A phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of atopic dermatitis

Johnny Peppers, PhD,[a] Amy S. Paller, MD,[b] Tomoko Maeda-Chubachi, MD, PhD,[c] Sterling Wu, PhD,[d] Kevin Robbins, BSc, LLM,[d] Kelly Gallagher, MS,[d] and John E. Kraus, MD, PhD[e]
Raleigh, Morrisville, and Research Triangle Park, North Carolina; Chicago, Illinois; and Collegeville, Pennsylvania

Background: Safe and efficacious topical treatments are needed for atopic dermatitis (AD).

Objective: We assessed the safety and efficacy of tapinarof cream (2 concentrations and 2 application frequencies) in patients with AD.

Methods: A double-blind, vehicle-controlled, randomized, 6-arm trial (1:1:1:1:1:1) in patients age 12 to 65 years, with body surface area involvement of at least 5% to 35% and an Investigator's Global Assessment score of 3 or higher (moderate to severe) at baseline. Primary end points included an Investigator's Global Assessment score of clear or almost clear (0 or 1) and a minimum 2-grade improvement (treatment success) at week 12. Secondary analyses included a 75% or greater improvement in Eczema Area and Severity Index score, reduction of numeric rating scale (NRS) score for itch from baseline, and other prespecified end points.

Results: The rates of treatment success with tapinarof cream at week 12 were 53% (a concentration of 1% twice daily), 46% (a concentration of 1% once daily), 37% (a concentration of 0.5% twice daily), 34% (0.5% once daily), 24% (vehicle twice daily), and 28% (vehicle once daily). The rate with a concentration of 1% twice daily (53%) was statistically significantly higher than the rate with vehicle twice daily (24%). Treatment success was maintained for 4 weeks after the end of tapinarof treatment. The rate of treatment-emergent adverse events was higher with tapinarof (93 of 165 [56%]) than with vehicle (34 of 82 [41%]), and the events were mild to moderate in intensity.

Limitations: Large confirmation trials are needed.

Conclusions: Tapinarof cream is efficacious and well tolerated in adolescent and adult patients with AD. (J Am Acad Dermatol 2019;80:89-98.)

Key words: atopic dermatitis; GSK2894512; tapinarof; therapeutic aryl hydrocarbon receptor modulating agent.

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disease[1] characterized by pruritus/burning sensations, xerosis, erythematous papules and plaques, exudation, crusting, and lichenification. Quality of life is affected through sleep deprivation on account of persistent, intense itching and the stigma associated with having visibly diseased skin.[2,3] Up to 30% of children[1] and up to 10.2% of

From PRA Health Sciences, Raleigh[a]; Feinberg School of Medicine, Northwestern University, Chicago[b]; Novan Inc, Morrisville[c]; GlaxoSmithKline, Collegeville[d]; and ICON plc, Research Triangle Park.[e]

Funding sources: Supported by GlaxoSmithKline (protocol 203121).

Disclosure: Dr Paller has been a consultant with honorarium and investigator for GlaxoSmithKline (GSK). Drs Maeda-Chubachi, Peppers, and Kraus were employees and stockholders of GSK when the study was conducted. Mr Robbins, Mr Wu, and Ms Gallagher are employees and shareholders of GSK.

Accepted for publication June 20, 2018.

Reprints not available from the authors.

Correspondence to: Kevin Robbins, BSc, LLM, 1250 S Collegeville Rd, Collegeville, Pennsylvania, 19426-0989. E-mail: kevin.x.robbins@gsk.com.

Published online July 3, 2018.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2018.06.047

adults[4] may be affected by AD at some point. Currently, no curative therapy exists. Stabilizing disease and reducing the number and severity of flares are primary goals of treatment. Suppressing skin inflammation and symptomatic relief of itching are key factors in disease management. Although treatment options are available, there remains a need for topical treatments that combine a high level of efficacy with an acceptable safety profile to permit application to large body surface areas (BSAs) without restrictions regarding treatment duration.

CAPSULE SUMMARY

- Novel topical treatments for atopic dermatitis have not been developed for many years.
- Tapinarof, a therapeutic aryl hydrocarbon receptor modulating agent delivered in a 1% cream, achieved a 75 percent or greater improvement in Eczema Area and Severity Index in more than 50% of patients treated once daily.
- Tapinarof is a potential new treatment option for atopic dermatitis.

The cause of AD is multifactorial, involving genetic and environmental factors, disturbed skin barrier function, and impaired immune responses.[5-7] The inflammatory component is thought to be mediated primarily by type 2 helper T-cell (Th2) and Th22 activation pathways, although in chronic AD skin lesions in adults, a shift toward a Th1-driven pathway has been described.[8]

Tapinarof (GSK2894512; 5-[(E)-2-phenylethenyl]-2-(propan-2-yl) benzene-1,3-diol), is a nonsteroidal topical agent representing a unique class of anti-inflammatory compounds called therapeutic aryl hydrocarbon receptor (AhR) modulating agents. Tapinarof's activity is mediated primarily through the AhR, which affects Th2 cytokine and skin barrier gene expression.[9] Moreover, tapinarof has inherent antioxidant properties through activation of the nuclear factor, erythroid 2 like 2 pathway. The anti-inflammatory effect of coal tar extracts, which have been used topically for AD for decades, may also result from activation of AhR/nuclear factor, erythroid 2 like 2.[9]

In this study, we have characterized the dose-response relationship of tapinarof and demonstrated its efficacy and acceptable safety profile in treating patients with AD.

METHODS

Study design and oversight

This phase 2, randomized, double-blind, vehicle-controlled, 6-arm, multicenter trial in 12- to 65-year-old patients with AD was designed to determine the optimal tapinarof concentration (0.5% or 1%) and dosing frequency (once daily or twice daily) compared with vehicle (for blinding details, see Supplemental Table I; available at http://www.jaad.org). The study was conducted from December 2015 to January 2017 at 53 sites in the United States, Canada, and Japan (ClinicalTrials.gov NCT02564055, GlaxoSmithKline study 203121).

The study consisted of 3 periods: screening (up to 4 weeks), double-blind treatment (12 weeks), and post-treatment follow-up (4 weeks). Study visits occurred at screening; at baseline; at weeks 1, 2, 4, 8, and 12 during the treatment period; and 2 and 4 weeks after the last application of study treatment (weeks 14 and 16) (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 provided written informed consent. The trial was designed by the study sponsor, GlaxoSmithKline.

Patients

Patients were assigned to study treatment in accordance with the randomization schedule, stratified by geographic region (North America or Japan) and age group (adults or adolescents). Patients meeting all inclusion and no exclusion criteria were randomized via an interactive web response system in a 1:1:1:1:1:1 ratio (tapinarof 1% twice daily, tapinarof 1% once daily, tapinarof 0.5% twice daily, tapinarof 0.5% once daily, vehicle twice daily, and vehicle once daily) (Fig 2). Key inclusion criteria required patients to be age 12 to 65 years, have a clinical diagnosis of AD, have a level of

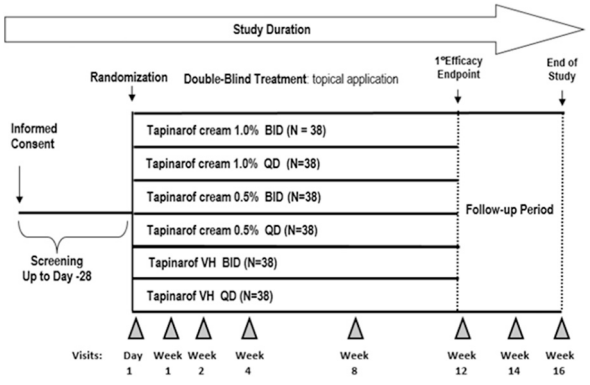

Fig 1. Study schematic. *BID*, Twice daily; *QD*, once daily; *VH*, vehicle.

Abbreviations used:

AE:	adverse event
AhR:	aryl hydrocarbon receptor
BSA:	body surface area
CI:	confidence interval
EASI:	Eczema Area and Severity Index
EASI75:	75% or greater improvement in Eczema Area and Severity Index score
IGA:	Investigator's Global Assessment
NRI:	nonresponder imputation
NRS:	numeric rating scale
TEAE:	treatment-emergent adverse event

BSA involvement between 5% and 35% (excluding the scalp) at screening and baseline, and have an AD Investigator's Global Assessment (IGA) score of 3 or higher at baseline. Key exclusion criteria prohibited an unstable (spontaneously improving or rapidly deteriorating) AD course, concurrent conditions and/or history of other diseases (ie, being immunocompromised or having chronic or acute infection requiring treatment), and ongoing serious illness (medical, physical, or psychiatric). Certain medications were prohibited during the study (Supplemental Table II; available at http://www.jaad.org).

Study treatment

Patients were instructed to apply a thin layer of treatment to all AD lesions (except on the scalp) once daily or twice daily, and to continue treatment of all original areas of involvement even after the lesion(s) cleared. New areas were treated at the first sign of flaring until the week 12 visit.

Efficacy and safety evaluation

The primary efficacy end point was the proportion of patients with a static 5-point IGA score of clear or almost clear (0 or 1) and a minimum 2-grade improvement in IGA score from baseline (treatment success) at week 12.[10] Secondary end points included the proportion of patients with a 75% or greater improvement in Eczema Area and Severity Index (EASI75) score from baseline to each study visit[11,12]; mean change in Eczema Area and Severity Index (EASI) score; mean change in weekly average of daily itch/pruritus score on a numeric rating scale (NRS); a minimum 3-point improvement in weekly average of itch/pruritus (NRS score) at each study visit; and mean change in percent of BSA affected (for brevity, this report focuses on treatment success in terms of IGA score, EASI75, and itch reduction). Primary safety assessments included the incidence and frequency of adverse events (AEs) and serious AEs, evaluation of local (application site) tolerability, clinical laboratory parameters, vital signs, electrocardiogram (ECG) changes, and physical examinations. An unblinded independent data monitoring committee monitored patient safety.

Sample size and statistical analysis

It was expected that 228 patients would be randomized to achieve approximately 204 evaluable patients. The sample size was determined on the basis of the response rates observed in earlier studies conducted by the previous asset

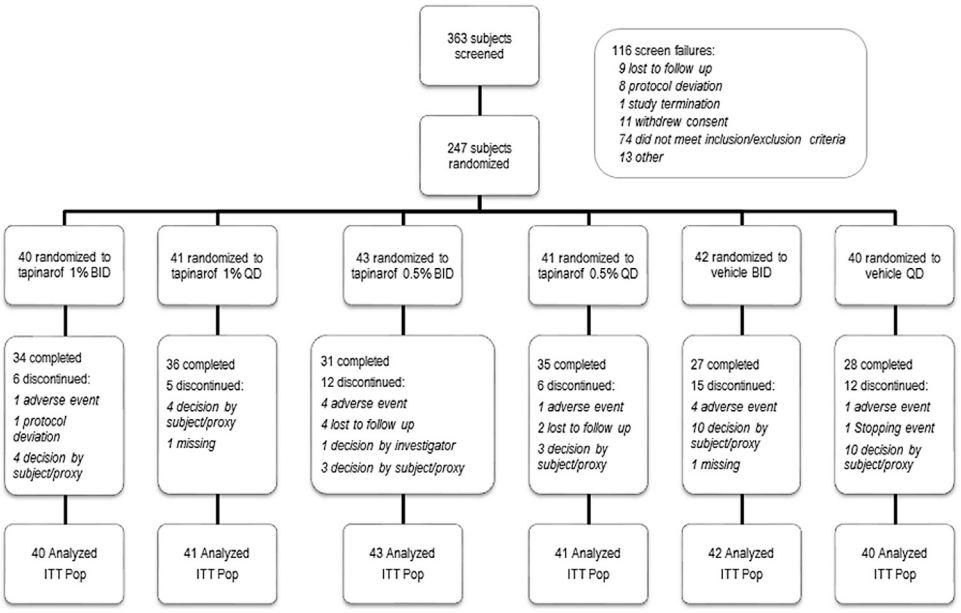

Fig 2. Trial profile. *BID*, Twice daily; *ITT*, intent-to-treat; *QD*, once daily.

Table I. Summary of demographic characteristics (safety population)

Characteristic	GSK2894512 1% bid (n = 40)	GSK2894512 1% qd (n = 41)	GSK2894512 0.5% bid (n = 43)	GSK2894512 0.5% qd (n = 41)	Vehicle bid (n = 42)	Vehicle qd (n = 40)	Total (N = 247)
Age, y							
n	40	41	43	41	42	40	247
Mean	28.5	31.6	29.0	29.3	27.9	29.4	29.3
SD	13.90	15.72	15.91	14.02	14.72	15.15	14.83
Median	27.0	27.0	24.0	26.0	23.5	24.0	25.0
Age group, y							
n	40	41	43	41	42	40	247
12-17	11 (28%)	13 (32%)	13 (30%)	12 (29%)	13 (31%)	11 (28%)	73 (30%)
18-65	29 (73%)	28 (68%)	30 (70%)	29 (71%)	29 (69%)	29 (73%)	174 (70%)
Sex							
n	40	41	43	41	42	40	247
Female	18 (45%)	24 (59%)	17 (40%)	22 (54%)	23 (55%)	17 (43%)	121 (49%)
Male	22 (55%)	17 (41%)	26 (60%)	19 (46%)	19 (45%)	23 (58%)	126 (51%)
Weight, kg							
n	40	41	43	41	42	40	247
Mean	71.76	79.31	75.66	81.96	70.20	81.06	76.63
SD	18.686	26.182	22.941	28.828	16.365	26.238	23.786
Median	69.20	74.00	73.70	78.40	65.55	82.30	73.00
Height, cm							
n	40	41	43	41	42	40	247
Mean	166.58	167.82	166.72	165.97	164.67	168.05	166.62
SD	9.294	11.090	10.589	11.972	9.636	9.621	10.372
Median	165.75	165.40	165.10	165.00	163.15	169.00	166.50
BMI, kg/m^2							
n	40	41	43	41	42	40	247
Mean	25.84	27.86	26.85	29.53	25.86	28.47	27.39
SD	6.460	7.858	6.469	9.133	5.650	8.638	7.506
Median	23.92	26.72	24.21	27.05	23.90	28.18	25.90

The safety population comprised all patients who received as least 1 dose of study treatment and was based on the treatment that the patient actually received.

bid, Twice daily; *BMI*, body mass index; *qd*, once daily; *SD*, standard deviation.

owner (Bissonnette et al[13,14]). Data from evaluable subjects (34 per group) would provide model-based[15] 95% confidence intervals (CIs) for the IGA response estimates, which were 21.5% wide on average. No formal hypothesis tests were planned. Instead, to compare treatment effect between arms, the differences in proportion of treatment success/responses along with 95% CI at each visit were calculated. If the CI did not include 0, the difference in treatment effect would be considered statistically significant.

The proportions of treatment successes/responses and proportions of patients who achieved a 3-point reduction in weekly average itch NRS score were summarized along with 95% CIs at each visit for each treatment arm. The mean percent change in EASI scores, weekly itch NRS score, and percent of BSA affected over time were also reported. The intent-to-treat population, which included all randomized patients, was used for primary efficacy analyses. To adjust for higher dropout rates in the vehicle groups, an ad hoc, nonresponder imputation (NRI) method was used for 3 end points (treatment success/response in IGA score or EASI75 and proportion of patients with a 3-point reduction in itch NRS score from baseline) in the intent-to-treat population to impute missing data in cases in which any missing values were treated as a nonresponse.

RESULTS

Patients

Of the 363 patients screened, 247 were randomized into the study and 191 (77%) completed the 12-week treatment phase (Fig 2). Higher dropout rates were observed in the vehicle groups (36% with vehicle twice daily and 30% with vehicle once daily vs 14% in the 1% treatment groups and 15%-28% in the 0.5% treatment groups). Overall, mean demographic and baseline characteristics

Table II. Summary of baseline characteristics (safety population)

Characteristic	GSK2894512 1% bid (n = 40)	GSK2894512 1% qd (n = 41)	GSK2894512 0.5% bid (n = 43)	GSK2894512 0.5% qd (n = 41)	Vehicle bid (n = 42)	Vehicle qd (n = 40)	Total (N = 247)
EASI							
n	40	41	43	41	42	40	247
Mean	9.79	10.93	13.05	11.40	11.11	11.09	11.25
SD	5.149	6.121	6.733	5.799	5.849	5.793	5.956
Median	8.90	9.50	12.00	10.80	10.05	10.85	10.00
%BSA affected							
n	40	41	43	41	42	40	247
Mean	14.82	18.71	19.69	17.56	14.54	16.03	16.91
SD	8.711	10.957	10.467	9.917	9.147	10.319	10.042
Median	11.75	15.00	17.00	15.00	11.75	11.50	14.00
%BSA to be treated							
n	40	41	43	41	42	40	247
Mean	14.30	18.44	19.34	17.32	14.17	15.78	16.58
SD	8.616	10.768	10.340	9.763	9.155	10.143	9.930
Median	11.25	15.00	16.00	15.00	11.50	11.50	14.00
IGA							
n	40	41	43	41	42	40	247
Mean	3.1	3.1	3.1	3.1	3.1	3.1	3.1
SD	0.22	0.30	0.26	0.26	0.35	0.30	0.29
Median	3.0	3.0	3.0	3.0	3.0	3.0	3.0
IGA category							
n	40	41	43	41	42	40	247
0 - Clear	0	0	0	0	0	0	0
1 - Almost clear	0	0	0	0	0	0	0
2 - Mild	0	0	0	0	0	0	0
3 - Moderate	38 (95%)	37 (90%)	40 (93%)	38 (93%)	36 (86%)	36 (90%)	225 (91%)
4 - Severe	2 (5%)	4 (10%)	3 (7%)	3 (7%)	6 (14%)	4 (10%)	22 (9%)
Duration of atopic dermatitis, y*							
n	40	41	43	41	42	40	247
Mean	15.8520	21.6417	18.2252	16.1085	18.7591	20.9769	18.5930
SD	10.4713	16.6065	13.5084	10.7046	13.9254	14.3000	13.4723
Median	15.5373	17.1855	15.6030	14.5161	15.5305	17.6961	15.6413
Itch/pruritus score†							
n	33	37	41	40	40	35	226
Mean	5.2	5.4	5.7	5.7	5.1	5.8	5.5
SD	2.32	1.91	2.53	2.03	2.02	1.89	2.12
Median	5.0	5.0	6.0	6.0	5.0	6.0	5.0

Baseline refers to the day 1 measurement (or the latest measurement before the first dose if the day 1 measurement is missing); n is the number of patients with available results. The safety population comprised all patients who received at least 1 dose of study treatment and was based on the treatment that the patient actually received.

bid, Twice daily; *%BSA*, percent of body surface area affected; *EASI*, Eczema Area and Severity Index; *IGA*, Investigator's Global Assessment; *qd*, once daily; *SD*, standard deviation.

*Duration of atopic dermatitis refers to the number of years between the date of diagnosis and screening date.

†A rating of 0 means absent, and a rating of 10 means worst imaginable.

were comparable across treatment groups (Table I). At baseline, most patients (91%) fell into the IGA score category of 3 (moderate). The mean baseline EASI score was 11.25 (of a possible 72), the mean itch/pruritus score was 5.5 (of a possible 10), and the mean percentage of BSA affected was 16.91% (Table II).

Efficacy

On the basis of NRI analysis, a higher proportion of patients overall with treatment success was observed in the tapinarof-treated groups than in the vehicle groups. Point estimates and 95% CIs were provided for the differences at each visit of each tapinarof twice-daily dose minus vehicle twice-daily

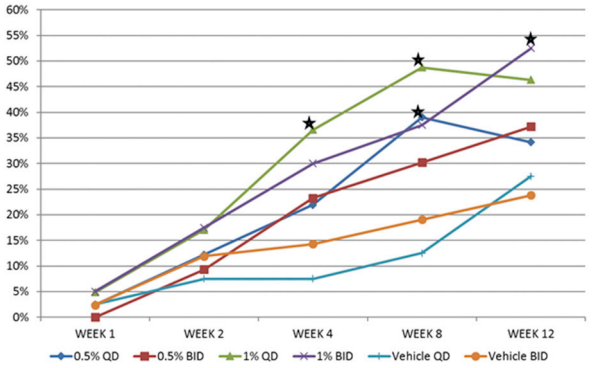

Fig 3. Proportion of patients who achieved an Investigator's Global Assessment score of clear or almost clear (0 or 1) and a minimum 2-grade improvement from baseline to each study visit with use of nonresponder imputation. Tapinarof 1% showed statistical significance compared with vehicle after 4 weeks of treatment at multiple time points. Stars indicate statistical significance (95% confidence interval for the difference excludes 0) compared with vehicle at the $\alpha = 0.05$ level. *BID*, Twice daily; *QD*, once daily.

dose and each tapinarof once-daily dose minus vehicle once-daily dose. Treatment success was higher with both tapinarof concentrations than with vehicle at all visits beyond week 2, and it was significantly higher at week 12 for 1% twice-daily tapinarof (53%) versus vehicle twice daily (24%) (95% CI of the difference: 6.5%-48.1%) (Fig 3 [statistically significantly higher rates are indicated by an asterisk]). At week 12, responses were also higher with twice-daily than with once-daily application (53% [1% twice daily] vs 46% [1% once daily]) but not at other time points. Overall, the groups treated with a 1% concentration showed a higher rate of response than did the groups treated with a 0.5% concentration. The IGA response was maintained in the groups treated with a 1% concentration at 2 and 4 weeks after treatment (35% [1% twice daily] and 37% [1% once daily] at week 14; 30% [1% twice daily] and 23% [1% once daily] at week 16). Fig 4 displays photographs of the clinical features of 2 patients (both randomized to tapinarof 1% once daily) at baseline, week 8, and week 12, which are representative of the improvement seen.

A main secondary end point was the proportion of patients with EASI75 from baseline to each study visit. According to NRI analyses, the proportion of patients achieving EASI75 at week 12 was highest in the groups treated with 1% tapinarof (60% [1% twice daily] and 51% [1% once daily]) and higher with tapinarof overall than with vehicle (51% and 39% in the groups receiving 0.5% tapinarof twice daily and once daily, respectively, and 26% and 25% in the groups receiving vehicle twice daily and once daily, respectively) (Fig 5). By week 2 of treatment, higher proportions of patients with EASI75 were observed in the groups treated with tapinarof than in the groups that received vehicle. The point estimates and 95% CIs for each set of tapinarof arms versus vehicle arms at each study visit (as for the IGA) showed significant differences for the tapinarof versus vehicle arms at multiple time points, although not in a dose- or frequency-dependent manner (Fig 5 [statistically significantly differences are indicated by an asterisk]). Maintenance of treatment success, as defined by achievement of EASI75 at both 2 and 4 weeks after dosing, were noted in the groups treated with 1% tapinarof (50% [twice daily] and 49% [once daily] at week 14 and 45% [twice daily] and 34% [once daily] at week 16). Although maintenance of EASI score was noted at the 4-week follow-up period, itch was observed to return ahead of a change in EASI score.

The reduction in itch/pruritus from baseline to each study visit up to week 8 was greater in the groups treated with tapinarof than in the groups treated with vehicle, and this improvement was maintained during the follow-up period (no data provided). The proportion of patients who achieved a minimum 3-point improvement in itch/pruritus with use of the NRI method was also greater at weeks 4 to12 in all groups treated with tapinarof than in the groups treated with vehicle (Fig 6). The tapinarof and vehicle groups showed a clear separation starting at week 2.

Safety

Treatment-emergent AEs (TEAEs) were reported in 51% of patients overall (70% with tapinarof 1% twice daily, 54% with tapinarof 1% once daily, 47% with tapinarof 0.5% twice daily, 56% with 0.5% tapinarof once daily, 45% with vehicle twice daily, and 38% with vehicle once daily). The majority of TEAEs were reported as mild to moderate in intensity (Table III). The most frequently reported TEAE was nasopharyngitis. The other TEAEs reported in at least 5% of patients in any arm or in total were folliculitis, AD (reported as worsening or flare of AD), upper respiratory tract infection, headache, acne, and impetigo (Table IV). Overall, 32 patients (13%) had TEAEs that were considered treatment related by the investigators (Supplemental Table III; available at http://www.jaad.org). TEAEs led to permanent discontinuation of the study treatment in 13 patients (5%). The frequency of discontinuation was higher in the vehicle groups

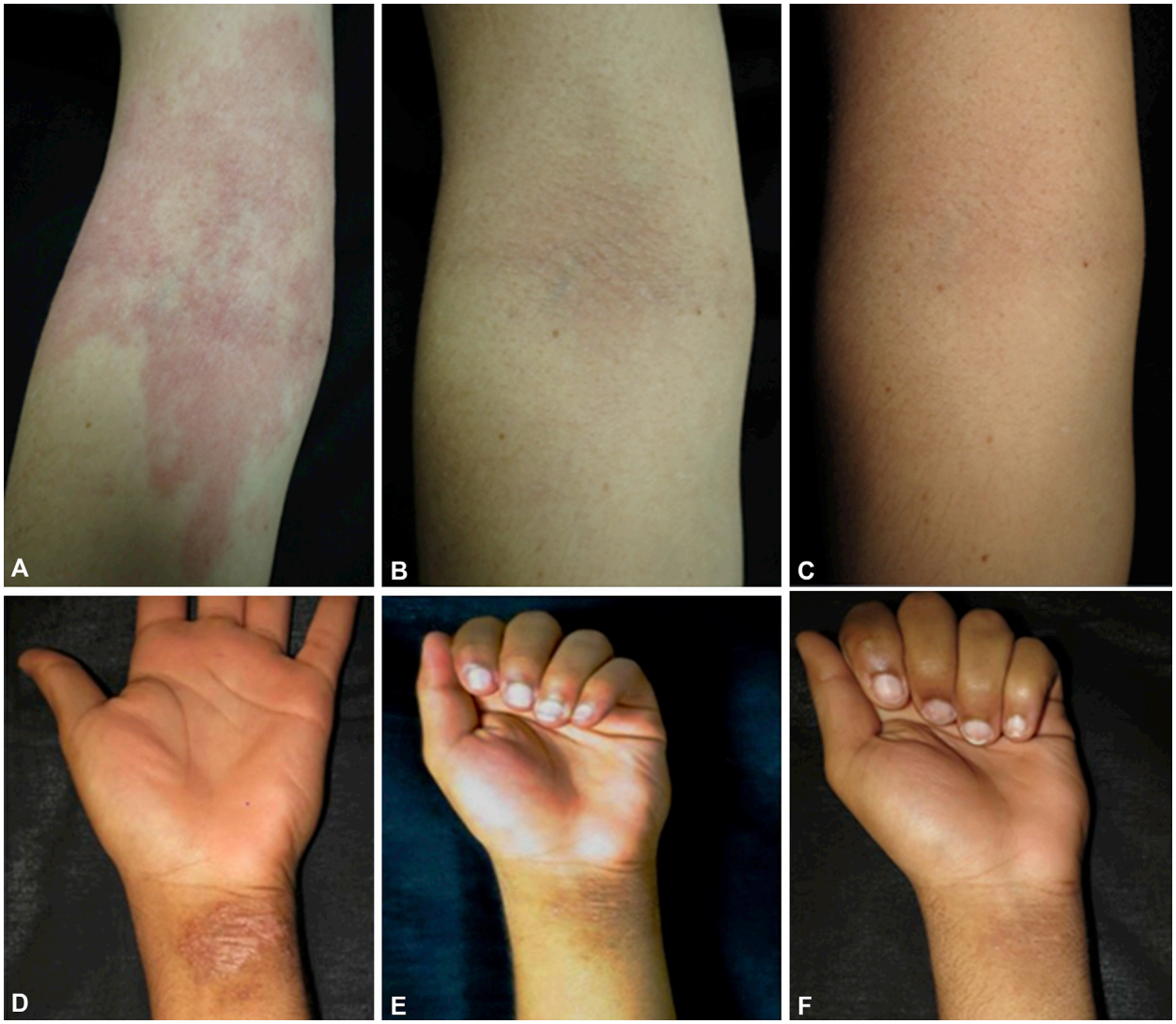

Fig 4. A-F, Clinical features of 2 patients with atopic dermatitis who received tapinarof (1% once daily). Photographs demonstrate improvement in Investigator's Global Assessment and Eczema Area and Severity Index scores at weeks 8 and 12.

(6 of 82 [7%]) than in the groups treated with tapinarof (7 of 165 [4%]). AD (reported as worsening or flare) was the most frequent TEAE that led to discontinuation of the study treatment. Four patients in the tapinarof arms had TEAEs of AD that led to discontinuation of the study treatment; all of them had been treated with tapinarof 0.5% (3 [7%] had been treated twice daily and 1 [2%] had been treated once daily).

A total of 49 of 247 patients (20%) had ECG findings at any postscreening visit across all treatment groups during the study (35 of 165 [21%] of those in the groups treated with tapinarof vs 14 of 82 [17%] of those in the vehicle groups). These ECG findings were not considered significant; they appeared to be transient, resolved over time, and never led to patient discontinuation. Elevations in liver enzyme levels (alanine transaminase/aspartate transaminase level more than twice the upper limit of normal) were seen in 6 patients treated with tapinarof, but they did not trigger the protocol-mandated liver-related criteria for stopping treatment. All patients continued treatment and all elevations resolved during the treatment period. There were no clinically significant changes in vital signs or in other significant laboratory evaluation results. No clinically significant changes in immunoglobulin levels (IgA, IgG, and IgM) were observed across all treatment groups receiving either tapinarof or vehicle regardless of dosing

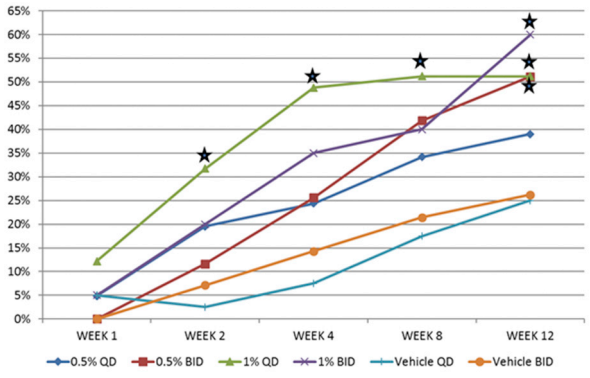

Fig 5. Proportion of patients with at least a 75% improvement in Eczema Area and Severity Index score from baseline to each study visit with use of nonresponder imputation. Tapinarof 1% once daily demonstrated statistical significance (*star*) over the vehicle the α = 0.05 level after 2 weeks of treatment. Stars indicate statistical significance (95% confidence interval for the difference excludes 0) compared with vehicle at the α = 0.05 level. *BID*, Twice daily; *QD*, once daily.

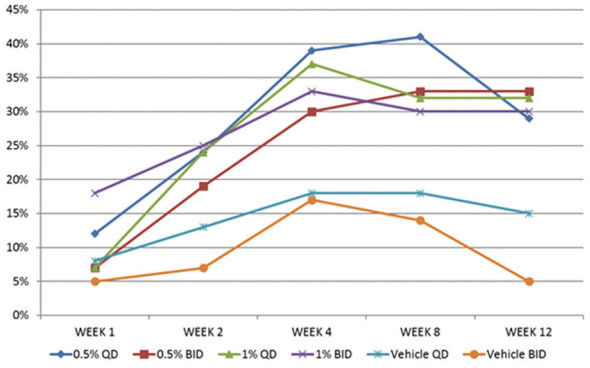

Fig 6. Patients who achieved a minimum 3-point improvement in weekly average of itch/pruritus numeric rating scale score from baseline to each study visit (nonresponder imputation [intent-to-treat Population]). A difference can be seen after 2 weeks between the groups treated with tapinarof and those treated with vehicle. *BID*, Twice daily; *QD*, once daily.

frequency. One patient in the group treated with tapinarof 1% twice daily experienced a serious AE of anxiety and attention-deficit/hyperactivity disorder that was considered unrelated to study treatment.

DISCUSSION

Prior clinical studies with a different formulation of tapinarof cream were conducted by Welichem Biotech (Burnaby, British Columbia, Canada), the previous asset owner. These studies provided evidence of efficacy for AD and a preliminary understanding of the safety profile of the compound.[13,14] Data from use of the current formulation of tapinarof further show the effectiveness of this mechanism of action (use of therapeutic aryl hydrocarbon receptor modulating agents) in the treatment of adults with AD that was previously reported (by Bissonnette et al[13,14]). In addition, this is, to our knowledge, the first study to provide insight into a possible role for tapinarof in an adolescent population. In this phase 2 dose-ranging study, tapinarof showed an acceptable safety and tolerability profile and a clear therapeutic effect compared with vehicle. Efficacy responses—measured by an IGA score of 0 or 1, EASI75, and overall signs and symptoms—began as soon as week 2 and continued through week 12. Treatment success after treatment was maintained for an additional 4 weeks in most patients (IGA score and EASI75). In addition, these improvements trended higher in 3 of the groups receiving tapinarof treatment (1% twice daily, 1% once daily, or 0.5% twice daily) than in the vehicle groups. The 1% concentration showed a higher efficacy than did the 0.5% concentration and resulted in a quicker onset of effect than did either the 0.5% concentration or vehicle. The reduction in itch/pruritus was comparable among the tapinarof arms and showed mean changes from baseline as compared with vehicle as soon as week 2. Because itch is a major symptom of AD, early alleviation of itch may contribute to increased adherence to treatment. Although maximum efficacy across most end points occurred at week 12, by week 8 significant differences from vehicle were noted. Although only 30% of the participants were adolescents, no notable difference in the treatment effects were noted.

The current topical treatments for AD, namely, topical corticosteroids and topical calcineurin inhibitors, have restrictions for use and a potential for local and systemic adverse effects. Additional efficacious treatments are still needed despite the recent availability of crisaborole, a topical PDE4 inhibitor for patients with mild-to-moderate disease[16] and dupilumab, a monoclonal anti–interleukin 4/interleukin 13 receptor antibody for patients with moderate-to-severe AD.[17]

In conclusion, tapinarof represents an important advance in development of topical medicine, with a unique mechanism of action that clearly distinguishes this compound from currently available AD therapies. Despite the small size of

Table III. Overall summary of adverse events (safety population)

Characteristic	GSK2894512 1% bid (n = 40)	GSK2894512 1% qd (n = 41)	GSK2894512 0.5% bid (n = 43)	GSK2894512 0.5% qd (n = 41)	Vehicle bid (n = 42)	Vehicle qd (n = 40)	Total (N = 247)
Patients with AEs	28 (70%)	24 (59%)	21 (49%)	24 (59%)	20 (48%)	16 (40%)	133 (54%)
No. of occurrences of AEs	58	43	47	46	34	30	258
Patients with TEAEs	28 (70%)	22 (54%)	20 (47%)	23 (56%)	19 (45%)	15 (38%)	127 (51%)
No. of occurrences of TEAEs	55	40	43	40	30	28	236
Patients with drug-related TEAEs	6 (15%)	6 (15%)	8 (19%)	4 (10%)	6 (14%)	2 (5%)	32 (13%)
Patients with serious TEAEs	1 (3%)	0	0	0	0	0	1 (<1%)
Patients with fatal serious TEAEs	0	0	0	0	0	0	0
Patients who permanently discontinued treatment because of TEAEs	1 (3%)	0	5 (12%)	1 (2%)	4 (10%)	2 (5%)	13 (5%)
Patients with TEAE by intensity							
Mild	14 (35%)	14 (34%)	11 (26%)	14 (34%)	12 (29%)	7 (18%)	72 (29%)
Moderate	14 (35%)	8 (20%)	6 (14%)	8 (20%)	4 (10%)	8 (20%)	48 (19%)
Severe	0	0	3 (7%)	1 (2%)	3 (7%)	0	7 (3%)

AE, Adverse event; *bid*, twice daily; *qd*, once daily; *TEAE*, treatment-emergent adverse event.

Table IV. Summary of the numbers of patients with TEAEs with at least 5% of patients in any arm or in total by frequency (safety population)

Preferred term	GSK2894512 1% bid (n = 40)	GSK2894512 1% qd (n = 41)	GSK2894512 0.5% bid (n = 43)	GSK2894512 0.5% qd . (n = 41)	Vehicle bid (n = 42)	Vehicle qd (n = 40)	Total (N = 247)
Overall population (N = 247)							
Any TEAE	28 (70%)	22 (54%)	20 (47%)	23 (56%)	19 (45%)	15 (38%)	127 (51%)
Nasopharyngitis	3 (8%)	5 (12%)	4 (9%)	1 (2%)	4 (10%)	3 (8%)	20 (8%)
Folliculitis	4 (10%)	8 (20%)	3 (7%)	3 (7%)	0	0	18 (7%)
Atopic dermatitis	2 (5%)	0	3 (7%)	1 (2%)	4 (10%)	5 (13%)	15 (6%)
Upper respiratory tract infection	4 (10%)	2 (5%)	3 (7%)	2 (5%)	3 (7%)	1 (3%)	15 (6%)
Headache	4 (10%)	1 (2%)	1 (2%)	3 (7%)	0	2 (5%)	11 (4%)
Acne	2 (5%)	0	1 (2%)	3 (7%)	1 (2%)	0	7 (3%)
Impetigo	1 (3%)	0	0	0	0	3 (8%)	4 (2%)

A TEAE is defined as an adverse event that occurred on or after the start date of the study treatment and on or before the last visit.
bid, Twice daily; *qd*, once daily; *TEAE*, treatment-emergent adverse event.

this phase 2 study, estimates of efficacy response and the overall safety profile support moving the 1% concentration toward additional study. A full understanding of the positioning of tapinarof in the treatment paradigm of AD cannot be made at this time; however, the results of the current study indicate that tapinarof may provide a new addition to the armamentarium for both adults and adolescents with AD. For the group treated with 1% once daily, the mean baseline EASI score was 10.93; however, tapinarof was observed to relieve symptoms in patients with an EASI score up to 32.2, suggesting potential effectiveness in a wide spectrum of disease severity. Further studies are warranted to better determine the full efficacy and safety profile of tapinarof within the population of patients with moderate-to-severe AD.

We would like to thank all the study participants, investigators, and clinical site staff involved in the 203121 study.

REFERENCES

1. Paller AS, Mancini AJ. Eczematous eruptions in childhoodIn: Paller AS, Mancini AJ, eds. *Hurwitz Clinical Pediatric Dermatology. A Textbook of Skin Disorders of Childhood and Adolescence*. 3rd ed. Philadelphia, PA: Elsevier Saunders; 2006: 49-84.
2. Carroll CL, Balkrishnan R, Feldman SR, Fleischer AB Jr, Manuel JC. The burden of atopic dermatitis: impact on the patient, family, and society. *Pediatr Dermatol*. 2005;22:192-199.
3. Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. *Int J Clin Pract*. 2006;60:984-992.

4. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol*. 2013;132(5):1132-1138.
5. Werfel T, Allam JP, Biedermann T, et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2016;138(2):336-349.
6. Egawa G, Kabashima K. Multifactorial skin barrier deficiency and atopic dermatitis: essential topics to prevent the atopic march. *J Allergy Clin Immunol*. 2016;138(2):350-358.
7. Otsuka A, Nomura T, Rerknimitr P, Seidel JA, Honda T, Kabashima K. The interplay between genetic and environmental factors in the pathogenesis of atopic dermatitis. *Immunol Rev*. 2017;278(1):246-262.
8. Weidinger S, Novak N. Atopic dermatitis. *Lancet*. 2016;387:1109-1122.
9. Smith SH, Jayawickreme C, Rickard DJ, et al. Tapinarof is a natural AhR agonist that resolves skin inflammation in mice and humans. *J Invest Dermatol*. 2017;137:2110-2119.
10. Rehal B, Armstrong A. Health outcome measures in atopic dermatitis: a systematic review of trends in disease severity and quality-of-life instruments 1985-2010. *PLoS One*. 2011;6(4):e17520.
11. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The Eczema Area and Severity Index (EASI): an assessment of reliability in atopic dermatitis. *Exp Dermatol*. 2001;10:11-18.
12. Rullo VEV, Segato A, Kirsh A, Sole D. Severity scoring of atopic dermatitis: a comparison of two scoring systems. *Allergol Immunopathol*. 2008;36(4):201-211.
13. Bissonnette R, Bolduc C, Maari C, et al. Efficacy and safety of topical WBI-1001 in patients with mild to moderate psoriasis: results from a randomized double-blind placebo-controlled, phase II trial. *J Eur Acad Dermatol Venereol*. 2012;26:1516-1521.
14. Bissonnette R, Poulin Y, Zhou Y, et al. Efficacy and safety of topical WBI-1001 in patients with mild to severe atopic dermatitis: results from a 12-week, multicentre, randomized placebo-controlled, double-blind trial. *Br J Dermatol*. 2012;166:853-860.
15. Fu H, Manner D. Bayesian adaptive dose-finding studies with delayed responses. *J Biopharm Stat*. 2010;20(5):1055-1070.
16. Paller AS, Tom WL, Lebwohl MG, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol*. 2016;75(3):494-503.
17. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet*. 2017;389:2287-2303.

Supplemental Table I. Study blinding

Role	Blinding status during study
Investigator/designated evaluator(s)	Blinded to concentration and frequency. Patients and study staff were instructed not to discuss frequency of application with the investigator/evaluator
Study center staff	Blinded to study treatment but not to frequency of application
Patient	Blinded to study treatment but not to frequency of application
Sponsor	The study physician, medicines development lead, study statistician, and safety development lead had access to by-treatment group data summaries/analyses at the interim analysis

Supplemental Table II. Prohibited concomitant medications, products, and procedures

Prohibited medications, products, or procedures	Washout period before day 1
Biologic agents (eg, 18 wk for omalizumab)	12 wk or 5 half-lives (whichever is longer)
Cyclosporine, methotrexate, azathioprine, or other systemic immunosuppressive or immunomodulating agents (eg, mycophenolate or tacrolimus)	8 wk
Other investigational products or procedures	Longer of 4 wk or 5 half-lives
Systemic corticosteroids or adrenocorticotropic hormone analogues	4 wk
Systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals (but permitted during the study for acute treatment of infections)	4 wk
Immunizations	2 wk
Sedating antihistamines (nonsedating antihistamines permitted)	2 wk
Topical treatments: corticosteroids, calcineurin inhibitors, coal tar (on the body)	2 wk
Topical antibiotics, antibacterial cleansing body wash/soap, or diluted sodium hypochlorite "bleach" baths	1 wk
Any other topical therapy (including emollients*) on AD lesions treated in this study	1 d

AD, Atopic dermatitis.

*Emollient/moisturizer use on a non-AD lesion that is adjacent to an AD lesion should be avoided during the study, if possible.

Supplemental Table III. Summary of numbers of patients with TEAEs related to study treatment (safety population)

Preferred term for system, organ, or class	GSK2894512 1% bid (n = 40)	GSK2894512 1% qd (n = 41)	GSK2894512 0.5% bid (n = 43)	GSK2894512 0.5% qd (n = 41)	Vehicle bid (n = 42)	Vehicle qd (n = 40)	Total (N = 247)
Any TEAE related to study treatment	6 (15%)	6 (15%)	8 (19%)	4 (10%)	6 (14%)	2 (5%)	32 (13%)
Infection and infestation							
Folliculitis	2 (5%)	3 (7%)	2 (5%)	2 (5%)	0	0	9 (4%)
Impetiginous eczema	0	1 (2%)	0	0	0	0	1 (<1%)
Herpes simplex	0	0	1 (2%)	0	0	0	1 (<1%)
Upper respiratory tract infection	0	0	1 (2%)	0	0	0	1 (<1%)
Skin and subcutaneous tissue disorder							
Atopic dermatitis	0	0	1 (2%)	0	2 (5%)	0	3 (1%)
Acne	1 (3%)	0	0	1 (2%)	0	0	2 (1%)
Contact dermatitis	0	0	1 (2%)	0	1 (2%)	0	2 (1%)
Dermal cyst	0	0	0	1 (2%)	0	0	1 (<1%)
Dry skin	0	0	1 (2%)	0	0	0	1 (<1%)
Hyperkeratosis follicularis et parafollicularis	0	1 (2%)	0	0	0	0	1 (<1%)
Pain of skin	1 (3%)	0	0	0	0	0	1 (<1%)
Rash	1 (3%)	0	0	0	0	0	1 (<1%)
General disorder and administration site conditions							
Application site pain	1 (3%)	0	1 (2%)	0	2 (5%)	1 (3%)	5 (2%)
Application site reaction	0	1 (2%)	1 (2%)	0	0	1 (3%)	3 (1%)
Application site erythema	0	0	0	0	1 (2%)	0	1 (<1%)
Application site oedema	0	0	1 (2%)	0	0	0	1 (<1%)
Application site pruritus	0	0	0	0	1 (2%)	0	1 (<1%)
Local reaction	1 (3%)	0	0	0	0	0	1 (<1%)
Nervous system disorder							
Headache	1 (3%)	0	1 (2%)	1 (2%)	0	0	3 (1%)
Burning sensation	0	1 (2%)	1 (2%)	0	0	0	2 (1%)
Hypoaesthesia	1 (3%)	0	0	0	0	0	1 (<1%)
Gastrointestinal disorder							
Diarrhea	0	0	0	1 (2%)	0	0	1 (<1%)
Nausea	0	0	0	0	0	1 (3%)	1 (<1%)
Investigation							
Hepatic enzyme increased	0	0	1 (2%)	0	0	0	1 (<1%)
Monocyte count decreased	0	0	1 (2%)	0	0	0	1 (<1%)

bid, Twice daily; *qd*, once daily; *TEAE*, treatment-emergent adverse event.