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 ORIGINAL ARTICLE

New Polymeric Once-Daily Tazarotene 0.045% Lotion Formulation for Moderate-to-Severe Acne: Pooled Phase 3 Pediatric Analysis

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ABSTRACT

Background: Acne vulgaris affects approximately 85% of adolescents. Topical tazarotene is efficacious and safe for acne treatment but irritation limits its use. The objective was to evaluate efficacy, safety, and tolerability of a new tazarotene 0.045% lotion formulation in patients aged 10-13 and 14-17 years with moderate-to-severe acne.

Methods: In two phase 3, double-blind, vehicle-controlled 12-week studies, patients with moderate-to-severe acne (N=1,614) were randomized (1:1) to receive tazarotene 0.045% lotion or vehicle once-daily. Efficacy assessments included changes from baseline in inflammatory/noninflammatory lesions and treatment success (≥2-grade reduction in Evaluator's Global Severity Score [EGSS] and a clear/almost clear score). Quality of life (QoL) and adverse events (AEs) were also assessed.

Results: Patients aged 10-13 years (n=136) and 14-17 years (n=548) were pooled. At week 12, mean percent reductions in inflammatory and noninflammatory lesion counts were significantly greater with tazarotene versus vehicle in both age groups (least-squares mean inflammatory 10-13 years: -55.6 vs -37.0%; 14-17 years: -53.3 vs -41.2%; noninflammatory 10-13 years: -47.7 vs -28.2%; 14-17 years: -52.7 vs -32.9%; $P<0.01$ all). More patients achieved treatment success with tazarotene versus vehicle in both age groups ($P<0.05$, both). There were no significant differences between tazarotene-treated age groups in lesion counts or treatment success. Acne-QoL scores at week 12 in both age groups were numerically improved in most domains with tazarotene 0.045% lotion versus vehicle. Most treatment-emergent AEs with tazarotene or vehicle were of mild or moderate severity in both age groups.

Conclusions: Tazarotene 0.045% lotion was efficacious and well tolerated in pediatric patients with moderate-to-severe acne.

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INTRODUCTION

Acne is one of the most common skin diseases[1,2] particularly in adolescence, affecting approximately 85% of adolescents and young adults.[2] Additionally, acne is increasingly occurring earlier in life, with a younger age associated with greater symptom severity.[3] Acne occurs in adolescence due to increases in androgen levels in puberty, which lead to increased sebum production and follicular occlusion, *C. acnes* bacterium proliferation, and release of proinflammatory factors in the skin.[4-6] Recent research reveals that inflammation is a crucial feature of the disease process.[7]

Acne can confer significant physical and psychological morbidity and diminished quality of life (QoL)[8,9] with permanent scarring, reduced self-esteem, depression, or anxiety.[2,10] Young patients may be difficult to treat as they tend to be less adherent to treatments[11] and may be more susceptible to cutaneous irritation.[12]

Topical retinoids, such as tazarotene, have anti-inflammatory and comedolytic properties and are a mainstay of topical acne treatment.[13] Efficacy, safety, and tolerability of retinoids are well documented for inflammatory and noninflammatory acne. Studies have consistently shown reductions in lesion numbers, significant improvement in acne severity/visible appearance of acne, and prevention of new acne lesion development by inhibiting microcomedone formation.[13-15] However, dose-dependent irritation, dryness, and erythema have limited retinoid use.[2] The use of moisturizers before the application of tazarotene 0.1% cream has demonstrated enhanced tolerability without altering efficacy, though need for a topical medication with lower irritability remains.[16]

To address the continued unmet need for an effective topical acne treatment with improved tolerability, a new tazarotene 0.045% lotion formulation utilizing polymeric emulsion technology was developed. The active ingredient and hydrating and moisturizing ingredients form an oil-in-water emulsion structured by a three-dimensional mesh matrix, ensuring rapid, even, and simultaneous release of ingredients.[17] In addition to being aesthetically pleasing, optimized active ingredient delivery with this formulation allows for a lower dose of active dermatological products in an easily applied, highly spreadable formulation. The simultaneous application of a low-dose tazarotene with emollients may also enhance tolerability and improve treatment compliance.

A phase 2 study comparing tazarotene 0.045% lotion with commercially available tazarotene 0.1% cream showed that tazarotene 0.045% lotion was more numerically effective than the higher concentration tazarotene 0.1% cream with fewer treatment-related adverse events (TEAEs).[18] In addition, two subsequent, identical phase 3 double-blind, randomized, vehicle-controlled 12-week studies showed tazarotene 0.045% lotion was efficacious versus vehicle and well tolerated in patients with moderate-to-severe acne.[19] The objective of this post hoc analysis was to evaluate safety and efficacy of tazarotene 0.045% lotion in pre-adolescent and adolescent patients (10-13 and 14-17 years of age, respectively) with moderate-to-severe acne using pooled data from the two phase 3 trials.

METHODS

Study Design and Patients

Data were pooled from two identical multicenter, double-blind, randomized, vehicle-controlled, parallel-group phase 3 studies (NCT03168334 and NCT03168321), details of which have been published.[19] Briefly, patients aged ≥9 years with Evaluator's Global Severity Scores (EGSS) indicating moderate (3) or severe (4) acne were eligible to enroll at 89 study centers. Eligible participants also had to have had 20-50 facial inflammatory lesions (papules, pustules, and nodules), 25-100 noninflammatory lesions (closed and open comedones), and two or less facial nodules. Patients were randomized (1:1) to tazarotene 0.045% lotion or vehicle lotion, applied to the face once daily for 12 weeks. All studies were conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice Guidelines, and local regulations. All patients or their legal guardians provided written informed consent. The studies were approved by relevant institutional review boards or independent ethics committees at each study center.

Efficacy Evaluation

Efficacy evaluations included inflammatory and noninflammatory lesion counts and treatment success, defined as the proportion of patients achieving ≥2-grade reduction from baseline in EGSS and a score of "clear" (0) or "almost clear" (1). Assessments were performed at screening, baseline, and weeks 2, 4, 8, and 12 (end of treatment). Separately, and independent of investigator assessments, patients completed an Acne Specific Quality of Life (Acne-QoL) questionnaire at baseline (prior to study drug application) and week 12. The validated Acne-QoL questionnaire comprises 19 questions divided into four different domains—self-perception, role-emotional, role-social, and acne symptoms. Questions within each domain are scored from 0 (extremely) to 6 (not at all), with higher scores indicating improved health-related QoL; domain scores range from 0-30 for self-perception, role-emotional, and acne symptoms and 0-24 for role-social.[20]

Safety Evaluation

Cutaneous safety (scaling, erythema, hypopigmentation, hyperpigmentation) was evaluated by investigators at each post-screening visit using a 4-point scale where 0=none and 3=severe. Patient assessments of tolerability (itching, burning, stinging) were reported at all post-screening visits using the same 4-point scale. Safety was also evaluated by monitoring adverse events (AEs) and serious adverse events (SAEs) throughout the study.

Statistical Analysis

In the individual phase 3 trials, co-primary efficacy endpoints were the absolute reductions from baseline to week 12 in inflammatory and noninflammatory lesion counts and the percentage of patients achieving treatment success at week 12. Secondary efficacy endpoints included percent change in inflammatory and noninflammatory lesion count from baseline to week 12. Patients who were randomized and received study drug comprised the intent-to-treat (ITT) population. The safety population consisted of all randomized patients who used study medication or vehicle at least once with a minimum of one post-baseline evaluation.

For this pooled post hoc analysis, patients were grouped into one of two age groups (pre-adolescent: 10-13 years; adolescent: 14-17 years). Although patients aged ≥9 years were eligible for enrollment, no patients aged <10 years were enrolled in either study. Analyses included the percentage of patients achieving treatment success at week 12, percent change from baseline in inflammatory and noninflammatory lesion counts by visit, and absolute change from baseline to week 12 in the four Acne QoL domains. In the pooled analysis, significant skewness was observed for mean percent changes from baseline in inflammatory and noninflammatory lesions; therefore, a nonparametric method was used in which data were rank transformed prior to the analysis of covariance (ANCOVA), with factor of treatment and the respective baseline lesion count as a covariate. For the comparison of percent changes in lesions counts between age groups, a ranked ANCOVA with factor of age group and respective baseline lesion count as a covariate was utilized. Treatment

success was evaluated using a logistic regression using Firth's Penalized Likelihood, with factor of treatment group (and with factor of age group when comparing the two age groups). For efficacy assessments, multiple imputation was used to impute missing values using the method of Markov Chain Monte Carlo. All statistical analyses were performed using SAS® version 9.3 or later. Statistical significance was based upon 2-tailed tests of the null hypothesis resulting in *P* values of 0.05 or less.

Acne-QoL domains were summarized using descriptive statistics with no imputation of missing values. Cutaneous safety and tolerability assessments were summarized using descriptive statistics. AEs were recorded and classified using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Imputations were not made for missing safety data.

RESULTS

Patient Disposition and Demographics

A total of 1614 patients were randomized in the two phase 3 studies. Of those, 684 were pediatric patients aged 10-17 years and were included in this pooled analysis (ITT population: 10-13 years, n=136; 14-17 years, n=548). Among these patients, more than 90% completed the study (Figures 1A and 1B). The most common reasons for study discontinuation were lost to follow up, patient request, and adverse events. The pediatric safety population comprised 676 patients; 8 patients were excluded due to absence of post-baseline safety evaluations.

Baseline patient demographics and disease characteristics are presented in Table 1. The majority of patients in the 10-13-year age group were female (64.0%) and in the 14-17-year age group, most patients were male (57.5%). More than 85% of patients in both age groups had moderate disease (EGSS 3), though the older age group had slightly worse disease severity given the higher mean number of inflammatory lesions and greater percentage of patients with severe disease (Table 1).

Efficacy

At week 12, among patients 10-13 years of age, more patients in the tazarotene 0.045% lotion arm achieved treatment success versus vehicle (22.9% vs 7.1%; *P*<0.05). Similarly, in patients aged 14-17 years, more patients treated with tazarotene 0.045% lotion achieved treatment success versus vehicle (24.4% vs 11.3%; *P*<0.001; Figure 2). At weeks 4 and 8, while more patients in the tazarotene 0.045% lotion arm achieved treatment success versus vehicle, there were no significant differences between tazarotene 0.045% and vehicle for any age group (data not shown).

Tazarotene 0.045% lotion also provided significant reductions in inflammatory lesion counts versus vehicle in both pre-adolescent and adolescent patients. Specifically, at week 12, there

FIGURE 1. Patient disposition in pre-adolescents (A) and adolescents (B).

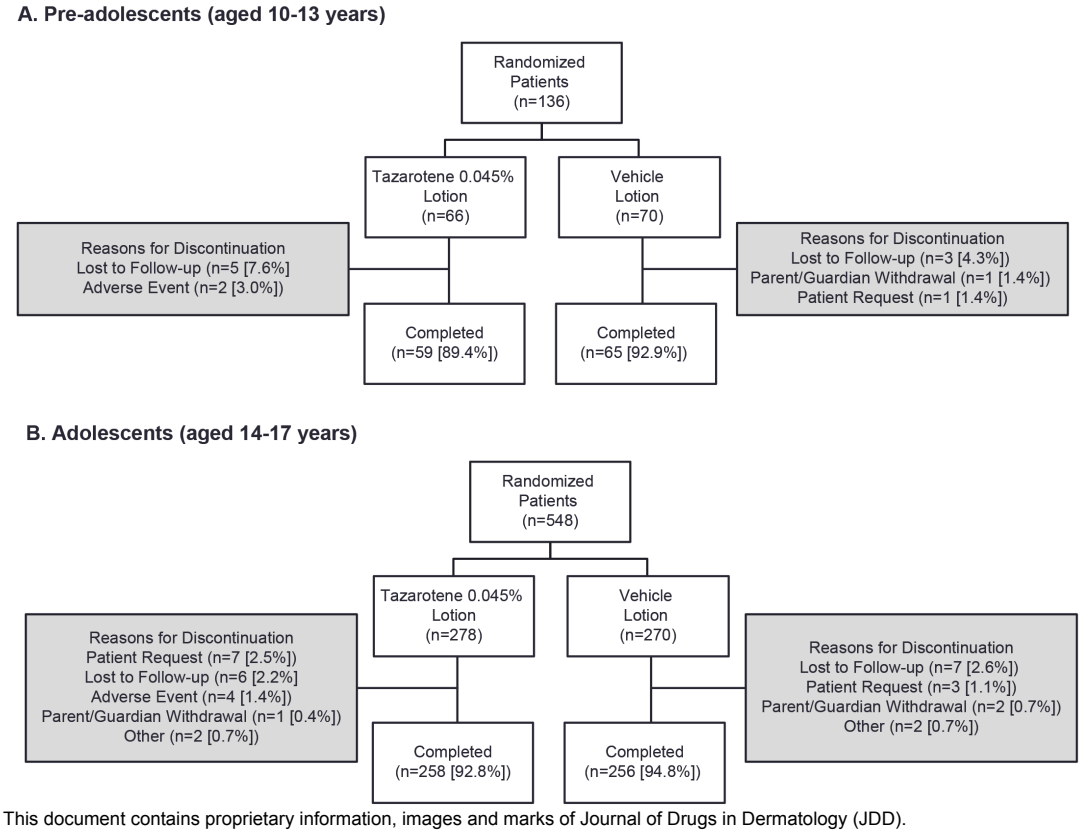


TABLE 1.

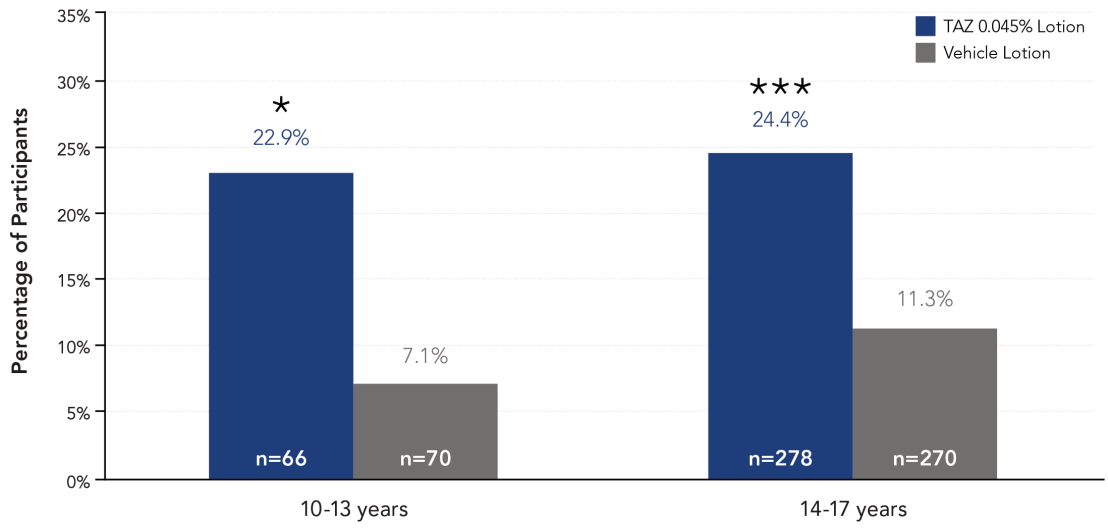
Patient Demographics and Baseline Characteristics (ITT Population, Pooled)				
	10-13 years		14-17 years	
	TAZ 0.045% Lotion (n=66)	Vehicle Lotion (n=70)	TAZ 0.045% Lotion (n=278)	Vehicle Lotion (n=270)
Age, mean (SD), y	12.1 (0.97)	12.3 (0.87)	15.5 (1.10)	15.5 (1.10)
Female, n (%)	43 (65.2)	44 (62.9)	118 (42.4)	115 (42.6)
Race, n (%)				
White	48 (72.7)	54 (77.1)	235 (84.5)	209 (77.4)
Black	12 (18.2)	11 (15.7)	17 (6.1)	36 (13.3)
Other[a]	6 (9.1)	5 (7.1)	26 (9.4)	25 (9.3)
Ethnicity, Non-Hispanic/Latino, n (%)	54 (81.8)	57 (81.4)	225 (80.9)	213 (78.9)
Inflammatory lesion count, mean (SD)	28.7 (6.4)	27.3 (6.6)	28.5 (7.5)	29.2 (7.5)
Noninflammatory lesion count, mean (SD)	46.4 (18.6)	46.4 (19.2)	44.4 (18.8)	43.7 (17.2)
Evaluator's Global Severity Score, n (%)				
3 – Moderate	63 (95.5)	65 (92.9)	248 (89.2)	242 (89.6)
4 – Severe	3 (4.5)	5 (7.1)	30 (10.8)	28 (10.4)

[a]American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, Asian, and Other/Multiple.
EGSS, Evaluator's Global Severity Score; ITT, intent-to-treat; SD, standard deviation; TAZ, tazarotene.

was a 55.6% reduction in mean percent change from baseline in inflammatory lesion counts in tazarotene-treated patients aged 10-13 years, compared with a 37.0% reduction in the vehicle arm (P<0.01; Figure 3). Among tazarotene-treated patients 14-17 years of age, mean percent inflammatory lesion count reduction was 53.3% compared with a 41.2% reduction with vehicle (P<0.001). At week 8, there was also a significant reduction in mean percent inflammatory lesion counts in the tazarotene 0.045% lotion group versus vehicle among patients 14-17 years of age (43.6% vs 34.6%, P=0.004; Figure 3). Mean percent reductions in noninflammatory lesion counts were significantly greater with tazarotene 0.045% than with vehicle in both age groups at weeks 4, 8, and 12 (P<0.05, all; Figure 4). Improvement in acne lesions are shown in Figure 5.

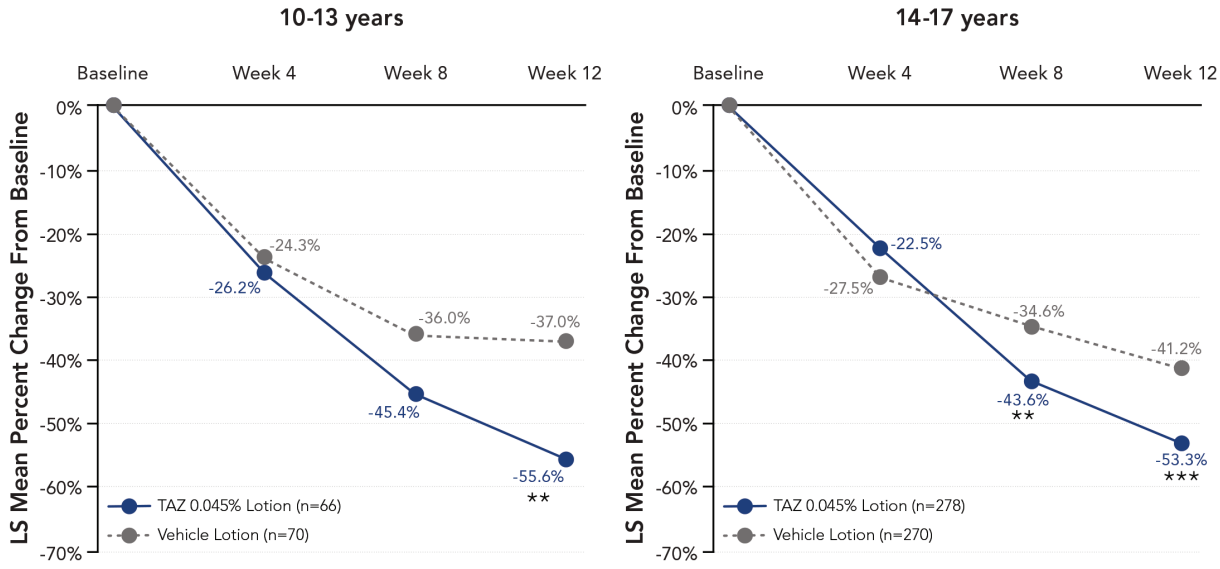
When comparing tazarotene-treated patients in both age groups, there were no statistically significant differences in lesion count reductions or percent of patients achieving treatment success at any timepoint.

FIGURE 2. Percentage of pediatric patients achieving treatment success at week 12 (ITT population, pooled).



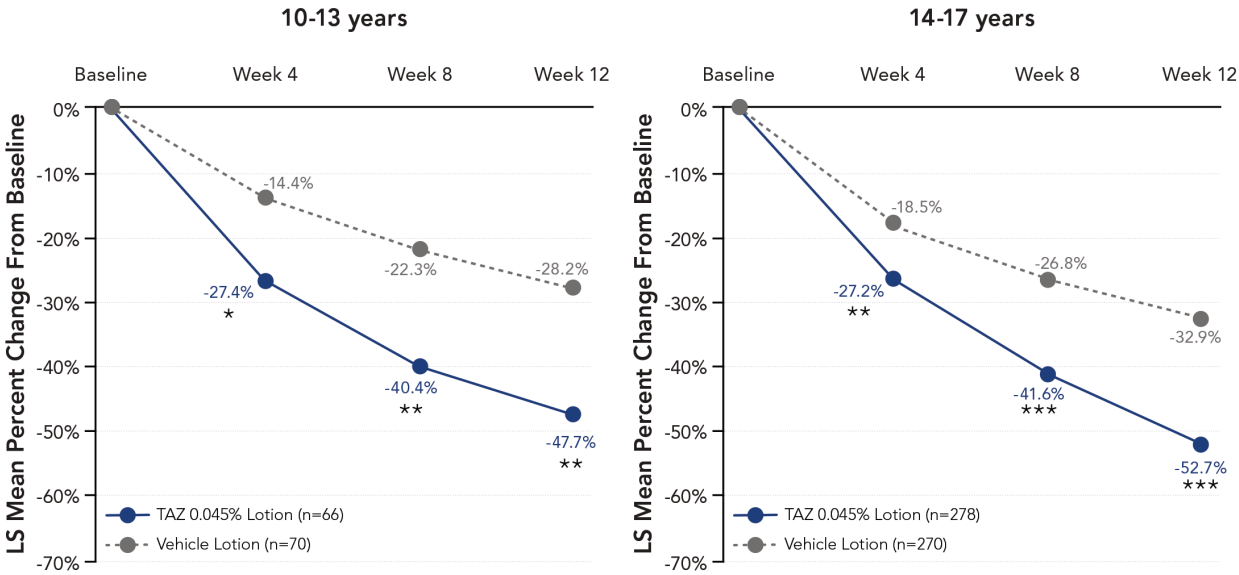
*P<0.05 versus vehicle; ***P<0.001 versus vehicle.
Treatment success = percentage of patients with ≥2-grade reduction from baseline in EGSS and "clear" or "almost clear."
There was no significance difference between tazarotene-treated age groups for treatment success.
EGSS, Evaluator's Global Severity Score; ITT, intent-to-treat; TAZ, tazarotene.

FIGURE 3. Mean percent change from baseline in inflammatory lesions in pediatric patients, by week (ITT population, pooled).



**P<0.01 versus vehicle; ***P<0.001 versus vehicle.
There was no significance difference between tazarotene-treated age groups for inflammatory lesions.
ITT, intent-to-treat; LS, least squares; TAZ, tazarotene.

FIGURE 4. Mean percent change from baseline in noninflammatory lesions in pediatric patients, by week (ITT population, pooled).



*P<0.05 versus vehicle; **P<0.01 versus vehicle; ***P<0.001 versus vehicle.
There was no significance difference between tazarotene-treated age groups for noninflammatory lesions.
ITT, intent-to-treat; LS, least squares; TAZ, tazarotene.

FIGURE 5. Acne improvement over time in a pre-adolescent and adolescent patient.

Photographs from 2 representative patients. Individual results may vary.
EGSS, Evaluator's Global Severity Score.

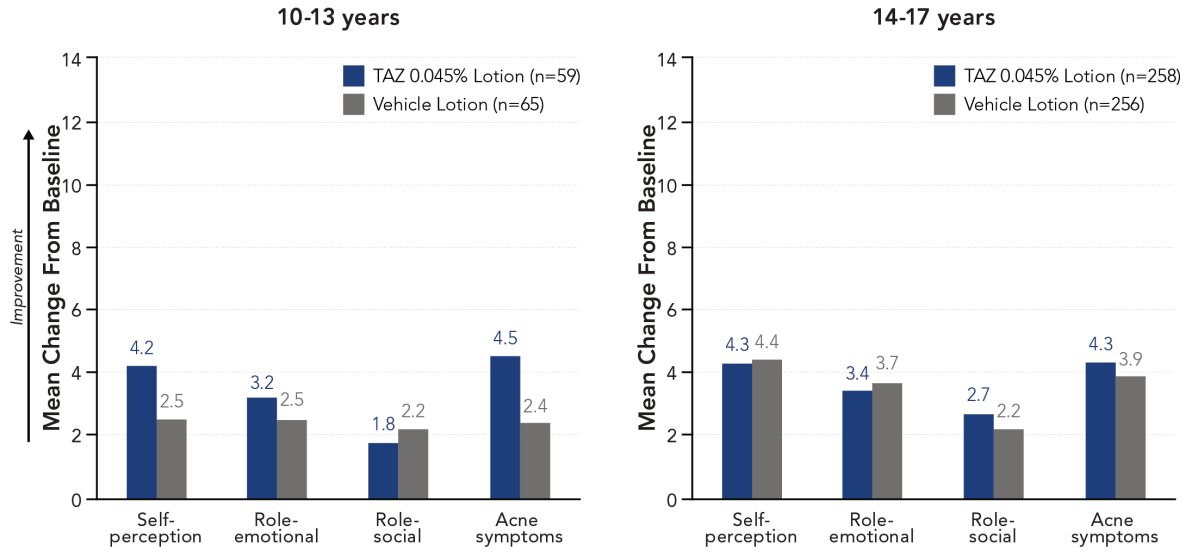
Quality of Life

Improvements in Acne QoL scores at week 12 in the 10-13 year age group were numerically greater for tazarotene 0.045% versus vehicle in 3 domains (self-perception, role-emotional, acne symptoms; Figure 6). In the 14-17-year age group, QoL score improvements at week 12 were numerically greater for tazarotene 0.045% versus vehicle in the role-social and acne symptoms domains. The greatest improvements were observed in the younger age group for the domains of self-perception and acne symptoms.

Safety

Adverse events and cutaneous safety and tolerability for the overall pooled population have been reported previously.[19] In this post hoc analysis, in the 10-13 year and 14-17-year age groups, TEAEs were reported in 27.7% and 22.9% of tazarotene-treated patients versus 19.1% and 22.4% in vehicle-treated patients (Table 2). No treatment-related SAEs were reported in either age group. No TEAEs in the overall pediatric population occurred in more than 5% of patients. The most common TEAEs (>2% of the tazarotene-treated pediatric population [n=340]) were at the ap-

FIGURE 6. Acne-QoL questionnaire responses in pediatric patients at week 12 (ITT population, pooled).



Significant differences between treatment and vehicle were not assessed.
Higher scores for each domain reflect improved health-related QoL.
Self-perception assesses the extent acne has affected a particular area of self-perception. Role-emotional assesses the emotional effect/impact of acne. Role-social assesses the impact of acne on intersocial relationships. Acne symptoms assesses the physical symptoms experienced by facial acne.
Acne-QoL, Acne-Specific Quality of Life Questionnaire; ITT, intent-to-treat; TAZ, tazarotene.

TABLE 2.

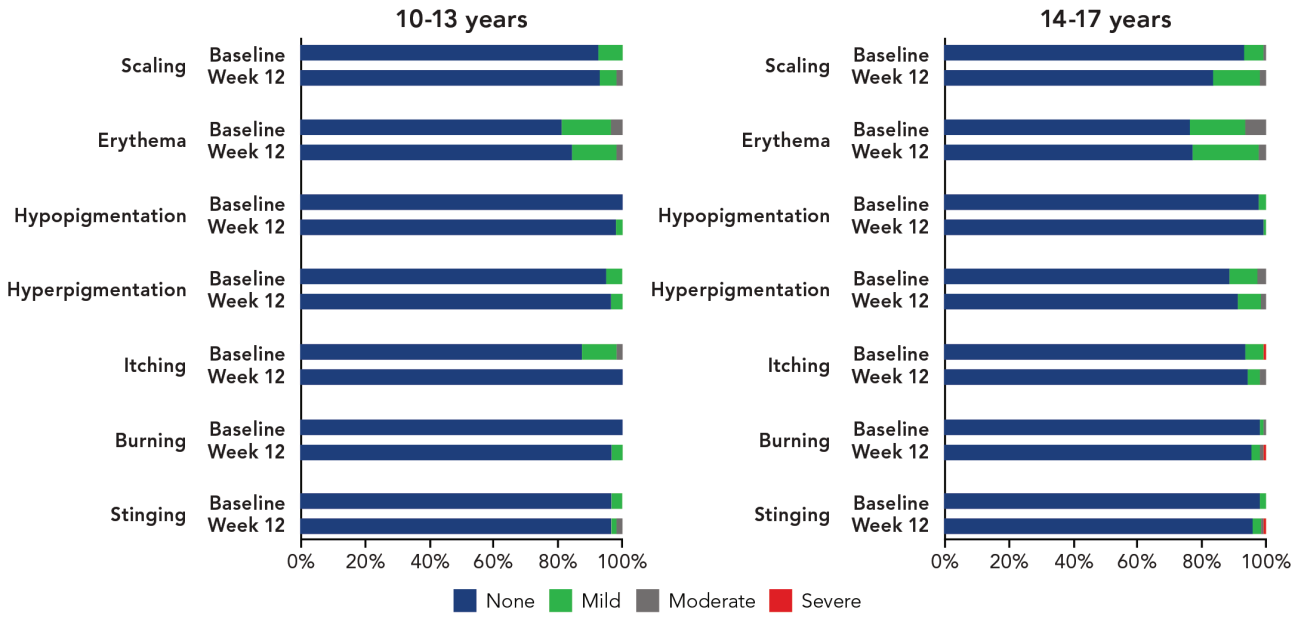
Treatment-Emergent and Related Adverse Events through Week 12 (Safety Population, Pooled)				
n (%)	10-13 years		14-17 years	
	TAZ 0.045% Lotion (n=65)	Vehicle Lotion (n=68)	TAZ 0.045% Lotion (n=275)	Vehicle Lotion (n=268)
Patients reporting any TEAE	18 (27.7)	13 (19.1)	63 (22.9)	60 (22.4)
Patients reporting any SAE[a]	0	0	1 (0.4)	1 (0.4)
Severity of TEAEs reported				
Mild	15 (23.1)	5 (7.4)	39 (14.2)	39 (14.6)
Moderate	3 (4.6)	8 (11.8)	21 (7.6)	20 (7.5)
Severe	0	0	3 (1.1)	1 (0.4)
Relationship to study drug				
Related	8 (12.3)	0	26 (9.5)	0
Unrelated	10 (15.4)	13 (19.1)	37 (13.5)	60 (22.4)

[a]None of the patients had SAEs that were considered by the investigator to be treatment related.
TAZ, tazarotene; TEAE, treatment-emergent adverse event; SAE, serious adverse event.

plication site (pain [n=17; 5.0%], dryness [n=9; 2.6%], erythema [n=7; 2.1%] and pruritus [n=7; 2.1%]); viral upper respiratory tract infection was also reported in 4.7% of pediatric patients though none of these instances were deemed related to treatment. Rates of application site irritation were low (0.6%).

The majority of the ratings for cutaneous safety and tolerability, including hypopigmentation and hyperpigmentation, were either 0 (none) or 1 (mild) in both age groups at week 12; in the tazarotene-treated 14-17 year age group, 1 patient reported severe burning and 1 reported severe stinging (Figure 7). For nearly all cutaneous safety and tolerability evaluations, there were transient increases in severity (primarily mild or moderate) following treatment with tazarotene 0.045% at weeks 2, 4, and 8 relative to baseline; however, by week 12 the percentage of patients with ratings of "none" were similar to or greater than baseline values. The exception was for scaling in the 14-17-year age group, in which 217 (83.8%) reported "none" at week 12 versus 257 (93.5%) at baseline (Figure 7).

FIGURE 7. Cutaneous safety and tolerability in tazarotene-treated pediatric patients at baseline and week 12 (Safety population, pooled).



DISCUSSION

Although prevalence of acne in adults is increasing,[9] acne is primarily a disease of adolescence.[2] Acne in adolescence can impact quality of life, leading to increased anxiety and depression, decreased self-confidence, and negative effects on school work and social activities.[10] Treating acne in adolescents may be difficult, however, especially in younger patients, due to greater irritation from topical treatments[12] and low medication adherence rates.[11] With this in mind, tazarotene 0.045% lotion was formulated with emollients to improve tolerability, which may improve treatment compliance.

Topical retinoids are recommended for acne treatment in adults and adolescents based on well-established safety and efficacy,[2,21,22] but they tend to be under prescribed.[2] They are very effective in addressing multiple aspects of acne pathology with comedolytic properties, resolution of preceding microcomedone lesions, and potent anti-inflammatory properties.[2,4] On the other hand, retinoids may exacerbate dermatitis or eczema and are somewhat limited by side effects such as irritation, skin dryness, erythema and pain. These adverse effects may be more pronounced in younger patients[12] and could compromise treatment adherence, highlighting the need to target retinoid delivery to increase efficacy and minimize side effects.[4]

Comparative studies have shown that tazarotene 0.1% lotion has superior efficacy to that of other retinoids such as adapalene 0.1% gel and tretinoin 0.1% microsponge.[23,24] Furthermore, the tazarotene 0.045% polymeric emulsion lotion formulation presents a novel modality for enhancing drug delivery and permeation into the skin while minimizing irritation in a non-greasy, highly spreadable formulation. In the current pooled, post hoc analysis, tazarotene 0.045% lotion significantly reduced inflammatory and noninflammatory lesions at week 12 versus vehicle in patients aged 10-13 and 14-17 years and more tazarotene-treated patients in both age groups achieved treatment success at week 12. In addition, most patients reported no or mild itching, burning, and stinging. Overall rates of application site dryness and irritation with tazarotene treatment (2.6% and 0.6%) were slightly lower than those reported in studies of pediatric patients with moderate-to-severe acne treated with topical tretinoin 0.05% lotion (dryness: 2.8%-3.6%; irritation: 0.7%-1.4%).[25,26]

Efficacy results from the present analysis are consistent with the overall pooled population (ages 10-65 years), which also had significantly greater reductions from baseline in both inflammatory and noninflammatory lesions versus vehicle (-57.9% vs -47.8% and -56.0% vs -42.0%, respectively) at week 12.[27] However, compared with the overall population, both the pre-adolescent and adolescent groups had greater numerical differences between tazarotene and vehicle treatment (Figures 4 and 5). In terms of safety and tolerability, tazarotene 0.045% lotion showed overall favorable safety and tolerability in the pediatric population, similar to the overall population.

CONCLUSION

This post hoc analysis of two phase 3 trials showed the polymeric, highly spreadable moisturizing formulation of tazarotene 0.045% lotion was effective and well tolerated in pre-adolescent and adolescent patients with moderate-to-severe acne. Overall AE rates were low, with favorable tolerability, which may improve patient treatment adherence and optimize efficacy, making this a promising new addition to the treatment armamentarium for acne.

DISCLOSURES

Dr. Lawrence F. Eichenfield has served as an investigator and/or consultant for Ortho Dermatologics, Galderma, Almirall and Cassiopea.

Dr. Emil Tanghetti has served as speaker for Novartis, Ortho Dermatologics, Sun, Lilly, Galderma, AbbVie, and Dermira; served as a consultant/clinical studies for Hologic, Ortho Dermatologics, and Galderma; and is a stockholder for Accure.

Dr. Eric Guenin is an employee of Ortho Dermatologics and may hold stock and/or stock options in its parent company.

Gina Martin and Dr. Radhakrishnan Pillai are employees of Bausch Health US, LLC and may hold stock and/or stock options in its parent company.

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