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 ORIGINAL ARTICLE

Tapinarof, a Novel, First-in-Class, Topical Therapeutic Aryl Hydrocarbon Receptor Agonist for the Management of Psoriasis

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ABSTRACT

Topical treatments remain the foundation of psoriasis management. Tapinarof (VTAMA®; Dermavant Sciences, Inc.) is a first-in-class, non-steroidal, topical, aryl hydrocarbon receptor (AhR) agonist approved by the US Food and Drug Administration for the treatment of plaque psoriasis in adults and is under investigation for the treatment of psoriasis in children, and atopic dermatitis in adults and children down to 2 years old. Here, we review the mechanism of action of tapinarof and the PSOARING phase 3 trial program in mild to severe psoriasis. AhR is a ligand-dependent transcription factor involved in maintaining skin homeostasis. Tapinarof specifically binds to AhR to decrease proinflammatory cytokines, decrease oxidative stress, and promote skin barrier normalization. In two identical, randomized, 12-week pivotal phase 3 trials, PSOARING 1 and 2, tapinarof cream 1% once daily (QD) demonstrated significant efficacy versus vehicle and was well tolerated in adults with mild to severe psoriasis. In the PSOARING 3 long-term extension trial of repeated, intermittent tapinarof cream in eligible patients completing the pivotal trials, a high rate of complete disease clearance (40.9%) and a remittive effect of approximately 4 months off therapy were demonstrated over 52 weeks, with no tachyphylaxis. The most common adverse event, folliculitis, was mostly mild or moderate and resulted in a low trial discontinuation rate in PSOARING 1 and 2 (≤1.8%). Tapinarof cream 1% QD provides a novel, non-steroidal, topical treatment option for patients with psoriasis and is highly effective and well tolerated with long-term use including when applied to sensitive and intertriginous skin.

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INTRODUCTION

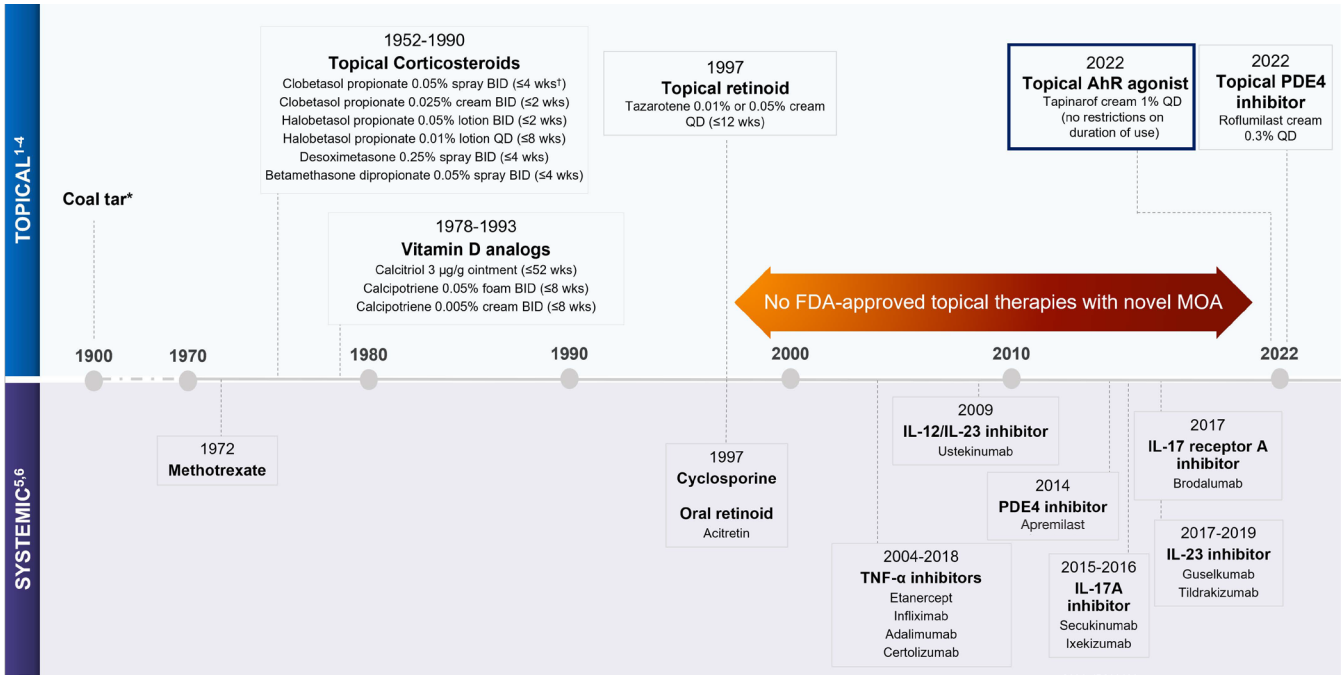
Current Treatments and Unmet Needs in Psoriasis

Psoriasis is a chronic, immune-mediated skin disease that affects approximately 8 million adults in the Unite States and 2% to 3% of people worldwide.[1-3] Psoriasis is characterized by scaly, erythematous, pruritic plaques that can be painful and unsightly, with itch being the most prevalent and burdensome symptom.[2,4] Although skin manifestations are the hallmark of psoriasis, it is considered to be a systemic inflammatory disease that often coexists with conditions such as psoriatic arthritis, obesity, and cardiovascular and psychiatric complications.[2,5,6] The significant physical, psychological, and socioeconomic burdens experienced by patients with psoriasis can include an increased risk of anxiety, depression, and suicidal ideation.[6-8]

Psoriasis is primarily managed by dermatologists, nurse practitioners, and physician assistants specializing in dermatology, and also by rheumatologists and primary care physicians. Treatment is guided by disease severity measured by the extent and location of skin affected (eg, using the Physician Global Assessment [PGA]), and by evaluation of patients' own experiences.[9]

Most patients with plaque psoriasis have mild to moderate disease, and topical therapy is considered to be an appropriate treatment.[5,10,11] In addition to their use in mild to moderate disease, topical therapies are often used as adjunctive treatment regardless of disease severity.[11] Treatments indicated for moderate to severe psoriasis include oral systemic medications

FIGURE 1. History of innovation in psoriasis therapy based on FDA approval in the US, including approved dosing regimen and restrictions regarding duration of use for topical agents.



*Available in the US (not approved by the FDA). †Greater than 2 weeks of treatment is limited to localized moderate/severe lesions that insufficiently improve.
AhR, aryl hydrocarbon receptor; BID, twice per day; FDA, US Food and Drug Administration; IL, interleukin; MOA, mechanism of action; PDE4, phosphodiesterase 4; QD, daily; TNF, tumor necrosis factor; wks, weeks.
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(eg, methotrexate, cyclosporine, apremilast, deucravacitinib, and acitretin), biologic therapies (including inhibitors of tumor necrosis factor-alpha, interleukin [IL]-12/IL-23, IL-23, and IL-17), and phototherapy.[5,9,12,13] Certain topical therapies are associated with restrictions on duration, extent, and site of application, and with local irritation and other adverse events (AEs).[11] Adherence challenges and low patient satisfaction with topical therapies can also be due to frequency and difficulty of application, the associated time burden, and properties of the formulation and vehicle, such as texture and odor.[14-16]

Here, we review the development of tapinarof (VTAMA®; Dermavant Sciences, Inc.), a first-in-class, non-steroidal, topical, aryl hydrocarbon receptor (AhR) agonist approved by the US Food and Drug Administration (FDA) in May 2022 for the treatment of plaque psoriasis in adults, and under investigation for the treatment of psoriasis in children down to 2 years of age and for atopic dermatitis (AD) in adults and children down to 2 years of age.

History of Psoriasis Treatments

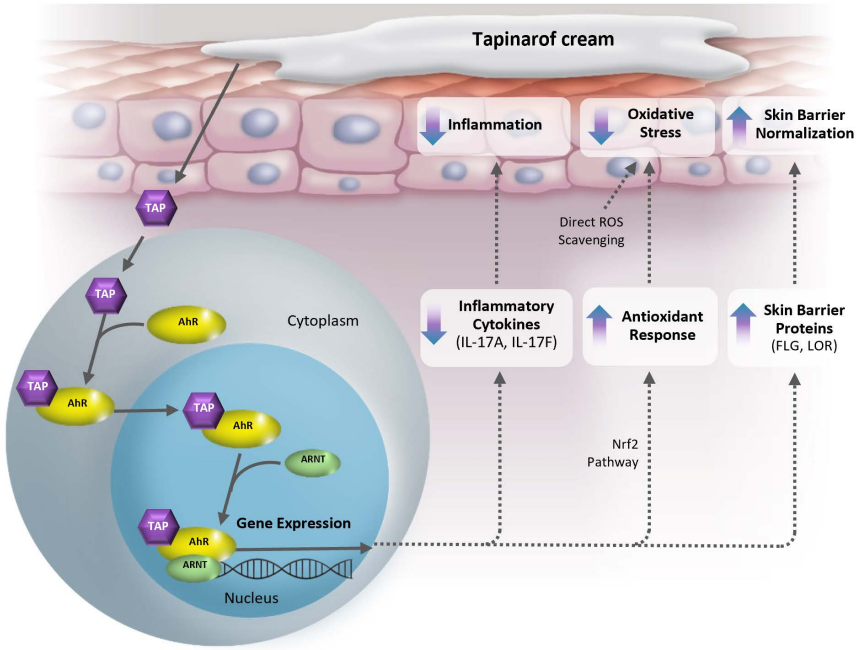
Progress in the development of psoriasis treatments over the last 50 years is summarized in Figure 1. Until recently, the only FDA-approved topical treatments for psoriasis were corticosteroids, vitamin D analogs, and retinoids.[11,17] Although these therapies may be efficacious, especially for short-term treatment of localized disease, they have limitations based on affected body surface area, duration of use, and location of application.[11] Use of corticosteroids may also be limited by the potential for skin atrophy, recurrence of symptoms after cessation of treatment, tachyphylaxis, and patient and/or prescriber aversion/fear of their use.[11,18] Other topical agents, including calcipotriene and tazarotene, have modest efficacy as monotherapies and well-documented AEs, including erythema and skin irritation.[11,19]

NOVEL TOPICAL THERAPY

Development of Tapinarof

The discovery of tapinarof was a fortuitous outcome of investigations into secondary metabolites of a bioluminescent bacterium, *Photorhabdus luminescens*, which lives symbiotically in soil-living nematode worms that parasitize insects.[17] Insects infected by the nematodes did not decay after death and the investigator hypothesized that metabolites produced by the bacteria were responsible for this effect.[17] One metabolite was purified and identified as 3,5-dihydroxy-4-isopropylstilbene (tapinarof), which demonstrated anti-inflammatory properties

FIGURE 2. Proposed mechanism of action of tapinarof in plaque psoriasis.



AhR, aryl hydrocarbon receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; FLG, filaggrin; IL, interleukin; LOR, loricrin; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; TAP, tapinarof. Bissonnette R, et al. *J Am Acad Dermatol.* 2021;84:1059-1067.

and potent binding to AhR.[17,20] Tapinarof is now synthetically produced and formulated in a topical cream.[21,22]

The Aryl Hydrocarbon Receptor Pathway and Tapinarof Mechanism of Action

AhR is a transcription factor expressed by various cell types, including immune cells and epithelial cells in barrier tissues such as skin, gastrointestinal tract, and lungs.[23] In the skin, AhR helps maintain homeostasis by mediating responses to chemical and environmental challenges. Transcription factors such as AhR regulate gene expression and directly mediate diverse effects by binding to specific DNA sequences. AhR can be activated by a wide range of molecules (ligands) found in endogenous, dietary, environmental, and microbial sources.[23] An important characteristic of AhR is its differential activation by a wide range of ligands, which elicits induction or suppression of various genes resulting in diverse signaling and biologic responses.[17] AhR can also signal through other transcription factors, leading to varied biologic effects that are highly dependent on the specific ligand.[23,24]

AhR has been shown to regulate the expression of T-helper (Th) 17 and Th22 immune cells, and IL-17 and IL-22 cytokines, which are implicated in psoriasis.[25] AhR is also implicated in Th2 cell differentiation, and IL-4 and IL-5 production, which are important in the pathogenesis of AD.[26] Furthermore, impaired skin barrier function in psoriasis and AD is associated with downregulation of skin barrier proteins (filaggrin, loricrin, and involucrin); these proteins are upregulated by AhR activation and signaling.[24]

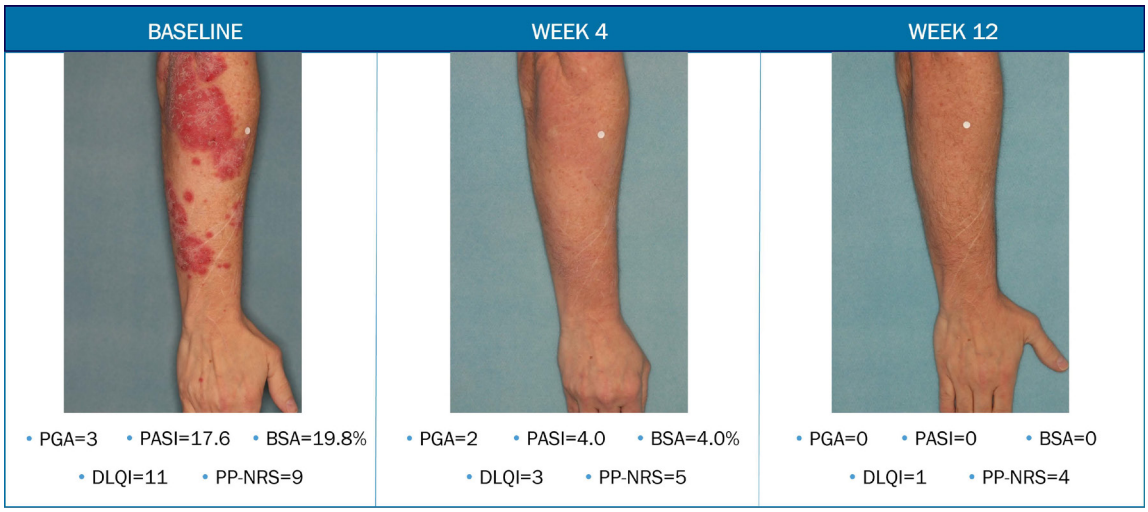
The proposed mechanism of action of tapinarof in psoriasis is shown in Figure 2. Once tapinarof binds to AhR, the tapinarof–AhR complex moves to the nucleus and binds to the AhR nuclear translocator (ARNT), creating a high-affinity DNA-binding transcription factor.[17,23,24] The tapinarof–AhR/ARNT complex binds to specific DNA recognition sites of AhR-responsive genes and modulates gene expression.[23,24]

The unique clinical profile of tapinarof results from specific binding to AhR. Tapinarof binds to and activates AhR to downregulate pro-inflammatory cytokines implicated in psoriasis (IL-17A and IL-17F), which most likely contributes to its rapid therapeutic benefit.[20] Additionally, tapinarof-activated AhR decreases oxidative stress through the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway; and the tapinarof molecule directly scavenges reactive oxygen species (Figure 2).[20] Tapinarof also promotes skin barrier normalization by increasing skin barrier proteins related to keratinocyte differentiation, including filaggrin and loricrin.[17,20]

Tapinarof Cream for Psoriasis and Atopic Dermatitis

The PSOARING phase 3 trial program that evaluated tapinarof cream to treat plaque psoriasis in adults launched in 2019 with two identical, multicenter, double-blind, vehicle-controlled trials, PSOARING 1 (NCT03956355) and PSOARING 2 (NCT03983980), followed by the long-term extension trial, PSOARING 3 (NCT04053387).[22,27] The ADORING phase 3 trial program of tapinarof cream for the treatment of AD in adults and children began in 2021.[28]

FIGURE 3. Clinical response of a patient with plaque psoriasis treated with tapinarof cream 1% QD who achieved primary and secondary efficacy endpoints at week 12 in the PSOARING 1 clinical trial. PGA and PASI are global efficacy assessments. Example of one representative target lesion of one tapinarof-treated patient from PSOARING 1 clinical trial.



BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily.

Efficacy of Tapinarof Cream for Psoriasis

Tapinarof cream 1% once daily (QD) demonstrated statistically significant efficacy vs vehicle and was well tolerated in adults with mild to severe plaque psoriasis in the two 12-week, pivotal phase 3 trials, PSOARING 1 (N=510) and PSOARING 2 (N=515).[22] Eligible patients had a PGA score of 2 (mild) to 4 (severe) and a percentage body surface area (%BSA) affected of 3% to 20% at baseline. Patients were randomly assigned 2:1 to tapinarof cream or vehicle cream QD for 12 weeks, after which eligible patients could enroll in PSOARING 3. The primary endpoint was PGA response, defined as a PGA score of 0 (clear) or 1 (almost clear), and a decrease of at least 2 points from baseline at week 12. This was achieved by a significantly higher proportion of patients in the tapinarof group vs vehicle in PSOARING 1 and 2: 35.4% vs 6.0% and 40.2% vs 6.3%, respectively (both $P<0.0001$).[22,29] All secondary efficacy endpoints were met for tapinarof cream vs vehicle in PSOARING 1 and 2 ($P\leq0.0005$). These included: the proportion of patients with a reduction of at least 75% in the Psoriasis Area and Severity Index (PASI) score (PASI75) at week 12 (36.1% vs 10.2% and 47.6% vs 6.9% in PSOARING 1 and 2, respectively); the proportion with a PGA score of 0 or 1 at week 12 (37.8% vs 9.9% and 43.6% vs 8.1%); the mean change from baseline in %BSA affected at week 12 (–3.5% vs –0.2% and –4.2% vs 0.1%); and the proportion with a reduction of at least 90% in the PASI score (PASI90) at week 12 (18.8% vs 1.6% and 20.9% vs 2.5%).[22,29,30] Figure 3 shows a patient treated with tapinarof cream who achieved primary and secondary efficacy endpoints at week 12.

Improvements with tapinarof cream were seen as early as the first clinical assessment at week 2 and continued to week 12; additional efficacy was achieved in the long-term extension trial, PSOARING 3.[30] The efficacy of tapinarof cream was consistent across a broad spectrum of disease severity (as evaluated by PGA score, %BSA affected, and duration of disease) and patient demographics (including sex, age, race, and country of enrollment [US or Canada]).[31]

PSOARING 3 assessed the safety, efficacy, and tolerability of tapinarof cream 1% QD, as well as durability of response on therapy (absence of tachyphylaxis), and duration of remittive effect off therapy.[27] Patients received up to 40 weeks of open-label treatment followed by 4 weeks of follow-up off treatment. Therefore, patients could be treated with up to 52 weeks of tapinarof from PSOARING 1 and 2 baseline through PSOARING 3 completion.[27]

In PSOARING 3, patients were treated based on their PGA score. Those entering the trial with PGA≥1 received tapinarof cream until complete disease clearance was achieved (PGA=0). Patients entering with, or achieving, PGA=0 discontinued treatment and were monitored for the duration of remittive effect, defined as off-therapy maintenance of PGA=0 or 1. Patients with PGA≥2 were treated or re-treated until PGA=0.

In total, 91.6% (n=763) of eligible patients completing PSOARING 1 and 2 elected to enroll in PSOARING 3. Overall, 40.9% (n=312) achieved complete disease clearance (PGA=0) at least once during the trial. Among patients entering with PGA≥2, 58.2% (n=302) achieved PGA=0 or 1. Among patients achieving PGA=0 at any time during the trial (n=312), the mean total duration of remittive effect off treatment was approximately 4 months

(130 days). For patients entering the trial with PGA=0 (n=79), the median duration of remittive effect off treatment was also approximately 4 months (115 days). Durability of response on treatment (ie, no tachyphylaxis) of up to 52 weeks was observed. Treatment with tapinarof cream in PSOARING 1 and 2 resulted in rapid, clinically meaningful, and statistically significant improvements in patient-reported outcomes. This included itch as measured by the Peak Pruritus Numerical Rating Scale, quality of life measured by the Dermatology Life Quality Index (DLQI), and psoriasis symptoms and functional health measured by Psoriasis Symptom Diary scores.[32] Continued and durable improvement in quality of life (DLQI) was demonstrated in PSOARING 3.[33]

Safety and Tolerability of Tapinarof Cream in Psoriasis

Tapinarof cream 1% QD was well tolerated with long-term use up to 52 weeks as reported by patients and investigators, including when applied to sensitive and intertriginous skin areas.[27]

Most treatment-emergent AEs in PSOARING 1 and 2 were mild or moderate in severity and did not lead to trial discontinuation.[22] The most common treatment-emergent AEs overall were folliculitis, nasopharyngitis, and contact dermatitis.[22] AEs of special interest, identified from phase 2 trials, were folliculitis, contact dermatitis, and headache, which were mostly mild or moderate. Tapinarof has a role in regulating skin barrier protein expression; consequently, tapinarof-induced folliculitis may involve follicular cornification and plugging following upregulation of components of the stratum corneum associated with keratinocyte differentiation.[24,34] Therefore, folliculitis may be an 'on-target' effect of topical tapinarof, is generally mild and self-limiting, and does not interfere with therapy.[35] There was only one severe (grade 3) event each of folliculitis, contact dermatitis, and headache occurring across the phase 3 PSOARING program with up to 52 weeks of treatment. Trial discontinuation rates due to AEs of special interest were low in PSOARING 1 and 2 (≤1.8%, ≤2.0%, and ≤0.6% for folliculitis, contact dermatitis, and headache, respectively) and PSOARING 3 (1.2%, 1.4%, and 0%, respectively).[22,27]

Patient Satisfaction with Tapinarof Cream for Psoriasis

In PSOARING 3, patient satisfaction with efficacy, formulation elegance, application ease, impact on daily life, and preference for tapinarof vs prior therapies was assessed at week 40 (or early termination) using a Patient Satisfaction Questionnaire®.[36] Most patients either strongly agreed or agreed that they could easily manage their psoriasis with tapinarof (85.8%), were satisfied with how well tapinarof worked (83.6%), felt that tapinarof cleared their skin and prevented psoriasis from returning (62.9%), had confidence in tapinarof (84.1%), would recommend tapinarof to other patients with psoriasis (84.0%), and would use tapinarof again or continue tapinarof if it was available (82.5%). Most patients were satisfied with the time spent applying tapinarof (93.2%) and felt that tapinarof was easy to apply (96.3%), was quickly absorbed (89.5%), felt good on their skin (79.9%), was not greasy (89.0%), and were satisfied with the look and feel of tapinarof (87.7%). In patients who had previously used other topical agents and those who had used systemic drugs, the majority considered tapinarof more effective, easier to use, and preferred versus previous agents.

Clinical Use of Tapinarof Cream to Treat Plaque Psoriasis

Patients should be advised to apply tapinarof cream as a thin layer once daily to affected areas.[37] Tapinarof cream has no warnings, restrictions on location of application or duration of use, precautions, contraindications, or drug interactions; it is not for oral, ophthalmic, or intravaginal use.[37] Pharmacokinetic evaluation of topical tapinarof in patients with psoriasis has demonstrated minimal systemic exposure, which supports the absence of restrictions and of drug–drug interactions.[24,34,37]

CONCLUSION

Tapinarof cream 1% QD is a novel, non-steroidal topical treatment that binds to a distinct site on AhR, creating unique biological outcomes that manifest clinically as therapeutic disease control for patients with psoriasis. The proposed mechanism of action includes decreasing pro-inflammatory cytokines, decreasing oxidative stress, and promoting skin barrier normalization. The remittive effect demonstrated in the long-term extension trial may be attributed to the additional roles of AhR in modulating T-cell responses that are a major component of psoriatic lesions.[38]

Tapinarof cream was efficacious and well tolerated in adult patients with mild, moderate, or severe plaque psoriasis, including on sensitive and intertriginous skin areas, and demonstrated an approximately 4-month remittive effect off therapy and no tachyphylaxis on therapy with long-term use. The most common AE was folliculitis, which was mostly mild or moderate in severity, likely representing an 'on target' effect of tapinarof, and resulted in few trial discontinuations. Tapinarof cream 1% QD is a new topical treatment indicated for patients with plaque psoriasis with no restrictions regarding duration of use, application site, concomitant therapies, and extent of body surface area affected.

DISCLOSURES

Margaret Bobonich has served as a speaker and/or consultant for AbbVie, Boehringer Ingelheim, Biofrontera, Bristol Myers Squibb, Dermavant Sciences, Inc., Eli Lilly, Novartis, and UCB Biopharma.

Joe Gorelick has served as a consultant and/or speaker for AbbVie, Bristol Myers Squibb, Eli Lilly, Incyte, Janssen, LEO Pharma, Novartis, Pfizer, Sun Pharmaceuticals, and UCB Biopharma.

Lakshi Aldredge has served as a speaker and/or consultant and/or involved in advisory boards for AbbVie, Amgen, Arcutis, Bristol Myers Squibb, Dermavant Sciences Inc, Eli Lilly, Incyte, Janssen, Leo Pharma, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharma, and UCB Biopharma.

Matthew J. Bruno has served as a consultant, and/or received payment for promotional presentations from AbbVie, Almirall, Bristol Myers Squibb, Dermavant Sciences, Inc., EPI Health, Journey Medical Corporation, Mayne Pharma, Medimetriks Pharmaceuticals, Pfizer, Regeneron/Sanofi-Genzyme, and Sun Pharmaceuticals.

Douglas DiRuggiero has served as a speaker and/or has been involved in advisory boards for AbbVie, Amgen, Arcutis, Bristol Myers Squibb, EPI Health, Eli Lilly, Incyte, Novartis, Regeneron, Sanofi, Sun Pharmaceuticals, and UCB Biopharma.

George Martin has served as a speaker and/or consultant and/or has been involved in scientific advisory boards for AbbVie, Almirall, Arcutis, Biofrontera, Bristol Myers Squibb, Dermavant Sciences, Inc., DUSA/SUN, Eli Lilly, Evelo, Galderma, Horizon, Incyte, Janssen, LEO Pharma, Ortho/Bausch Health, Organogenesis, Pfizer, Sanofi/Regeneron, Trevi, and UCB Biopharma.

Anna M. Tallman is an employee of Dermavant Sciences Inc., with stock options.

Linda Stein Gold has served as a consultant, and/or has received payment for the development of educational presentations, and/or has received grants from Amgen, Arcutis, Bristol Myers Squibb, Dermavant Sciences, Inc., Eli Lilly, LEO Pharma, Ortho Dermatologics, Pfizer, and UCB Biopharma.

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