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# Phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of plaque psoriasis



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**Background:** There is a significant need for novel, safe, and efficacious topical treatments for psoriasis.

**Objective:** We assessed the safety and efficacy of tapinarof in a new cream formulation at 2 concentrations and with 2 application frequencies in adults with psoriasis.

**Methods:** Double-blind, vehicle-controlled, randomized, 6-arm trial (1:1:1:1:1:1) in adults, with psoriasis with body surface involvement  $\geq 1\%$  and  $\leq 15\%$  and Physician Global Assessment (PGA) score  $\geq 2$  at baseline. Primary endpoint included PGA of 0 or 1 at week 12 and a 2-grade improvement from baseline. Additional analyses included assessment of  $\geq 75\%$  improvement of Psoriasis Area and Severity Index and mean percent change in Psoriasis Area and Severity Index and body surface area involvement.

**Results:** Treatment success defined by PGA 0 or 1 and a 2-grade improvement at week 12 was statistically significantly higher (at a .05 significance level) in the tapinarof groups (65% [1% twice daily], 56% [1% once daily], 46% [0.5% twice daily], and 36% [0.5% once daily]) than in the vehicle groups (11% [twice daily] and 5% [once daily]) and was maintained for 4 weeks posttreatment. Treatment-emergent adverse events were more frequent in patients treated with tapinarof (85/152, 56%) than vehicle (19/75, 25%) and mild-to-moderate in intensity. Severe treatment-emergent adverse events were reported in all tapinarof groups except the 0.5% once daily group.

**Limitations:** Large confirmation trials are needed.

**Conclusions:** Tapinarof cream is efficacious and well tolerated in adult patients with psoriasis. (J Am Acad Dermatol 2019;80:714-21.)

**Key words:** GSK2894512; psoriasis; TAMA; tapinarof; therapeutic AhR (aryl hydrocarbon receptor) modulating agent.

Psoriasis vulgaris is a chronic, relapsing skin disease with a multifactorial pathogenesis influenced by genetic, environmental, and immunopathologic factors. It is relatively common, affecting 2%-3% of white persons.<sup>1,2</sup> Although the

treatment of moderate-to-severe psoriasis has been revolutionized with the introduction of highly effective biologics, topical therapies continue to play a key role in the management of mild-to-moderate psoriasis; up to 80% of patients use topicals as their

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From GSK, Collegeville<sup>a</sup>; Innovaderm Research Inc, Montreal<sup>b</sup>; Novan Inc, Morrisville<sup>c</sup>; PRA Health Sciences, Raleigh<sup>d</sup>; and ICON plc, Research Triangle Park.<sup>e</sup>

Funding sources: Supported by GSK (protocol 203120).

Conflicts of interest: Dr Bissonnette served as a consultant, investigator, advisory board member, or speaker or received honorarium and/or grants from Abbvie, Amgen, Boehringer Ingelheim, BMS, Celgene, Eli Lilly, Galderma, Immune Tolerance, Incyte, Janssen, Kineta, Leo Pharma, Merck, Novartis, Pfizer, Xenoport, and GSK. Dr Bissonnette is a shareholder of Innovaderm Research. Drs Maeda-Chubachi, Peppers, and Kraus were employees and stockholders of GSK when the

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study was conducted. Mr Robbins, Ms Ye, and Ms Gallagher are employees and shareholders of GSK.

Accepted for publication October 22, 2018.

Reprints not available from the authors.

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Published online October 26, 2018.

0190-9622/\$36.00

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<https://doi.org/10.1016/j.jaad.2018.10.037>

main or only therapy.<sup>3,4</sup> Of topical treatment options, vitamin D analogs are moderately efficacious as monotherapy, while application of topical corticosteroids—particularly potent ones—is restricted in terms of the body areas that can be treated and duration of use because of the well-known risks for skin atrophy and systemic adverse drug reactions.<sup>5</sup> Although new systemic treatments offer highly efficacious treatment options to those with moderate-to-severe psoriasis, most patients have limited body surface area (BSA) involvement and might not be eligible for biologics. For this population, there has been no new class of topical drugs approved in the past 20 years, and there is a need for a topical treatment with a high level of efficacy and an acceptable safety profile, permitting application to all involved areas and an extended duration of treatment.

Psoriatic skin lesions contain elevated numbers of activated T cells, which have a key role in the pathogenesis of inflammatory diseases through the proliferation and secretion of pro-inflammatory cytokines (eg, interleukin [IL] 17A and tumor necrosis factor  $\alpha$ ).<sup>6</sup> In recent years, the role of immune system dysregulation has been strongly implicated in the pathogenesis of plaque psoriasis, involving autoantigens (ADAMTSL5 and LL37 are significantly decreased by IL-17 or tumor necrosis factor  $\alpha$  blockade), aberrant cellular infiltrates, production of inflammatory mediators, and keratinization.<sup>7-9</sup> Central to this process are the T-helper cell 17-type cytokines (IL-17A, IL-17F, and IL-22), which drive keratinocyte hyperproliferation and chemokine production that perpetuates leukocyte recruitment.<sup>10,11</sup>

Tapinarof [GSK2894512; 5-[(E)-2-phenylethenyl]-2-(propan-2-yl) benzene-1,3-diol] is a nonsteroidal topical agent that represents a unique class of anti-inflammatory compounds known as therapeutic aryl hydrocarbon receptor (AhR)—modulating agents. This molecule has a novel mechanism of action of directly binding the AhR and activating the AhR pathway in multiple cells and tissue-based systems, resulting in reduced expression of IL-17A.<sup>12</sup> It has been demonstrated that AhR activation significantly reduces the inflammatory profile in both samples from psoriasis patients and a mouse model of

psoriasiform skin.<sup>12,13</sup> The transcription factor AhR controls the expression of IL-21 and IL-22 and plays an important role in the differentiation of T-helper 17 cells in vivo and in vitro.<sup>14</sup> In addition, tapinarof functions as an antioxidant by inhibiting reactive oxygen species both via inherent antioxidant activity of the stilbene structure and partial activation of the nuclear factor erythroid 2—related factor 2 pathway.<sup>12</sup> This unique pattern of inhibition of pro-inflammatory mediators clearly distinguishes this compound from immunosuppressive agents commonly used to treat psoriasis. By targeting AhR, tapinarof might represent an important advance in topical medicine development for immunoinflammatory skin diseases.

Here, we report the results of a phase 2 clinical study performed to evaluate the safety and efficacy of 2 concentrations (0.5% and 1%) and 2 application frequencies (once daily or twice daily) of tapinarof cream in adult patients with plaque psoriasis.

## METHODS

### Study design and oversight

This randomized, double-blind, vehicle-controlled, 6-arm, multicenter phase 2 study was designed to determine the optimal tapinarof concentration (0.5% or 1%) and dosing frequency (once daily or twice daily) compared with a cream containing no active drug (vehicle). The study was conducted during November 2015–October 2016 at 17 sites in the United States, 12 sites in Canada, and 11 sites in Japan in adults (aged 18–65 years) with psoriasis ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02564042) NCT02564042).

The study consisted of 3 periods: up to 4 weeks screening, 12 weeks double-blind treatment, and 4 weeks posttreatment follow-up. Study visits occurred at screening; baseline; weeks 1, 2, 4, 8, and 12 during the treatment period; and 2 and 4 weeks after the last application of study treatment (Fig 1).

The study was conducted in compliance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. Approval was obtained from the local ethics committee or institutional review board at each study center. All patients

## CAPSULE SUMMARY

- Novel topical treatments for psoriasis have not been developed for many years.
- Tapinarof, a therapeutic aryl hydrocarbon receptor—modulating agent, is a potential new treatment option for psoriasis patients. Tapinarof, delivered in a 1% cream, achieved  $\geq 75\%$  improvement in Psoriasis Area and Severity Index in 60% of patients treated once daily.

*Abbreviations used:*

AE:	adverse event
AhR:	aryl hydrocarbon receptor
BSA:	body surface area
CI:	confidence interval
PASI:	Psoriasis and Area Severity Index
PASI75:	≥75 improvement in Psoriasis and Area Severity Index
PGA:	Physician Global Assessment
PASI:	Psoriasis Area and Severity Index
IL:	interleukin
TEAE:	treatment-emergent adverse event

provided written informed consent. The trial was designed by the study sponsor, GSK.

**Patients**

Patients were assigned to study treatment in accordance with the randomization schedule, which was stratified by geographic region (North America or Japan). Patients meeting all enrollment criteria were randomized via an interactive web response system in a ratio of 1:1:1:1:1:1 (1% tapinarof twice daily: 1% tapinarof once daily: 0.5% tapinarof twice daily: 0.5% tapinarof once daily: vehicle twice daily: vehicle once daily). Key inclusion criteria were that patients (male or female) had to be 18-65 years of age and have a clinical diagnosis of chronic, stable plaque psoriasis for ≥6 months, BSA involvement ≥1% and ≤15% (excluding scalp) at screening and baseline, and a Physician Global Assessment (PGA)

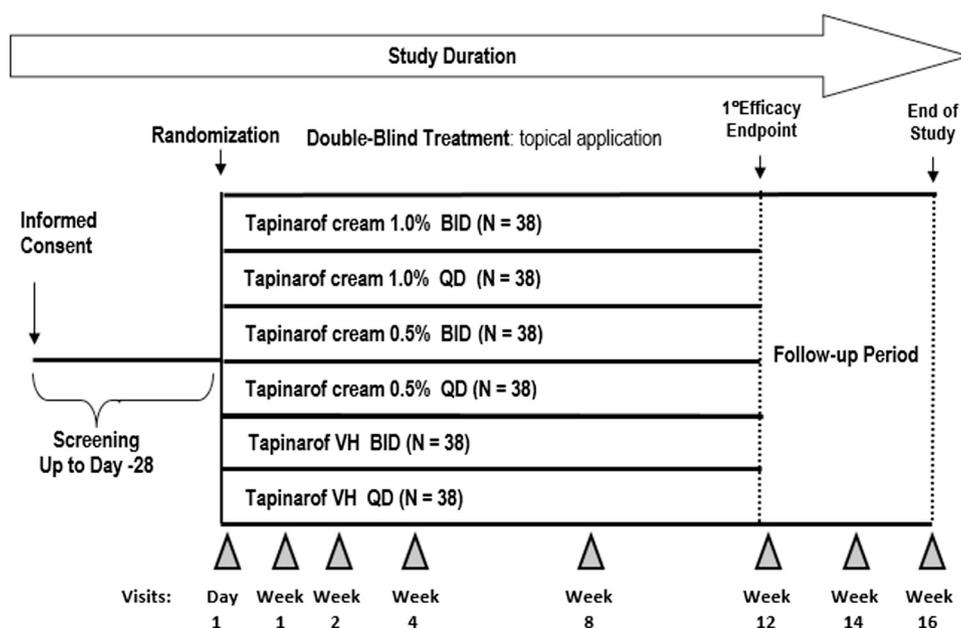
of psoriasis score ≥2 at baseline. Key exclusion criteria were any sign of infection of any psoriatic lesion(s) and a history or ongoing serious illness (medical, physical, or psychiatric). Certain medications were prohibited during the study.

**Study treatment**

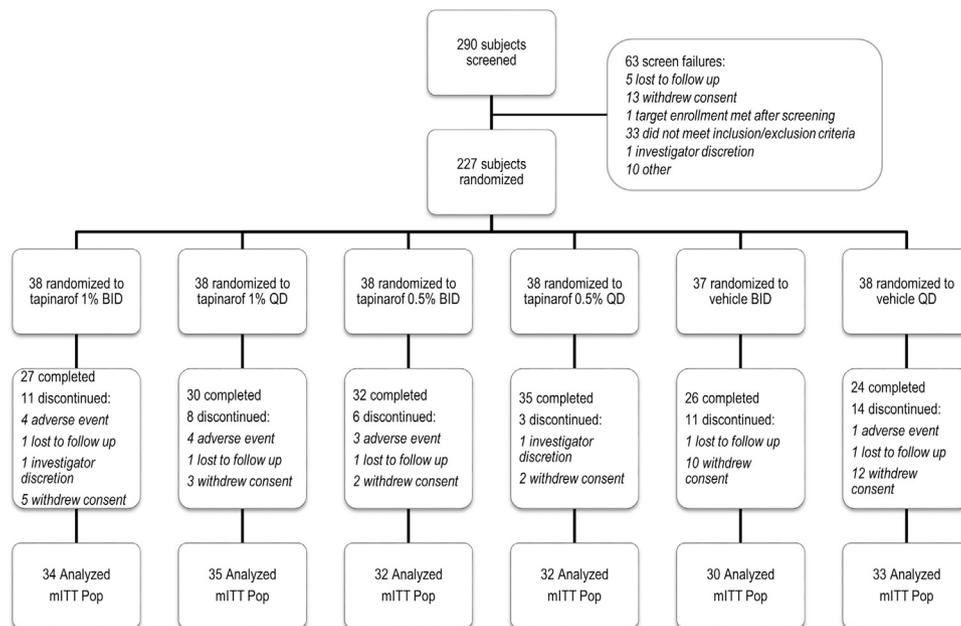
Patients were instructed to apply a thin layer of study treatment to all psoriasis lesions (excluding scalp) once daily or twice daily (approximately the same time daily or ~12 hours apart). Patients were to continue to treat all original areas of involvement, even in the event of lesions clearing, and apply the treatment to any new lesions.

**Efficacy and safety evaluation**

The primary efficacy endpoint was the proportion of patients with a PGA score of clear or almost clear (0 or 1) at week 12 and a minimum 2-grade improvement in the static 5-point PGA score from baseline to week 12 (treatment success defined by PGA).<sup>15</sup> At each specified time point, PGA scoring was performed without reference to previous scores. Secondary endpoints included the proportion of patients with ≥75% improvement in Psoriasis Area and Severity Index (PASI75) from baseline to each study visit.<sup>16</sup> Additional secondary endpoints included PGA assessment at each visit and mean percent change in PASI and BSA. Primary safety assessments included incidence and frequency of



**Fig 1.** Study schematic. *BID*, Twice daily application; *QD*, once daily application; *VH*, vehicle.



**Fig 2.** Trial profile. *BID*, Twice daily application; *QD*, once daily application; *mITT pop*, modified intent-to-treat population.

adverse events (AEs) and serious AEs, evaluation of local (application site) tolerability, clinical laboratory parameters, vital signs, electrocardiogram changes, and physical examinations. An unblinded independent data monitoring committee monitored the patient safety.

### Sample size and statistical analysis

For the sample size, it was expected that 228 patients would be randomized to achieve ~204 evaluable patients overall. Complete data from the expected evaluable patients would provide model-based 95% confidence intervals (CIs) for the PGA response estimates that were 19.3% wide on average.

The primary objective of this study was to estimate the clinical dose response of tapinarof cream; no formal hypothesis testing was planned.

Summary statistics of frequency counts and percentages and 95% exact CIs were provided for each treatment group at each study visit for PGA treatment success and PASI75. The point estimate and 95% CI were provided for the difference between each active twice daily dose and vehicle twice daily and the difference between each active once daily dose and vehicle once daily at each study visit. Differences are considered statistically significant at an  $\alpha$  of 0.05 level where the 95% CI excludes 0.

For percent changes in PASI score and change in percent BSA affected from baseline to each study visit, summary statistics of the mean, standard

deviation, median, minimum, maximum, and number of observations were provided.

The primary efficacy analyses were conducted on observed cases using a modified intent-to-treat population (which comprised all randomized patients minus the patients whose eligibility could not be confirmed). For observed case data, there was no imputation for missing data or for patients who discontinued investigational product before week 12; any data after the last known administration of investigational product was excluded from the efficacy analyses.

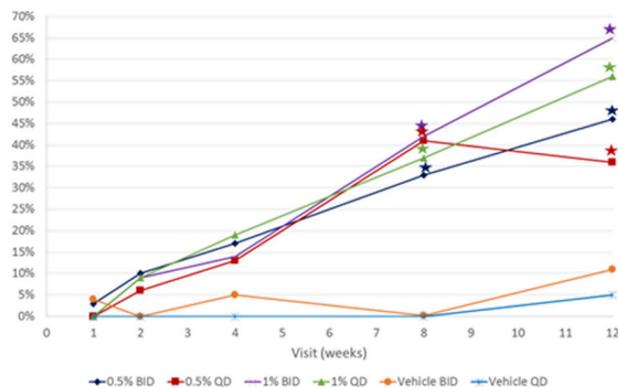
## RESULTS

### Patients

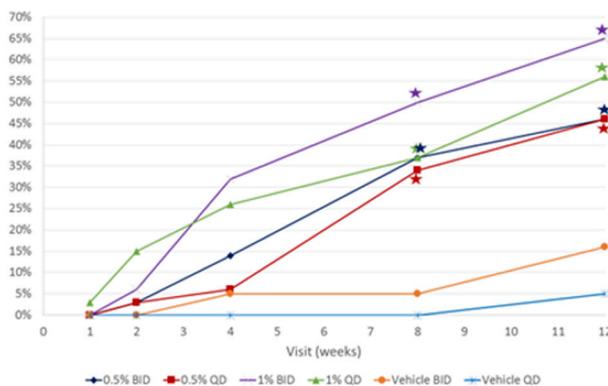
Of the 290 patients originally screened, a total of 227 patients were randomized, and 175 patients completed the 12-week treatment phase (modified intent-to-treat population included 196 patients) (Fig 2). Overall, mean demographic and baseline characteristics were comparable across treatment groups. Most patients (80%) had a baseline PGA category of moderate (score of 3) and a baseline mean PASI score of 8.81.

### Efficacy

The PGA response rates at week 12 were significantly higher (at a 0.05 significance level) in the tapinarof groups (65% [1% twice daily], 56% [1% once daily], 46% [0.5% twice daily], and 36% [0.5% once daily]) than the vehicle groups



**Fig 3.** Percentage of patients who achieved a PGA score of 0 or 1 and a minimum 2-grade improvement from baseline (modified intent-to-treat population, observed cases). All tapinarof groups showed a clear separation from vehicle reaching statistical significance after 8 weeks of treatment, with the 1% concentration showing the highest response rates. \*Significantly greater than the vehicle at an  $\alpha$  of 0.05. *BID*, Twice daily; *PGA*, Physician Global Assessment; *QD*, once a day.



**Fig 4.** Percentage of patients with  $\geq 75\%$  improvement in PASI from baseline (modified intent-to-treat population, observed cases). All tapinarof groups showed a clear separation from vehicle reaching statistical significance after 8 weeks of treatment, with the 1% concentration showing the highest response rates. \* Significantly greater than the vehicle at an  $\alpha$  of 0.05. *BID*, Twice daily; *PASI*, Psoriasis Area and Severity Index; *QD*, once a day.

(11% [twice daily] and 5% [once daily]) (Fig 3). Differences between the active and vehicle groups were 54.7% (95% CI 25.9%-76.6%) for 1% twice daily, 51.0% (95% CI 22.2%-73.2%) for 1% once daily, 35.6% (95% CI 6.3%-60.5%) for 0.5% twice daily, and 30.7% (95% CI 1.6%-55.9%) for 0.5% once daily. PGA treatment success was also significantly greater (at a 0.05 significance level) in the tapinarof treatment groups (58% [1% twice daily], 54% [1% once daily], 35% [0.5% twice daily], and 36% [0.5% once daily]) than in the vehicle groups (5% [twice daily], and 0 [once daily]) at week 12, and this improvement was maintained for 4 weeks after the end of the study treatment (at week 16), except for the 0.5% twice daily group (Fig 3).

PASI75 response rates at week 12 were significantly higher (at 0.05 significance level) in the tapinarof

groups (65% [1% twice daily], 56% [1% once daily], 46% [0.5% twice daily], and 46% [0.5% once daily]) than in the vehicle groups (16% [twice daily] and 5% [once daily]). Differences between the active and vehicle groups were 49.4% (95% CI 20.1%-72.4%) for 1% twice daily, 51.0% (95% CI 22.2%-73.2%) for 1% once daily, 30.4% (95% CI 1.0%-56.1%) for 0.5% twice daily, and 41.4% (95% CI 12.7%-65.0%) for 0.5% once daily. Treatment success of PASI75 indicated tapinarof provided clinically meaningful responses starting around week 2, with efficacy generally maintained for 4 weeks after the end of study treatment (up to week 16), demonstrating a durability of the effect of tapinarof after the treatment period (Fig 4). Mean percent reductions in PASI scores from baseline to week 12 were 76.8% and 77.3% for the tapinarof 1% concentration treatment groups, 63.6% and 68.3% for

**Table I.** Summary of adverse events (safety population)

Category	Tapinarof 1% BID, N = 38, n (%)	Tapinarof 1% QD, N = 38, n (%)	Tapinarof 0.5% BID, N = 38, v	Tapinarof 0.5% QD, N = 38, n (%)	Vehicle BID, N = 37, n (%)	Vehicle QD, N = 38, n (%)	Total, N = 227, n (%)
Patients with AEs	27 (71)	20 (53)	23 (61)	19 (50)	9 (24)	11 (29)	109 (48)
Occurrences of AEs	65	36	43	29	11	12	196
Patients with TEAEs	26 (68)	20 (53)	22 (58)	17 (45)	9 (24)	10 (26)	104 (46)
Occurrences of TEAEs	60	35	41	23	11	11	181
Patients with treatment-related TEAEs	10 (26)	10 (26)	6 (16)	8 (21)	1 (3)	1 (3)	36 (16)
Patients with serious TEAEs	1 (3)	3 (8)	3 (8)	0	0	0	7 (3)
Patients with treatment-related serious TEAEs	0	0	0	0	0	0	0
Patients with fatal serious TEAEs	0	0	0	0	0	0	0
Patients with treatment-related fatal serious TEAEs	0	0	0	0	0	0	0
Patients permanently discontinued treatment due to TEAEs	5 (13)	5 (13)	4 (11)	1 (3)	0	1 (3)	16 (7)
Patients with TEAE by intensity							
Mild	10 (26)	8 (21)	11 (29)	12 (32)	5 (14)	8 (21)	54 (24)
Moderate	12 (32)	9 (24)	7 (18)	5 (13)	3 (8)	1 (3)	37 (16)
Severe	4 (11)	3 (8)	4 (11)	0	1 (3)	1 (3)	13 (6)

An AE is defined as any untoward medical occurrence in a patient under clinical investigation, temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. A TEAE is defined as an AE which occurred on or after study treatment start date and on or before the last visit.  
 AE, Adverse event; BID, twice a day; QD, once a day; TEAE, treatment-emergent adverse event.

the tapinarof 0.5% concentration treatment groups, and 16.6% and 28.1% for the vehicle groups.

Mean reductions in percentage of total BSA affected from baseline to week 12 were 3.6%-4.9% in the tapinarof groups and 1%-1.6% in the vehicle groups.

### Safety

Treatment-emergent adverse events (TEAEs) were reported in 46% of patients (68% [1% twice daily], 53% [1% once daily], 58% [0.5% twice daily], 45% [0.5% once daily], 24% [vehicle twice daily], and 26% [vehicle once daily]) with most TEAEs reported as mild-to-moderate intensity (Table 1). The most commonly ( $\geq 5\%$ ) reported TEAEs (regardless of relationship to study treatment) were folliculitis (20/227, 9% [19/152, 13% tapinarof groups and 1/75, 1% vehicle groups]) and contact dermatitis (12/227, 5%; all in the tapinarof groups [12/152, 8%]). Folliculitis was also the most frequent ( $\geq 5\%$ ) treatment-related TEAE (16/227, 7% overall; 15/152 [10%] tapinarof groups vs 1/75 [1%] vehicle groups). Other treatment-related TEAEs were contact dermatitis (3%, all in the tapinarof groups), application site dermatitis, application site irritation, allergic dermatitis, monocyte count decrease and headache (1% each, all cases in tapinarof groups except for 1 of monocyte count decrease). TEAEs led to permanent discontinuation of study treatment in 16 of 227 (7%) patients: 15 of 152 (10%) patients in the tapinarof groups and 1 of 75 (1%) patients in the vehicle groups. Contact dermatitis was the most common reason for study treatment permanent discontinuation, occurring in 6 of 227 (3%) patients (all in the tapinarof groups); patch testing was not performed to evaluate if these were cases of allergic or irritant contact dermatitis. Two patients treated with 1% tapinarof (1 in the once daily group and 1 in the twice daily group) permanently discontinued treatment because of application site dermatitis. Tolerability improved from week 1 to week 12 in both concentration groups and with both frequencies of application. On the basis of a lower frequency of TEAEs, the 1% once daily treatment appeared to have a slightly better tolerability profile than the 1% twice daily treatment. Eight serious AEs (alcoholic pancreatitis, dehydration, malignant melanoma [not at the application site], hemolytic uremic syndrome, coronary artery disease, enlarged uvula, acute cardiac failure, and atrial fibrillation) were reported in 7 patients (3%), all of which were in the tapinarof groups, but none of which were treatment-related as judged by the study investigators. All patients, except the patient with malignant melanoma, had a pre-existing illness related to the event. In addition, there were no clinically significant

differences in mean changes in vital signs, electrocardiogram parameters, and laboratory evaluations between study groups during the study.

### DISCUSSION

Clinical studies (phase 1 and 2) of tapinarof cream with up to 12 weeks of treatment were conducted by Welichem, the previous asset owner, using a different formulation. These studies provided evidence of efficacy in treating psoriasis and atopic dermatitis and provided a preliminary understanding of potential AEs and the overall safety profile.<sup>17,18</sup> Due to encouraging levels of efficacy, further clinical studies using an improved cream formulation (to enhance stability) were initiated by GSK. In this study, statistically significant differences (at 0.05 significance level) were demonstrated between the tapinarof treatment groups and the vehicle groups in treatment success, as defined by PGA scores and PASI75 rates. Almost all patients who achieved either PGA 0 or 1 or PASI75 using tapinarof demonstrated maintenance of the efficacy level for 4 weeks after the end of the 12-week study treatment. Clinically meaningful responses were noticeable at week 2 and increased in magnitude throughout the study for the tapinarof treatment groups. These data provide confirmation that tapinarof is efficacious, with an acceptable safety profile in the adult plaque psoriasis population. Improvement over time was observed for the mean percent reduction in PASI scores for tapinarof treatment groups (once daily and twice daily). For future studies, it is reasonable to use once daily application considering that patients would prefer a once-daily dosing regimen and this would enhance treatment compliance.<sup>19</sup> A total of 3% of patients experienced adverse events of contact dermatitis, which led to treatment cessation in some patients. Patch testing was not performed to evaluate if these were cases of allergic or irritant contact dermatitis. The mechanism of action by which tapinarof might induce folliculitis and contact dermatitis in some patients is not yet understood. However, most incidences were mild to moderate and only in 2 cases caused withdraw of treatment. The overall frequency of skin irritation and dermatitis is comparable to the most frequent adverse events for Dovonex cream (LEO Laboratories, Dublin, Ireland). As reported in the Dovonex US label, skin irritation and dermatitis occurred in ~10%-15% of patients.<sup>20</sup> Further studies are needed to provide more information on local tolerability including information on the incidence and type of contact dermatitis seen with tapinarof.

This study was conducted with the patients whose affected BSA was up to 15% and included mild (PGA

2) patients: baseline PASI score was 8.81. It is known that PASI scores are not linear; they are skewed when the involved BSA is <10%,<sup>21,22</sup> and demonstrating PASI75 is difficult when the baseline PASI score is low. Hence, it is noteworthy that PASI75 of  $\geq 50\%$  was shown to be achievable by topical treatment, not systemic therapy, after 12 weeks of treatment and maintained for 4 weeks after treatment discontinuation.<sup>23-25</sup>

In conclusion, current topical therapies for psoriasis have significant limitations with few new topical treatment options approved for over a decade. Although this phase 2 study was relatively small, it demonstrated that the estimates of efficacy response and the overall safety profile support moving tapinarof cream toward additional study in patients with psoriasis.

We would like to thank all the study participants, investigators, and clinical site staff involved in the 203120 study.

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