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 ORIGINAL ARTICLE

Appraisal of Ruxolitinib 1.5% Cream as a First-Line Topical Therapeutic Agent for Adolescents and Adults With Mild-to-Moderate Atopic Dermatitis

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ABSTRACT

Dermatology has entered the long-awaited paradigm shift from steroidal to non-steroidal therapeutics for the topical treatment of atopic dermatitis. Topical Janus kinase (JAK) inhibitors have garnered a strong recommendation for the treatment of adult atopic dermatitis (AD) by the American Academy of Dermatology in the most recent updated guidelines as of 2023. Ruxolitinib 1.5% cream is the only FDA-approved topical JAK inhibitor available in the US and is approved for the short-term and intermittent chronic treatment of mild-to-moderate AD in adolescents and adults aged >= 12 years with up to 20% affected body surface area (BSA). Since approval in 2021, ruxolitinib cream has been shown to be consistently effective across disease severities, age groups, and anatomic sites of special interest (ie, head and neck region, hands). Real-world usage as monotherapy and in combination with other topicals have confirmed its efficacy in practice and further led to reduced usage of topical corticosteroids. Ruxolitinib cream also has the potential to reduce economic costs due to AD-related decline in work productivity. Here, we review the most up-to-date clinical trial and real-world efficacy data that position ruxolitinib 1.5% cream as a first-line AD therapeutic.

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INTRODUCTION

The topical therapeutic landscape of atopic dermatitis (AD) has entered the "golden age" of drug development. Until now, the landscape was comprised of 3 major mechanistic classes: (1) corticosteroids, calcineurin inhibitors (tacrolimus and pimecrolimus), and phosphodiesterase-4 (PDE-4) inhibitors (crisaborole and, more recently, roflumilast). The current topical pipeline also includes the aryl hydrocarbon receptor (AhR) agonist tapinarof, which is undergoing the regulatory approval process in the United States (US).[1]

Janus kinase (JAK) proteins are critical transducers of cytokine inflammatory signals intracellularly. In particular, JAK1 and JAK2 are activated by the core AD cytokines interleukin (IL)-4, IL-13, IL-22, IL-31, thymic stromal lymphopoietin (TSLP), among others, to recruit signal transducer and activator of transcription (STAT) proteins that are then phosphorylated. STAT proteins subsequently dimerize and cause DNA transcriptional changes in various immune and non-immune cell types to ultimately cause increased expression of additional pro-inflammatory cytokines. As such, targeting JAK1/2 has been a highly sought-after therapeutic approach for AD, resulting in 2 oral

FDA-approved JAK1 inhibitors (abrocitinib and upadacitinib) and 1 topical JAK 1/2 (ruxolitinib cream 1.5%). Ruxolitinib inhibits JAK family kinases with the following IC_{50} values: JAK1, 6.4 nM; JAK2, 8.8 nM; JAK3, 487 nM; and TYK2, 30.1 nM.[2] JAK inhibitors have garnered much attention given their ability to rapidly clear skin and reduce itch.[3]

With the rapidly evolving landscape in topical AD therapeutics, the American Academy of Dermatology has recently updated its guidelines for topical management of AD in 2023.[4] Topical JAK inhibitors have been given a strong recommendation for adults with mild-to-moderate AD. At this time, topical ruxolitinib 1.5% cream is the only FDA-approved topical JAK inhibitor therapy for AD currently available in the US. Here, we gather the currently available up-to-date data on ruxolitinib cream with respect to efficacy and safety in clinical trials as well as real-world usage.

AD Skin Clearance With Ruxolitinib Cream

Treatment with ruxolitinib 1.5% cream twice daily as monotherapy has shown significant improvements in Eczema Area and Severity Index (EASI) and Investigator's Global Assessment (IGA) scores in adolescents and adults (age >= 12 years of age) with mild-to-moderate AD. IGA treatment success (IGA-TS) is defined as a score of 0 (clear) or 1 (almost clear) with a >= 2-grade improvement from baseline.

In the 2 pivotal randomized, double-blind, vehicle-controlled, 8-week phase 3 clinical trials (TRuE-AD1/2), ruxolitinib 1.5% cream twice daily as monotherapy again showed superiority to the vehicle in obtaining skin clearance in subjects >= 12 years of age.[5] At baseline, subjects exhibited an IGA of 2 or 3, mean affected BSA of 10.0 +/- 5.4, and mean EASI of 8.0 +/- 5.0 with median duration of disease of 16.0 (0-70.7) years. At week 8, 53.8% and 51.3% (TRuE-AD1 and TRuE-AD2, respectively) of subjects in the ruxolitinib 1.5% treatment group achieved IGA success vs 15.1% and 7.6% in the vehicle arms, respectively. A greater percentage of subjects in the ruxolitinib 1.5% treatment group achieved EASI-75 compared with the vehicle group (62.1% and 61.8% vs 24.6% and 14.4%, respectively).

With respect to the 44-week long-term safety (LTS) period of the study subsequent to the vehicle-controlled period, subjects initially randomized to ruxolitinib 1.5% cream twice daily and continued to receive ruxolitinib after week 8, whereas those initially randomized to the vehicle were re-randomized to either ruxolitinib 0.75% or 1.5% cream.[6] Of note, ruxolitinib was used on an as-needed basis to simulate real-world usage (ie, subjects were instructed to treat only active AD lesions, stop treatment 3 days after lesion clearance, and restart treatment at first signs of recurrence). At week 52, disease control was maintained in subjects who initially started on and continued with ruxolitinib 1.5% cream (77.8% achieved IGA 0/1, mean total affected BSA 1.4%). Similar efficacy was also observed in the vehicle-to-ruxolitinib 1.5% cream group (74.1% achieved IGA 0/1, mean total affected BSA 1.7%).

Sub-analyses based on age stratification have also been conducted. Eichenfield et al performed a pooled analysis of adolescents from the 2 phase 3 randomized trials and found at week 8, significantly more adolescent (age >= 12-17 years) subjects receiving ruxolitinib 1.5% cream vs vehicle to achieve IGA-TS (50.6% and 14.0%, respectively) and EASI-75 (60.9% and 34.9%, respectively).[7] Moreover, adolescent IGA-TS and EASI-75 with ruxolitinib cream was comparable to subjects 18-64 years of age (52.2% and 61.0%, respectively) and >= 65 years of age (60.5% and 73.7%, respectively). In the long-term safety (LTS) period with as-needed use of ruxolitinib cream, 68.8% (53/77) of those who continued on ruxolitinib cream had clear or almost clear skin (IGA 0/1). For those who switched from vehicle to ruxolitinib cream, there was a substantial increase in the percentage of subjects achieving clear or almost clear skin at week 12 compared to week 8 [60% (12/20) vs 28.6% (6/21)]. This success was sustained through week 52 [63.2% (12/19)].

Simpson et al. further performed a post hoc analysis of the pivotal phase 3 trials (TRuE-AD1/2), which included subjects who, at baseline, had an IGA score of 3, EASI >= 16, and affected BSA >= 10%.[8] This analysis intended to assess the success of ruxolitinib cream in a subset of subjects with moderate and/or more extensive disease who meet the severity threshold for systemic therapy. At week 8, ruxolitinib cream was superior to the vehicle with respect to skin clearance (IGA 0/1), with 59.4% (19/32) and 0.0% (0/13), respectively, achieving success. Ruxolitinib cream also outperformed vehicle with respect to EASI-75 with success rates of 71.9% (23/32) and 7.7% (1/13), respectively. During the LTS period with as-needed ruxolitinib cream usage, the percent of subjects achieving clear or almost clear skin (IGA 0/1) further increased in those who initially applied ruxolitinib cream from the vehicle-controlled period [78.3% (18/23)]. Mean affected BSA also decreased from 18.0% at baseline to 5.2% and 2.5% at weeks 8 and 52, respectively. Percentages of subjects achieving IGA 0/1 and reduction in mean affected BSA were similar among patients who applied ruxolitinib cream from day 1 and those who crossed over from the vehicle.

Recent findings from the TRuE-AD3 trial, which followed a similar design to the TRuE-AD1/2 studies and the LTS extension, also demonstrated that significantly more patients aged 2-11 years who applied ruxolitinib 1.5% cream achieved both IGA-TS (56.5%) and EASI-75 (67.2%) by week 8 compared to those treated with vehicle (10.8% and 15.4%, respectively).[9] Efficacies were sustained during the 44-week as-needed treatment period of the LTS. These results highlight the efficacy of ruxolitinib cream in younger pediatric populations with AD.

Atopic Dermatitis of the Head and Neck

Patient quality of life is not only related to disease severity but also to body regions that are differentially affected.[10] For example, AD involvement in highly visible areas (ie, the face) is associated with a greater reduction of quality of life compared with other non-visible areas (ie, the back).[11,12] The head and neck region is also particularly challenging to treat, given that irritation and burning may be exacerbated with topical crisaborole and calcineurin inhibitors.[4,13] Adverse events from topical corticosteroid use (ie, hypopigmentation, skin atrophy, periorificial dermatitis, rebound dermatitis, striae, etc.) may also be amplified in the head and neck.[14,15]

A pooled sub-group analysis by Simpson et al examined the efficacy of ruxolitinib cream monotherapy across the head and neck from the phase 3 TRuE-AD studies.[16] 663 subjects (age >= 12 years of age) at baseline had head and neck involvement. Least squares mean (LSM) percentage improvements from baseline in total EASI score in the head and neck region were significantly greater than vehicle at all time points (weeks 2, 4, and 8) with EASI subscores for induration, erythema, excoriation, and lichenification all exhibiting significantly greater improvements over vehicle as early as week 2. The pooled total percentages of subjects achieving EASI-50, EASI-75, and EASI-90, as well as IGA treatment success (defined as an IGA-TS score of 0/1 with ≥2-point improvement), were significantly greater with ruxolitinib cream compared with vehicle at week 8 (P<.0001). Itch NRS4 success was also significantly greater with ruxolitinib cream (P<.0001). These treatment successes correlated with significant improvements in the Dermatology Life Quality Index (DLQI) observed at week 2 and sustained through week 8.

Improvement of Chronic Hand Eczema With Ruxolitinib Cream

Chronic hand eczema (CHE) is a condition of multifactorial etiology, and a subset of CHE patients have atopic dermatitis of the hands (~34%).[17] A systematic review and meta-analysis encompassing over 17,000 patients found that hand eczema has a moderate-to-severe impact on quality of life that is comparable to other chronic diseases.[18] Disease severity is measured by the validated Hand Eczema Severity Index (HECSI), a clinical severity scoring tool ranging from 0 to 360 points based on assessments of severity across 6 different morphological signs (erythema, infiltration/papulation, vesicles, fissures, scaling and edema).[19] Higher HECSI scores strongly correlated with DLQI scores.[18] Furthermore, patients afflicted with CHE exhibit substantial concern over the use of topical corticosteroids for the treatment of their condition.[20]

Although therapeutic advancements in CHE treatment have been notable, particularly with systemic therapies (eg, dupilumab, abrocitinib, upadacitinib), significant progress in the topical space remains a major unmet need. To date, there is no FDA-approved medication for the treatment of CHE; however, oral alitretinoin and topical delgocitinib (a pan-JAK inhibitor available in 2024) are approved in Europe.[21] Ruxolitinib 1.5% cream has been preliminarily studied for CHE by Smith et al in an investigator-initiated, open-label, single-site study.[22] Recruited subjects exhibited moderate-to-severe CHE, and all had failed topicals (corticosteroid and/or calcineurin inhibitors) and, in some cases, systemic (eg, oral corticosteroids, methotrexate, and phototherapy) treatments. Treatment with ruxolitinib 1.5% cream twice daily for 4 weeks resulted in 100% and 64% of subjects achieving 50% (HECSI-50) and 75% (HECSI-75) improvement, respectively. Significant improvement in DLQI scores was also noted. Given this success, a phase 2 randomized controlled trial for chronic hand eczema is underway (NCT05906628).

Real-World Efficacy and Reduced Utilization of Topical and Oral Corticosteroids and Biologics

In addition to the aforementioned trials, the real-world efficacy of ruxolitinib cream for AD has been noted in the literature. A single-center retrospective study assessed 92 adult patients with mild-to-moderate AD.[23] Majority of patients had moderate disease (63%), were female (64%) and White (59%). Most patients (63%) achieved clear or almost clear skin at their first follow-up visit, with the average time between initiation of ruxolitinib cream and follow up being 3.5 months.

Real-world physician satisfaction of AD disease control with ruxolitinib cream was demonstrated in a US Adelphi study.[24] A cross-sectional survey of physician-reported data between 2022 and 2023 captured 149 patients (84.6% with moderate AD) who received ruxolitinib cream as monotherapy or in combination for >= 1 month (median duration of treatment, 26 weeks). After treatment, 48.3% of patients achieved clear or almost clear skin (IGA 0/1), and 81.2% were not currently experiencing a flare of their condition. Physicians were satisfied with disease control for 87.3% of all treated patients and for 91.5% of those who received monotherapy.

Furthermore, real-world U.S. claims data studies revealed that within 6 months following ruxolitinib cream initiation, there was a decrease in utilization of other AD treatments, including topical and oral corticosteroids, topical calcineurin inhibitors, topical PDE4 inhibitors, and biologics.[25] This continued through the following 7 to 12 months after treatment initiation.[26] Among patients who did not receive AD biologic therapy during the baseline period, >90% remained off biologics during the follow-up periods. Among patients who received AD biologic therapy during the

baseline period, 26% did not continue biologics. The mean cumulative prednisone-equivalent dose was also reduced by 44% during months 7 to 12 of the follow-up period. This helps lower healthcare costs while also reducing the safety risks associated with prolonged use of systemic agents, offering a safer, more cost-effective alternative for long-term disease management.

Effect of Ruxolitinib 1.5% Cream on Itch

Itch has been cited as the most burdensome symptom by patients afflicted with atopic dermatitis; reducing itch is the cornerstone of breaking the "itch-scratch" cycle that perpetuates AD.[27] In the TRuE-AD1/2 phase 3 pivotal trials, baseline mean worst itch numerical rating scale (NRS) was 5.1 +/- 2.5 out of a maximum score of 10.[5] The proportion of subjects achieving success in itch reduction (defined as a 4-point reduction in NRS [NRS4]) at week 8 was significantly greater in the ruxolitinib 1.5% cream treatment group (52.2% and 50.7%) vs vehicle (15.4% and 16.3%). For subjects with baseline itch NRS >= 4, NRS4 success was also significantly greater by day 2 (~36 hours after the first treatment application) for ruxolitinib 1.5% cream (11.6% and 10.8%, respectively) vs vehicle (2.9% and 1.3%, respectively).

A pooled analysis of the phase 3 trials using itch NRS2 (2-point reduction in worst itch NRS, which is clinically relevant[28]) found ruxolitinib cream to improve itch as early as 12 hours following the first application.[29]The median time to reach itch NRS2 was also shorter for subjects applying ruxolitinib 1.5% cream (4.0 days) vs vehicle (17.0 days). The median time to reach itch NRS4 was 13.0 days for the ruxolitinib 1.5% cream treatment group; however, this endpoint was not met in the vehicle group. When stratified by age (12-17 years, 18-64 years, >= 65 years), itch NRS4 was achieved by 52.1%, 51.1%, and 53.8% of subjects, respectively, receiving ruxolitinib 1.5% cream compared to vehicle (17.4%, 15.3% and 17.6%, respectively).[7] This suggests that ruxolitinib cream has a comparable positive effect on itch reduction regardless of age. In a subset analysis of TRuE-AD1 & True-AD2 subjects with extensive disease who met the severity threshold for systemic therapy (IGA = 3, EASI >= 16, BSA >= 10%), 61.1% vs 27.3% achieved itch NRS4 at week 8 in the ruxolitinib 1.5% cream and vehicle groups, respectively, compared to 51.5% in the overall TRuE-AD1/2 population.[8]

Blauvelt et al further evaluated the achievement of an itch-free state (defined as worst itch NRS 0/1) in another pooled analysis of TRuE-AD1 and TRuE-AD2.[30] Achievement of itch NRS 0/1 was significantly greater in the ruxolitinib 1.5% cream group compared to vehicle (19.0% vs 4.6%, respectively) as early as day 2 (~36 hours after first application) and remained significant through week 8. The median time to achieve itch NRS 0/1 was 9.0 days for ruxolitinib 1.5% cream vs not estimable for vehicle. Of note, a multivariable proportional hazards regression model found age to be the only demographic factor associated with faster itch response (<18 years, median 11.0 days; >= 18 years, median 17.0 days). A greater percentage of subjects who applied ruxolitinib cream vs vehicle reported no days of itch. Furthermore, a serum proteomic analysis of 1,012 proteins comparing subjects from the Phase 2b trial (NCT03011892) who achieved itch NRS 0/1 vs those who did not at week 8 revealed a total of 53 proteins to be more downregulated and 4 proteins to be more upregulated in those who achieved an itch-free state, thus correlating with reduced systemic inflammation.[31]

With regards to the younger pediatric population (ages 2-11), Eichenfield et al. found greater success in itch reduction (NRS4) in patients treated with ruxolitinib 1.5% cream (43.5%) vs vehicle (29.7%).[9] This outcome was similar to phase 3 results in adolescents and adults.

A 28-day phase 2, open-label, single-site study (SCRATCH-AD; NCT04839380) in adult subjects aged 18 to 65 years with AD for >= 6 months also assessed the short-term benefits of ruxolitinib 1.5% cream twice daily to control itch.[32] The study assessed change from baseline in modified peak pruritus numerical rating scale (mPP-NRS; current itch intensity) at short intervals on day 1 (15 and 30 minutes, and at 1, 2, 4, 6, and 12 hours post-treatment) as well as days 2 through 29. At baseline, subjects exhibited a mean (SD) pretreatment mPP-NRS score of 6.4 (1.72), and 89.1% had an IGA of 3. Itch reduction was observed as early as 15 minutes [mPP-NRS -2.3 (2.34)], peaked at 4 hours post-treatment [-4.2 (2.12)], and was further improved and sustained through 28 days of treatment. Of note, transepidermal water loss (TEWL) of lesional AD skin was also measured from baseline through the 4 weeks, and it substantially decreased to levels similar to nonlesional skin with ruxolitinib treatment.

Efficacy of Ruxolitinib Cream Directly Compared to Topical Corticosteroid

A phase 2, randomized, double-blind, dose-ranging, vehicle- and active-controlled 8-week study in adult patients (age 18 - 70 years) with mild-to-moderate AD >= 2-year history of disease assessed the efficacy of vehicle twice daily (n=52), ruxolitinib 1.5% cream twice daily (n=51) and triamcinolone 0.1% cream twice daily (n=51) over 4 weeks in the initial portion of the trial.[33] Mean percentage improvement from baseline in EASI score for ruxolitinib, triamcinolone, and vehicle were 71.6%, 59.8%, and 15.5%, respectively. The proportion of IGA responders were also 38.0%, 25.5%, and 7.7%, respectively. Of note, the authors found a direct correlation between serum concentration of thymus and activation-regulated cytokine (TARC) and EASI score. This is in agreement with the prior notion of TARC serum levels being a biomarker of disease severity.[34] Ruxolitinib 1.5% cream applied twice daily resulted in the greatest reduction in TARC concentrations.

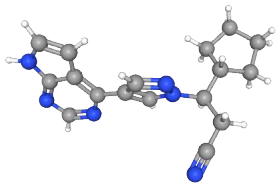
CONCLUSION

Ruxolitinib 1.5% cream is the first FDA-approved topical JAK inhibitor for mild-to-moderate AD in patients >= 12 years of age up to 20% affected BSA without any topical drug interaction warning (ie, it can be used as monotherapy or in combination with other topical medications as deemed fit). It can also be used on a non-continuous as-needed basis, given its efficacy in the pivotal 44-week as-needed treatment period (LTS). JAK inhibitors are appreciated for their rapidity of effect on itch and skin clearance, along with their magnitude of effect. The 2023 AAD guidelines have given a strong recommendation for topical JAK inhibition, with ruxolitinib cream being the first and only in class while exhibiting numerous advantages (Figures 1 and 2).[4] Not only has ruxolitinib cream shown superiority to vehicle cream in the pivotal phase 3 trials,it has also shown favorable efficacy compared to triamcinolone 0.1% cream in a phase 2 active comparator study. Utility of ruxolitinib cream has also been demonstrated in various special anatomic sites, such as the head and neck region, and treatment-recalcitrant chronic hand eczema. Real-world assessments have repeatedly shown a quick onset of action, especially when ruxolitinib cream is used in combination therapy (due to lack of drug interactions), suggesting that it can be used across the spectrum of AD. These outcomes correlate with high physician and patient satisfaction. Ruxolitinib 1.5% cream is also associated with improved work productivity with expected incremental annual indirect cost savings of over $4000.[35] Lastly, ruxolitinib cream is very well tolerated with minimal systemic absorption and a clean safety profile (detailed in the second portion of this supplement). As such, ruxolitinib 1.5% cream is a welcomed first-line topical therapeutic for any AD patient over the age of 12 years with less <= 20% affected BSA to be used either as monotherapy or in combination with other topical AD treatments without need for lab monitoring, and offers flexibility for long-term management, as it can be applied on an as-needed basis for chronic treatment, providing both efficacy and convenience in maintaining disease control.

FIGURE 1. Current landscape of topical ruxolitinib 1.5% cream for the treatment of adolescent and adult patients with atopic dermatitis. Nitrogen atoms are colored blue, while carbon atoms are colored gray.

Significant Skin Clearance

- Superior to vehicle at week 8, but as early as week 2
- Similar effectiveness in adolescents and adults
- Effective in anatomic sites of special interest (i.e. head and neck, chronic hand eczema)
- Improvement in skin barrier with reduction in transepidermal water loss (TEWL)



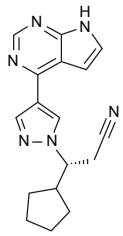
Ruxolitinib 1.5% Cream

Established Safety Profile

- Comparable to vehicle in pivotal phase 3 trials
- Infrequent and unrelated adverse events of special interest in long-term safety (LTS) trial
- Maximal-use and pharmacokinetic profiling consistently revealed plasma concentrations below that required for bone marrow suppression

Powerful Itch Reduction

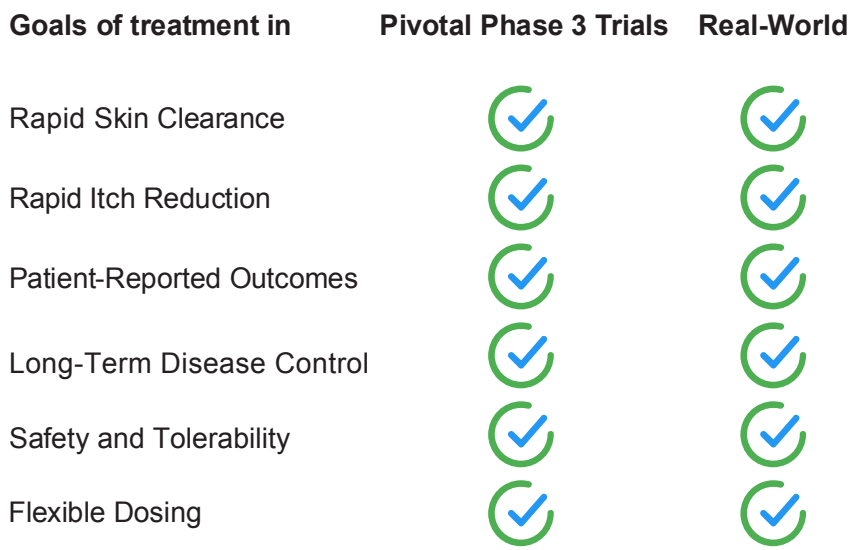
- Clinically meaningful reduction in itch as early as 12 hours (NRS2) and 36 hours (NRS4)
- 15-minute rapid itch reduction in open-label, single-arm monotherapy Phase 2b study
- Itch-free state (NRS 0/1) achieved by ~20% of subjects treated in phase 3 trials within 36 hours



Improved Patient Reported-Outcomes

- DLQI and other QoL indices significantly improved
- Increased patient work productivity and reduction in activity impairment resulting in significant annual indirect cost savings

FIGURE 2. Goals of treatment in atopic dermatitis achieved in pivotal phase 3 clinical trials as well as real-world usage data.



DISCLOSURES

Christopher G. Bunick has served as an investigator for AbbVie, Almirall, Apogee, Daiichi Sankyo, LEO Pharma, Ortho Dermatologics, Sun Pharma, Timber, and Palvella; a consultant for AbbVie, Almirall, Apogee, Arcutis, Connect BioPharma, Eli Lilly, EPI Health/Novan, Incyte, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer, Sanofi-Regeneron, Takeda, and UCB; and a speaker for and received honoraria from Allergan, Almirall, LEO Pharma, and UCB.

Pearl Kwong MD PhD serves on the speaker bureau, advisory board, and/or as a consultant or principal investigator for the following pharmaceutical companies: Abbvie, Arcutis, Apogee, Dermavant, Eli Lilly, Pfizer, Sanofi, Regeneron, Ortho, Leo, Galderma, L'Oréal, Incyte, Sun, UCB, Verrica, and Pelthos.

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