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Tazarotene 0.045% Lotion for the Once-Daily Treatment of Moderate-to-Severe Acne Vulgaris in Adult Males

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ABSTRACT

Background: There has been an increasing interest in gender differences both in the pathogenesis and treatment of acne vulgaris (acne). However, while acne prevalence among adolescents is comparable across sexes, acne is much more common in adult women than in adult men which has been largely ignored. Acne is likely less common in adult men because of the declining rate of sebum secretion observed with increasing age, and yet it can be more severe than in adult women. In addition, adherence to topical medications is especially poor in adult men where tactile and sensory perceptions are low. The first lotion formulation of tazarotene was developed using polymeric emulsion technology to provide an important alternative option to treat these acne patients, especially those who may be sensitive to the irritant effects of other tazarotene formulations.

Objective: To evaluate the efficacy and safety of a new tazarotene 0.045% lotion formulation based on polymeric emulsion technology in treating adult male subjects with moderate or severe acne, in comparison with adolescent males treated with the same tazarotene 0.045% lotion.

Methods: Post hoc analysis of two multicenter, randomized, double-blind, vehicle-controlled phase 3 studies in moderate-or-severe acne. Subjects (aged 10 and older, N=1614) were randomized (1:1) to receive tazarotene 0.045% lotion or vehicle, once-daily for 12 weeks. Efficacy assessments included changes in baseline inflammatory and noninflammatory lesions and treatment success (at least 2-grade reduction in Evaluator's Global Severity Score [EGSS] and clear or almost clear). Quality of Life was assessed using the validated Acne-QoL scale. Safety, adverse events (AEs) were evaluated throughout; cutaneous tolerability (using a 4-point scale where 0=none and 3=severe) at each study visit.

Results: A total of 268 male subjects (85≥18 years old and 183<18 years old) were treated with tazarotene 0.045% lotion once-daily for 12 weeks. At week 12, percent reductions in inflammatory and noninflammatory lesions with tazarotene 0.045% lotion were 62.3% and 59.5% in the adult male population, compared with 49.4% (P=0.001) and 49.5% (P=0.016) in the adolescent male population. Treatment success was achieved by 33.0% of adult male subjects treated with tazarotene 0.045% lotion, compared with 21.6% in the adolescent male population (P=0.059). Quality of life (as assessed by Acne-QoL domain scores) was better in adolescent males at baseline. Improvements in QoL domain scores were similar to those seen in the overall study population, with greater absolute change in domain scores in the adult males. Improvement in acne symptom scores was significantly greater in adult males (P=0.029). Tazarotene 0.045% lotion was well-tolerated. The number of subjects reporting any AE in the adult male population was 11 (13.6%) compared with 39 (21.4%) in the adolescent male population. There was only one (1.2%) treatment-related AE (application site pain) reported in the adult males compared with 11 (6.0%) in the adolescent males, where the most common treatment-related AEs were application site pain (3.3%), dryness (1.1%), and erythema (1.1%). Mean scores for hyper- and hypopigmentation were very low at baseline in both groups with no appreciable change with treatment.

Conclusions: Tazarotene 0.045% lotion provides greater efficacy and better tolerability in adult males (above 18 years old) than the adolescent male population with moderate-to-severe acne patients.

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INTRODUCTION

Although acne prevalence is comparable among adolescents of both genders,[1] it is much more common in adult females than adult males.[2,3] While there has been increased interest in adult female acne,[4] acne in adult males has largely been ignored and data specifically looking at their management sparse.

The mechanisms behind the development of acne lesions are multifactorial. Increased sebum production has been shown to play an important role,[5,6] and it has been suggested that acne may be less common in adult males because of the declining rate of sebum secretion observed with increasing age.[7] If acne pathogenesis in men is more dependent on sebum production, treatments that can reduce sebum such as retinoids may be beneficial.[8-10]

Other gender differences may be important. Women with acne were significantly more embarrassed than their male counterparts about their skin disease and sought medical care more frequently. Also, the psychological impact caused by the presence of acne seems to affect more female patients than male patients.[11] In addition, adherence to medication can play an important role in acne treatment; male patients being less compliant than females,[12] with side effects being the main reason for non-adherence, especially in older patients. The poor adherence of males to topical medications may also be due to their limited experience with using topical products generally.

There are no clinical studies that have specifically looked at the treatment of acne in the adult male population. There are a few studies that have reported post hoc analyses of gender as a clinically relevant outcome variable.[13-16] Only one study has presented data specifically on adult males.[16] A study with dapsone 5% gel in moderate acne suggested that females experienced a significantly greater reduction in acne lesions compared to male acne patients after 12 weeks treatment.[13] The data were not analysed to look at age differences. A post hoc analysis reported at the same time with clindamycin phosphate 1.2%/BP 2.5% gel also looked at gender differences, as well as stratifying by age.[16] The net reduction in lesion counts (active minus vehicle) was much greater in the adolescent population; and treatment success (at least a 2-grade improvement in acne severity) favored adult males and adolescent females. A subsequent study with clindamycin phosphate 1.2%/BP 3.75% gel appeared to demonstrate greater efficacy in females, but the data were only stratified by age for the females.[15] One study, with adapalene 0.3% /benzoyl peroxide 2.5% gel reported comparable efficacy by gender and by age.[11] No specific data on adult males was presented.

Topical retinoids have played an important role in the management of acne, supported by extensive clinical data. Tazarotene has generally been considered to be the most effective, but the less well tolerated.[17-26] Recently, data on a novel formulation of tazarotene have been published.[27] Tazarotene 0.045% lotion utilizes polymeric emulsion technology to provide more efficient delivery into the dermal layers, and less irritancy on application to the skin. Tazarotene 0.045% lotion was significantly more effective than vehicle in reducing lesion counts, and comparable to tazarotene 0.1% cream despite the two-fold difference in tazarotene concentrations. Tazarotene 0.045% lotion was also better tolerated.

Here we present a post hoc analysis of the two phase 3 studies looking at the efficacy of tazarotene in adult males with moderate or severe acne and comparing the data to the adolescent male population.

METHODS

Study Design and Oversight

Two multicenter, double-blind, randomized, vehicle-controlled, parallel-group phase 3 studies to assess safety, tolerability, and efficacy of tazarotene 0.045% lotion in subjects with moderate or severe acne (with an Evaluator's Global Severity Score [EGSS] of 3 [moderate] or 4 [severe]). Tazarotene 0.045% lotion or vehicle (randomized 1:1) was topically applied once-daily to the face (excluding mouth, eyes, inside the nose, and lips) for 12 weeks.

Subjects provided written informed consent before study-related procedures were performed; protocol and consent were approved by institutional review boards (IRBs) or ethics committees at all investigational sites. The studies were conducted in accordance with the principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

Study Population

Approximately 1600 subjects (800 in each study) were planned for enrollment. The initial topical applications were made at the investigational center. Subsequently, subjects were asked to apply their daily treatment in the evening at home. They were permitted to use only approved cleansers, moisturizers, and sunscreens, and noncomedogenic makeup and shaving products. The post hoc analysis was in adult (≥18 years of age) and adolescent (<18 years) male subjects with moderate or severe acne.

Key inclusion criteria included subjects with moderate (EGSS=3) or severe (EGSS=4) acne. Specifically, subjects had 20-50 facial inflammatory lesions (papules, pustules, and nodules), 25-100 noninflammatory lesions (open and closed comedones) and two or less facial nodules. Mandatory washout periods and restrictions applied to subjects who had used previous prescription of over-the-counter acne treatments: topical astringents and abrasives (1 week); topical anti-acne products, including soaps containing antimicrobials, and known comedogenic products (2 weeks); topical retinoids, retinol, and systemic acne treatments, such as hormonal or antibiotic treatments (4 weeks); and systemic retinoids (6 months).

Efficacy assessments were carried out at screening, baseline, weeks 4, 8, and 12 (end of treatment). The EGSS was determined prior to performing lesion counts. Subjects also completed a validated Acne-Specific Quality of Life (Acne-QoL) questionnaire that asked questions pertaining to their QoL as it related to their facial acne, at baseline and week 12. Adverse events (AEs) were recorded throughout the study and cutaneous tolerability at weeks 2, 4, 8, and 12.

Statistical and Analytical Plan

The intent-to-treat (ITT) population comprised all subjects randomized and provided with study drug. The safety population comprised all randomized subjects who were presumed to have used the study medication or vehicle at least once and who had at least one post baseline evaluation. The primary method of handling missing efficacy data in the ITT analysis set was based on estimation using the Markov Chain Monte Carlo multiple imputation method. For analyses of the changes from baseline in noninflammatory and inflammatory lesion counts in both pivotal phase 3 studies, significant skewness was observed, and a nonparametric method used in which the changes in lesion counts were rank-transformed prior to being submitted to the ANCOVA. Values were adjusted for multiple imputations. Significance of EGSS reductions were obtained from logistic regression (using Firth's Penalized Likelihood) with factors of treatment group and analysis center. Values were adjusted for multiple imputations. Descriptive statistics were used to summarize the results of the Acne-QoL questionnaire. In subjects who discontinued treatment before week 12 or missed visits between baseline and final evaluation, the last observation was carried forward. All statistical analyses were conducted using SAS® version 9.3 or later. Statistical significance was based on 2-tailed tests of the null hypothesis resulting in *P* values of 0.05 or less. All AEs occurring during the studies were recorded and classified on the basis of medical dictionary for drug regulatory activities terminology (MedDRA) for the safety population.

Study Assessment

Efficacy

Co-primary endpoints were EGSS and absolute reduction in inflammatory lesion and noninflammatory lesion counts. Subjects who had at least a 2-grade reduction from baseline EGSS at week 12, and an EGSS of 'clear' or 'almost clear' were considered a treatment success. Additional assessments included percent change in inflammatory and noninflammatory lesion counts from baseline at each study visit, percent of subjects who achieved treatment success, and absolute change in Acne-QoL domain scores.

Safety

Safety evaluations, including AEs, cutaneous safety evaluations and tolerability, vital signs, laboratory evaluations, and physical examinations were performed; information on reported and observed AEs obtained at each visit, cutaneous safety and tolerability at each study visit.

Cutaneous safety (individual assessments of scaling, erythema, hypopigmentation, and hyperpigmentation at the drug application site) was reported by the investigator/evaluator at all postscreening study visits using a 4-point scale, where 0=none and 3=severe. Tolerability (individual assessments of itching, burning, and stinging) was reported by the subjects at all postscreening study visits. Subjects were asked to provide an average evaluation of each parameter over the period since the previous study visit using a 4-point scale, where 0=none and 3=severe.

Vital sign measurements were recorded, blood samples collected, and an abbreviated physical examination performed at baseline and week 12. A medical history was taken at screening, and confirmed and revised at baseline, if necessary.

RESULTS

Subject Disposition

Overall, 550 male subjects were randomized to tazarotene 0.045% lotion (N=268) or vehicle lotion (N=282) and included in the ITT population. In the two studies, there were 186 adult males (≥18 years old) and 364 adolescent males (>18 years old).

Demographics and Baseline Characteristics

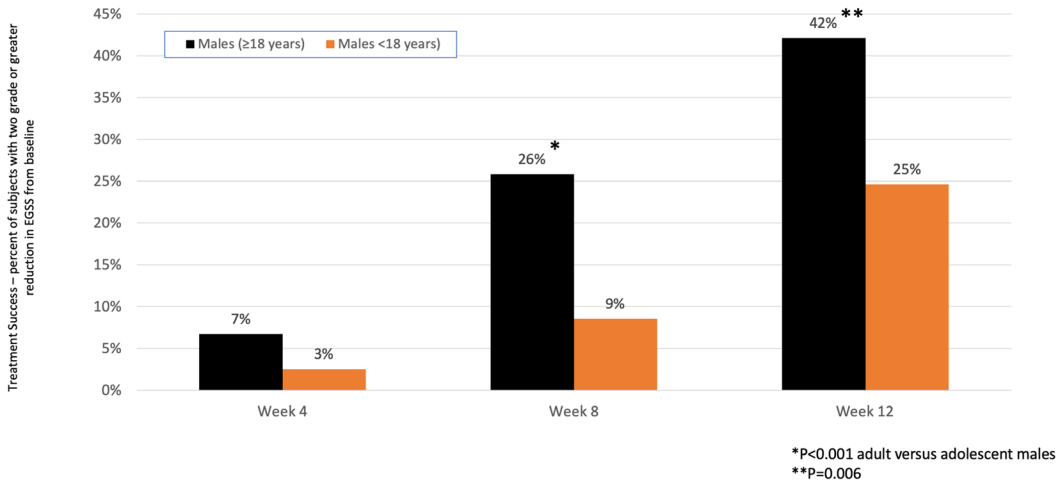
Comparing the two male subject populations treated with tazarotene 0.045% lotion, there were a few differences between the two groups (Table 1). There were more Caucasian adolescent

TABLE 1.

Demographics and Baseline Characteristics (ITT Population Adult [≥18 years old] and Adolescent [<18 years old] Males, Pooled Data, Subjects Treated With Tazarotene 0.045% Lotion)

	Adult Males (≥18 years) (N=85)	Adolescent Males (<18 years) (N=183)	Total (N=268)
Age (years), mean (SD)	22.9 (5.76)	15.1 (1.46)	17.6 (4.99)
Range	18-44	10-17	10-44
Ethnicity (N/%)			
Hispanic	28 (32.9%)	28 (15.3%)	56 (20.9%)
Non-Hispanic	57 (67.1%)	155 (84.7%)	212 (79.1%)
Race (N/%)			
American Indian or Alaska Native	1 (1.2%)	1 (0.5%)	2 (0.7%)
Asian	12 (14.1%)	6 (3.3%)	18 (6.7%)
Black or African American	14 (16.5%)	11 (6.0%)	25 (9.3%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
White	54 (63.5%)	155 (84.7%)	209 (78.0%)
Other/Multiple	4 (4.7%)	10 (5.5%)	14 (5.2%)
Inflammatory Lesion Count (mean [SD])	30.8 (7.40)	29.3 (7.78)	29.8 (7.68)
Noninflammatory Lesion Count (mean [SD])	39.8 (15.12)	45.5 (18.91)	43.7 (17.97)
Evaluator Global Severity Score (EGSS), N/%			
3=Moderate	74 (87.1%)	162 (88.5%)	236 (88.1%)
4=Severe	11 (12.9%)	21 (11.5%)	32 (11.9%)

FIGURE 1. Treatment success. Patients with at least a 2-grade improvement at each study visit (ITT population pooled data). Adult male subjects (≥18 years old) and adolescent males (<18 years old) treated with tazarotene 0.045% lotion.



males (84.7% versus 63.5%) and the mean baseline noninflammatory lesion count was a little higher than that noted in the adult males (45.5 versus 39.8), although the proportion of subjects classified as severe (EGSS=4) was slightly lower in the adolescent male population (11.5% versus 12.9%). In the overall study populations, efficacy of tazarotene 0.045% lotion in Caucasian or Black subjects was similar, so it is unlikely that these differences would have influenced efficacy in the two male populations.

Efficacy Evaluation

Evaluator's Global Severity Score (EGSS)

Significantly more adult male subjects achieved at least a 2-grade improvement in EGSS with tazarotene 0.045% lotion compared with adolescent male subjects at week 12 (42.1% versus 24.6%, *P*=0.006); see Figure 1. Differences were significant from week 8. In addition, 33.0% of adult males were considered 'treatment successes' (defined as at least a 2-grade improvement in EGSS and 'clear' or 'almost clear') compared with 21.6% of adolescent subjects treated with tazarotene 0.045% lotion (*P*=0.059).

Lesion Counts

Tazarotene 0.045% lotion was more effective in achieving an absolute reduction in lesion counts in adult males. At week 12, the absolute reduction in inflammatory and noninflammatory lesion count relative to baseline for the adult male group was

FIGURE 2. Percent change in inflammatory lesions from baseline to week 12 (ITT population, pooled data, LS mean). Adult male subjects (≥18 years old) and adolescent male subjects (<18 years old) treated with tazarotene 0.045% lotion.

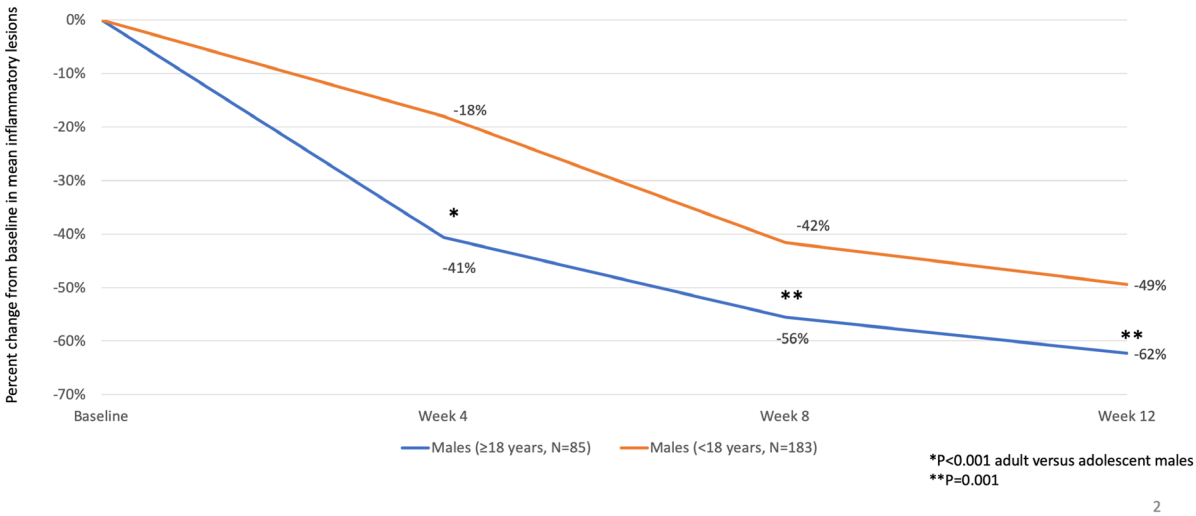
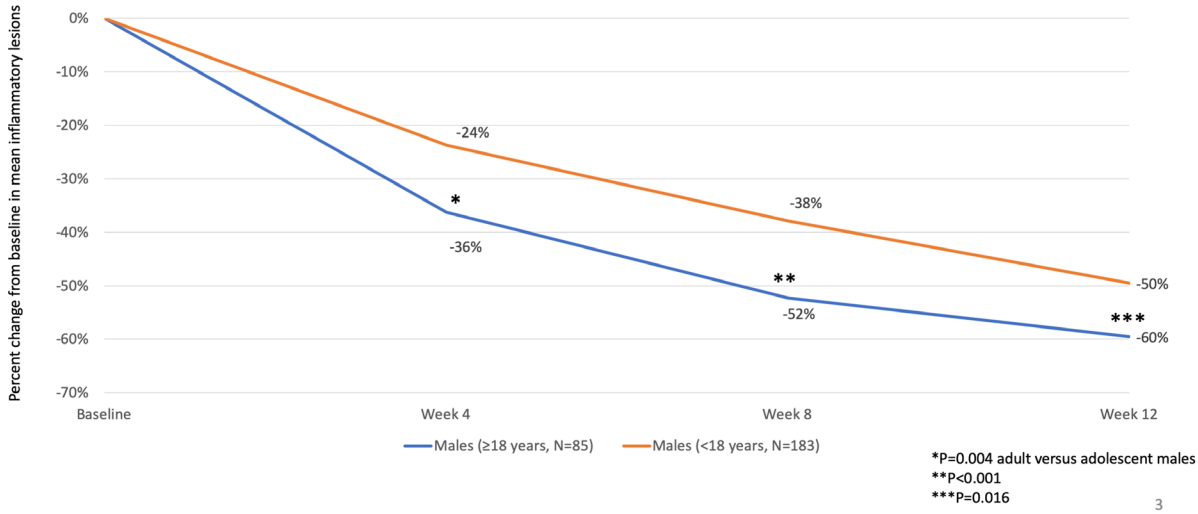


FIGURE 3. Percent change in noninflammatory lesions from baseline to week 12 (ITT population, pooled data, LS mean). Adult male subjects (≥18 years old) and adolescent male subjects (<18 years old) treated with tazarotene 0.045% lotion.



19.1 and 24.2, compared with 14.4 and 21.5, respectively, in the adolescent males.

By week 12, in the adult males there was a 62.3% and 59.5% change in inflammatory and noninflammatory lesion counts from baseline (LS mean) with tazarotene 0.045% lotion, compared with 49.4% (*P*=0.001) and 49.5% (*P*=0.016) in the adolescent males (Figures 2 and 3). Efficacy differences between the adult and adolescent males were significant from week 4.

Acne-Specific QoL

At baseline, the mean scores for Self-Perception, Role-Emotional, Role-Social, and Acne Symptoms in those subjects subsequently treated with tazarotene 0.045% lotion were higher (ie, better QoL) in the adolescent males: 27.2, 27.0, 23.8, and 22.5 compared with 20.1, 21.3, 18.1, and 19.2, respectively, in the adult males. By week 12 the absolute change from baseline in Self-Perception, Role-Emotional, Role-Social and Acne Symptom domains were 3.0, 1.7, 1.8, and 3.9, respectively, in

FIGURE 4. Absolute change from baseline in Acne-QoL domain scores by age (ITT population, pooled data). Adult male subjects (≥18 years old) and adolescent males (<18 years old) treated with tazarotene 0.045% lotion.

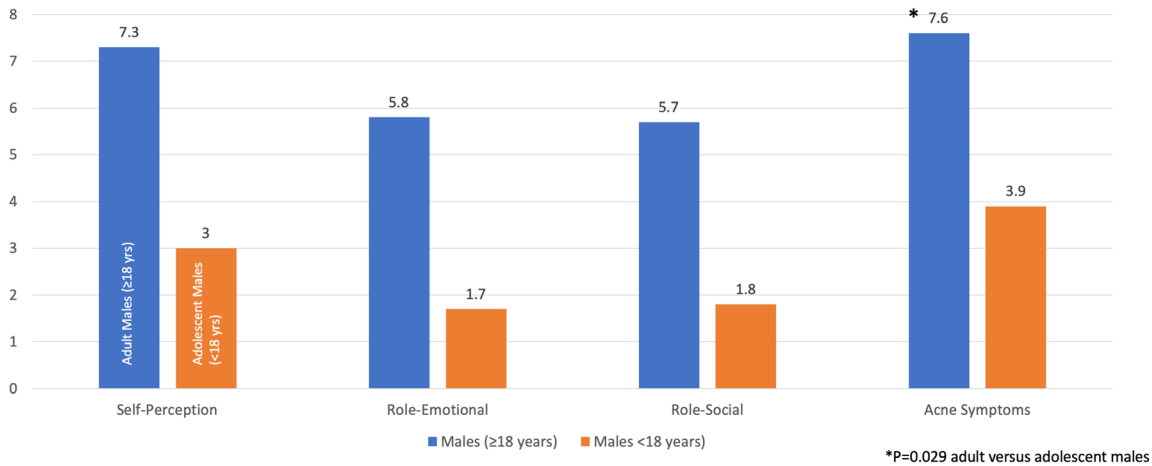
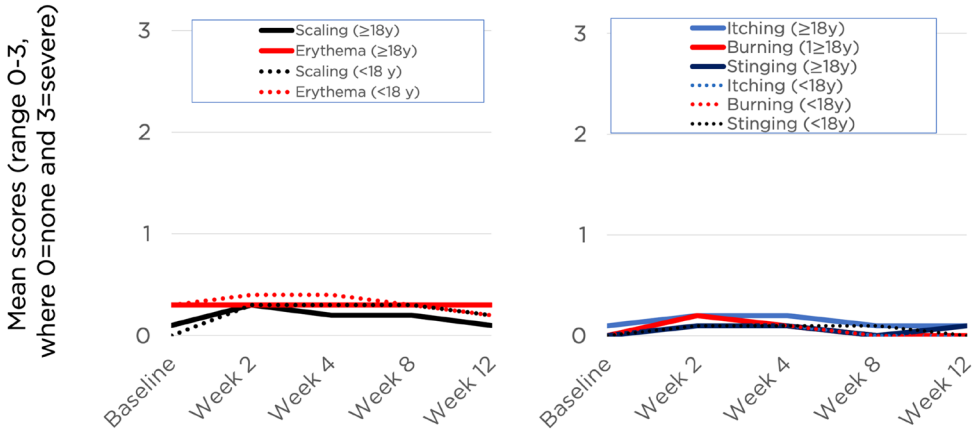


FIGURE 5. Cutaneous safety and tolerability assessment from baseline to week 12 (safety population, pooled data). Adult male subjects (≥18 years old) and adolescent male subjects (<18 years old) treated with tazarotene 0.045% lotion. Adult males in sold lines and adolescent males in dotted lines.



the adolescent males were much lower than those seen in the adult male population (7.3, 5.8, 5.7, and 7.6) treated with tazarotene 0.045% lotion (Figure 4). Only the change in acne symptom score was statistically significant (*P*=0.029).

TABLE 2.

Treatment-Emergent Adverse Event (AE) Characteristics through Week 12 (Safety population, pooled data) Adult male subjects (≥18 years old) and Adolescent Male Subjects (<18 years old) Treated With Tazarotene 0.045% Lotion.

	Adult Males (N=81)	Adolescent Males (N=182)
Subjects reporting and AE	11 (13.6%)	39 (21.4%)
Subjects reporting any SAE	0 (0.0%)	1 (0.5%)
Subjects who prematurely discontinued study/drug due to AE	1 (1.2%)	2 (1.1%)
Severity of AE		
Severe	0 (0.0%)	2 (1.1%)
Moderate	4 (4.9%)	11 (6.0%)
Mild	7 (8.6%)	26 (14.3%)
Strongest relationship to study drug		
Related	1 (1.2%)	11 (6.0%)
Not Related	10 (12.3%)	28 (15.4%)
Treatment Related AEs		
Application site pain	1 (1.2%)	6 (3.3%)
Application site dryness	0 (0.0%)	2 (1.1%)
Application site erythema	0 (0.0%)	2 (1.1%)
Application site dermatitis	0 (0.0%)	1 (0.5%)
Application site exfoliation	0 (0.0%)	1 (0.5%)
Application site pruritus	0 (0.0%)	1 (0.5%)

Safety Evaluation

Overall, 13.6% (N=11) of adult male subjects and 21.4% (N=39) adolescent male subjects treated with tazarotene 0.045% lotion reported AEs (Table 2). The majority were mild and there were no severe or serious AEs reported in the adult male population. There was one serious AE reported in the adolescent male population. Only one AE (1.2%) with tazarotene 0.045% lotion in adult males was considered treatment-related AEs (application site pain), compared with 11 (8.0%) in the adolescent males.

Cutaneous Safety and Tolerability

There were slight transient increases in mean severity scores for scaling (from week 2 in both groups) and erythema (from week 2 in the adolescent males). Over the 12-week treatment period, no score was greater than 0.4 (where 1=mild), with similar severity at the end of the study compared with baseline (Figure 5). Hyper- and hypopigmentation was rare at baseline, and throughout the study period.

DISCUSSION

Acne is a very common skin disorder that is predominantly seen in adolescence. However, data suggest that the prevalence in adults is increasing, especially in females.[2] While the prevalence of adolescent acne is similar between genders, post-adolescent acne appears to affect more women than men, with a prevalence of three percent in men and 12% in women in a population of randomly selected individuals with similar demographic characteristics.[2] Although there has been a significant increase in interest in adult female acne as a result, data on the treatment of adult males with moderate or severe disease remains sparse.

A post hoc analysis on the treatment of moderate-to-severe acne with the fixed combination clindamycin (1.2%)/benzoyl peroxide

(2.5%) gel provided data in adult (≥18 years old) and adolescent (<18 years old) males.[16] Reduction in inflammatory (56.7%) and noninflammatory (44.0%) lesion counts at week 12 was greater in the adult males; but the differences between adult and adolescent males were not significant (*P*=0.308 and *P*=0.761). Treatment success was also greater in the adult males (32.6% versus 23.0%), however again differences were not significant (*P*=0.089). In our analysis we were able to show greater efficacy of tazarotene 0.045% lotion in adult males, whereby changes in both lesion counts and achievement of treatment success were statistically significant compared to adolescent males. The efficacy of tazarotene 0.045% lotion in adult males was also greater than that reported in the overall study populations.[28]

The psychological impact caused by the presence of acne seems to affect more female patients than male patients.[11] In our study, QoL at baseline was much better in the adolescent males compared with the adult males. As a result, absolute increases in mean domain scores following treatment with tazarotene 0.045% lotion were greatest in adult males, however only in terms of acne symptoms was the difference significant in favor of the adult males.

Evidence-based guidelines for acne have shown retinoids to have an essential role in the management of acne.[17,29] Limitations to their widespread use have included a perception of poor efficacy in inflammatory lesions and cutaneous irritation.[29] Our data show tazarotene 0.045% lotion to have a comparable effect on both inflammatory and comedonal lesions, confirming other clinical data that have shown retinoids to both reduce visible lesions and inhibit the development of microcomedones and new lesions.[30-32]

Local skin reactions, such as erythema, scaling, dryness, burning, and stinging are well-known with retinoids. In adult males treated with tazarotene 0.045% lotion, there was a transient increase in mean scaling and burning scores at week 2, otherwise cutaneous tolerability was similar to that reported at baseline. Treatment-related AEs with tazarotene 0.045% lotion were rare, with only one report of application site pain. In contrast, AEs in the adolescent male population were similar to those reported in the overall study population.

A common complication of acne is residual postinflammatory hyperpigmentation (PIH), which causes further psychological and social distress in affected patients. Tazarotene has also been shown to significantly decrease post-inflammatory hyperpigmentation (PIH) and be more effective than other retinoids.[33,34] In our study, PIH was relatively rare both at baseline and throughout treatment, perhaps in part due to the high proportion of Caucasian male subjects enrolled (78%), with no increase in mean scores over the 12-week treatment period. A longer-term study in subjects more prone to PIH is warranted.

CONCLUSIONS

Tazarotene 0.045% lotion is more effective and better tolerated in adult male acne than in adolescent males, with better results than those reported in the overall study populations.

DISCLOSURES

Dr Cook-Bolden and Dr Gold are advisors and/or investigators with Ortho Dermatologics. Dr Guenin is an employee of Bausch Health.

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