arms [tapinarof cream 1% twice daily (65%; $n = 34$), 1% once daily (56%; $n = 35$), 0.5% twice daily (46%; $n = 32$) and 0.5% once daily (36%; $n = 32$) than in the vehicle cream twice daily (11%; $n = 30$) and once daily (5%; $n = 33$) groups. The proportion of patients achieving treatment success (PGA 0 or 1 and a ≥2-grade improvement from baseline on the 5-point PGA scale) in the tapinarof cream 1% twice daily (58%), 1% once daily (54%), 0.5% twice daily (35%) and 0.5% once daily (36%) was also significantly higher ($p < 0.05$ for all comparisons) than that in the vehicle cream twice daily (5%) and once daily (0%) groups. A significant treatment difference was evident from 8 weeks and was maintained at 4 weeks after ceasing treatment in all tapinarof cream groups apart from the 0.5% twice daily treatment arm [22, 23]. Improvements in PGA scores from baseline were significantly higher ($p < 0.001$ for all comparisons) [23] and the proportion of patients achieving a PASI 75 response was significantly greater ($p < 0.05$ for all comparisons) [22] at 12 weeks with all tapinarof dose regimens compared with vehicle cream. By week 12, the mean % reduction in PASI scores were 76.8% and 77.3% in the tapinarof cream 1% twice daily and once daily groups, 63.6% and 68.3% in the tapinarof cream 0.5% groups and 16.6% and 28.1% in the vehicle cream groups. Total BSA affected had reduced by a mean 3.6–4.9% in the tapinarof cream arms and by 1–1.6% in the vehicle cream arms at 12 weeks [22]. Tapinarof cream was effective in reducing the severity of plaque psoriasis, regardless of baseline % BSA affected, duration of psoriasis, Fitzpatrick skin type [24] and body region affected [25].

2.3.2 Atopic Dermatitis

Treatment with tapinarof cream significantly improved the signs and symptoms of atopic dermatitis in a 12-week, randomized, double-blind, phase 2b trial (NCT02564055) that was designed to identify the optimal tapinarof cream concentration and dosing frequency in patients aged 12–65 years with atopic dermatitis [26]. Eligible patients had a clinical diagnosis of atopic dermatitis with BSA involvement of 5–35% and an IGA score ≥ 3; at baseline, 91% of patients had an atopic dermatitis Investigator's Global Assessment (IGA) score of 3, a mean Eczema Area and Severity Index (EASI) score of 11.25 and a mean % BSA affected of 16.91%. Patients were randomized to receive tapinarof cream 1% once or twice daily, tapinarof cream 0.5% once or twice daily or vehicle cream once or twice daily [26].

Treatment success [IGA score of clear or almost clear (0 or 1) and ≥2-grade improvement in the static 5-point IGA score from baseline] at week 12 (primary endpoint) was seen in 53% of those in the tapinarof cream 1% twice daily arm ($n = 40$), 46% of those in the 1% once daily arm ($n = 41$), 37% of those in 0.5% twice daily arm ($n = 43$) and 34% of those in the 0.5% once daily arm ($n = 41$) compared with 24% and 28% of those in the vehicle cream twice daily ($n = 42$) and once daily ($n = 40$) arms. The treatment success rate in the tapinarof cream 1% twice daily arm was significantly higher than that in the vehicle cream twice daily arm ($p = 0.008$ [27]). At 4 weeks after ceasing treatment, the IGA response was maintained in 30% of patients in the tapinarof cream 1% twice daily group and in 23% of those in the 1% once daily group [26]. At week 12, a ≥ 75% improvement in EASI score (EASI 75) from baseline was achieved in significantly more tapinarof cream 1% twice daily (60% vs 26%; p = 0.002), tapinarof cream 1% once daily (51% vs 25%; p = 0.016) and tapinarof cream 0.5% twice daily (51% vs 26%; p = 0.018) recipients than vehicle cream recipients [27] and at 4 weeks after ceasing treatment, EASI 75 was maintained in 45% and 34% of patients in the tapinarof cream 1% twice daily and 1% once daily groups [26]. At 12 weeks, a significant reduction from baseline in mean % BSA was seen in significantly more tapinarof cream 1% twice daily (−68% vs −23%; $p = 0.002$), tapinarof cream 1% once daily (−48% vs −5%; $p = 0.006$) and tapinarof cream 0.5% once daily (−56% vs −5%; $p < 0.001$) recipients than vehicle cream recipients, and the significant differences between reductions in the tapinarof cream and vehicle cream groups was still evident 4 weeks after ceasing treatment [27].

Key clinical trials of tapinarof cream 1%

Drug(s)	Indication	Population	Phase	Status	Location(s)	Sponsor	Identifier
Tapinarof	Plaque psoriasis	Pediatric	3	Recruiting	USA, Canada	Dermavant Sciences	NCT05172726
Tapinarof	Plaque psoriasis	Adult	3	Completed	USA, Canada	Dermavant Sciences	NCT04053387; PSOARING 3
Tapinarof, vehicle cream	Plaque psoriasis	Adult	3	Completed	USA, Canada	Dermavant Sciences	NCT03983980; PSOARING 2
Tapinarof, vehicle cream	Plaque psoriasis	Adult	3	Completed	USA, Canada	Dermavant Sciences	NCT03956355; PSOARING 1
Tapinarof	Plaque psoriasis	Adult	2	Completed	USA	Dermavant Sciences	NCT04042103
Tapinarof, vehicle cream	Plaque psoriasis	Adult	2	Completed	USA, Canada, Japan	GlaxoSmithKline	NCT02564042
Tapinarof	Atopic dermatitis	Adult, pediatric	3	Recruiting	USA, Canada	Dermavant Sciences	NCT05142774; ADORING 3
Tapinarof, vehicle cream	Atopic dermatitis	Adult, pediatric	3	Recruiting	USA, Canada	Dermavant Sciences	NCT05032859; ADORING 2
Tapinarof, vehicle cream	Atopic dermatitis	Adult, pediatric	3	Recruiting	USA, Canada	Dermavant Sciences	NCT05014568; ADORING 1
Tapinarof	Atopic dermatitis	Pediatric	2	Recruiting	USA	Dermavant Sciences	NCT05186805
Tapinarof, vehicle cream	Atopic dermatitis	Adult	2	Completed		GlaxoSmithKline	NCT02564055

2.4 Adverse Events

Topical tapinarof cream was generally well tolerated in clinical trials in patients with plaque psoriasis [19–21] and atopic dermatitis [26]. Adverse events were reported in 50.3% of tapinarof cream 1% recipients and 22.4% of vehicle cream recipients in the 12-week PSOARING 1 (NCT03956355) trial and in 54.5% and 26.2% of patients, respectively, in the 12-week PSOARING 2 (NCT03983980) trial; most adverse events were mild or moderate [20]. In pooled data from PSOARING 1 and PSOARING 2 ($n = 1025$), the most common adverse reactions occurring in ≥ 1% of tapinarof cream 1% recipients ($n = 683$) and more frequently than in vehicle cream recipients ($n = 342$) were folliculitis (20% vs 1%), nasopharyngitis (11% vs 9%), contact dermatitis (7% vs 1%), headache (4% vs 1%), pruritus (3% vs 1%) and influenza (2% vs 1%) [7]. Folliculitis in tapinarof cream 1% recipients in the PSOARING 1 and PSOARING 2 trials was mostly mild, resulted in a low rate of study discontinuation (< 1.8%), localized to the hair follicle and did not occur with a higher frequency in areas of skin prone to acne [28]. Grade 3 folliculitis (1 patient) and grade 3 contact dermatitis (1 patient) were reported during treatment with tapinarof cream 1% in the PSOARING 1 and PSOARING 2 trials [20] and 2 patients developed urticaria [7]. Adverse events leading to trial discontinuation were reported in 5.6% of tapinarof cream 1% recipients and 0% of vehicle cream recipients in PSOARING 1 and 5.8% and 0.6% of patients in the respective groups in PSOARING 2 [20]. Adverse reactions leading to discontinuation of treatment with tapinarof cream 1% included contact dermatitis (2.9%) and folliculitis (2.8%) [7]. Application site irritation with tapinarof cream 1%, as rated by both patients and investigators, was no worse than 'mild', including when applied to sensitive or intertriginous areas [20].

Tapinarof cream 1% continued to be well tolerated during longer-term treatment in the open-label PSOARING 3 trial (NCT04053387) [7, 21]. In 763 patients who were treated with tapinarof cream 1% for up to an additional 40 weeks, the only adverse reactions reported in addition to those occurring in PSOARING 1 and PSOARING 2 were urticaria (1%) and drug eruption (0.7%) [7].

In a phase 2a maximal use study of tapinarof cream 1% once daily in patients with plaque psoriasis with ≥ 20% BSA involvement, treatment-emergent adverse events (TEAEs) were reported in 12 of 21 patients (57.1%) [19]. Folliculitis (in 4 patients) and headache (in 2 of 4 patients reporting the adverse event) were considered to be related to treatment. Tapinarof cream 1% was well tolerated at all application sites, including sensitive areas such as the face, axilla, neck, anal crux, inframammary areas and genitalia [19].

In a phase 2 dose-finding trial in patients with atopic dermatitis (NCT02564055), TEAEs were reported in 51% of subjects (56% of tapinarof cream recipients and 41% of vehicle cream recipients); most TEAEs were mild to moderate in intensity [26]. Patients aged 12–65 years ($n = 247$) were randomized to receive tapinarof cream 1% or 0.5% twice daily, tapinarof cream 1% or 0.5% once daily or vehicle cream once or twice daily for 12 weeks. The most frequent TEAEs in ≥ 5% of patients in any arm or in total were

nasopharyngitis (8%), folliculitis (7%), worsening/flare of atopic dermatitis (6%) and upper respiratory tract infection (6%). TEAEs considered to be treatment related occurred in 13% of patients (32/247) and 5% of patients (13/247) discontinued treatment due to TEAEs, mainly in the vehicle cream arms [7% (6/82) of vehicle cream vs 4% (7/165) of tapinarof cream recipients) [26].

2.5 Ongoing Clinical Trials

The majority of ongoing trials of tapinarof cream 1% are in patients with atopic dermatitis. These include trials comprising the phase 3 ADORING program in patients aged ≥2 years with moderate to severe atopic dermatitis [ADORING 1 (NCT05014568); ADORING 2 (NCT05032859); ADORING 3 (NCT05142774)] [29] and a phase 2 maximal use trial in pediatric patients with extensive atopic dermatitis (NCT05186805), all of which are currently recruiting. A phase 3 trial in pediatric patients with plaque psoriasis (NCT05172726) is also recruiting.

3 Current Status

Tapinarof cream 1% received its first approval on 23 May 2022 for the topical treatment of plaque psoriasis in adults in the USA [7, 8].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-022-01748-6.

Declarations

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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