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Once-Daily Polymeric Tazarotene 0.045% Lotion for Moderate-to-Severe Acne: Pooled Phase 3 Analysis by Sex

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ABSTRACT

Background: Two identical phase 3 randomized, double-blind, vehicle-controlled, 12-week studies (NCT03168321 and NCT03168334) demonstrated the efficacy and safety of tazarotene 0.045% lotion in participants with moderate-to-severe acne. Data from these studies were pooled and analyzed post hoc to evaluate outcomes by sex.

Methods: Patients aged ≥9 years with moderate-to-severe acne (score 3 or 4 on the Evaluator's Global Severity Score [EGSS]) were randomized (1:1) to once-daily tazarotene 0.045% lotion or vehicle lotion for 12 weeks. Outcomes comprised inflammatory/noninflammatory lesion counts, treatment success (proportion of participants achieving ≥2-grade reduction from baseline in EGSS and score of 0 ["clear"] or 1 ["almost clear"]), and treatment-emergent adverse events (TEAEs).

Results: A total of 1,064 females and 550 males were included in this analysis. For both sexes, least-squares mean percent changes from baseline to week 12 in lesion counts were significantly greater with tazarotene 0.045% lotion versus vehicle (inflammatory: females, -60.1% vs -52.1%; males, -53.6% vs -39.8%; noninflammatory: females, -57.6% vs -44.9%; males, -52.9% vs -36.5%; $P<0.001$, all). The percentage of participants achieving treatment success at week 12 was also significantly higher with tazarotene 0.045% lotion versus vehicle in females and males ($P<0.001$, both). Compared with tazarotene-treated males, tazarotene-treated females had significantly greater changes from baseline in inflammatory and noninflammatory lesions and a greater proportion achieved treatment success at week 12 ($P<0.05$, all). TEAE rates were similar between tazarotene- and vehicle-treated males; rates were higher for tazarotene-treated females than vehicle-treated females.

Conclusions: Tazarotene 0.045% lotion was efficacious and well tolerated in the treatment of moderate-to-severe acne in female and male participants.

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INTRODUCTION

Acne is a common dermatologic condition, affecting up to 85% of adolescents and young adults.[1] The prevalence of adult acne appears to be increasing in both females and males; however, there are differences in treatment needs and physiology between the sexes that should be taken into account when prescribing acne treatments. While most patients experience onset during adolescence, persistent adult acne is more common in female patients.[2,3] Additionally, females are more likely to experience recurrences of acne throughout their lives, requiring long-term maintenance treatment.[3,4] In terms of skin physiology, males tend to have less epidermal water loss, higher sebum production, and a lower pH than females.[5] In females, sebum production is not only lower, it also decreases with age leading to drier skin later in life.[5] Along these lines, females are more likely to report dry, sensitive skin,[4] which may become more apparent with age.[6] These differences between female and male patients with acne could affect treatment efficacy, tolerability, or adherence.

Topical retinoids are the mainstay of acne treatment due to their comedolytic and anti-inflammatory properties.[7] Several retinoids are commercially available (eg, tretinoin, adapalene, trifarotene, and tazarotene)[1,8] but studies have shown that tazarotene 0.1% cream may be more effective than tretinoin 0.025%

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or adapalene 0.1% or 0.3% in treating acne.[9-11] While the efficacy and safety of topical retinoids are well established,[12,13] adverse effects such as irritation, erythema, peeling, and dryness can occur in the first weeks of treatment, especially at higher concentrations.[7,12] To address these issues, a new tazarotene 0.045% lotion formulation was developed utilizing polymeric emulsion technology.[14] An oil-in-water emulsion—structured by a three-dimensional mesh matrix containing tazarotene along with hydrating and moisturizing agents—allows for more uniform release and increased absorption of ingredients. This easily spreadable and easy-to-use lotion formulation also allows for a lower tazarotene concentration, and when combined with optimized delivery of active and hydrating ingredients, may improve tolerability.[14]

Results from a phase 2 study comparing commercially available tazarotene 0.1% cream or vehicle with the new tazarotene 0.045% lotion demonstrated that tazarotene 0.045% lotion was comparable in efficacy to the higher concentration tazarotene 0.1% cream with fewer treatment-related adverse events.[15] Furthermore, data from two identical phase 3 randomized, double-blind, vehicle-controlled, 12-week studies showed tazarotene 0.045% lotion was more efficacious than vehicle and well tolerated in participants with moderate-to-severe acne.[16] The objective of this post hoc analysis was to evaluate the safety, efficacy, and tolerability of tazarotene 0.045% lotion in female and male participants with moderate-to-severe acne using data pooled from the two phase 3 trials.

METHODS

Study Design and Participants

Data were pooled from two identical multicenter, randomized, double-blind, vehicle-controlled, parallel-group phase 3 studies (NCT03168321 and NCT03168334), the details of which have been published previously.[16] Briefly, patients aged ≥9 years with moderate-to-severe acne (ie, score of 3 or 4 on the Evaluator's Global Severity Score [EGSS]) were eligible to enroll. Patients also had to have 20–50 facial inflammatory lesions (papules, pustules, and nodules), 25–100 noninflammatory lesions (closed and open comedones), and ≤2 facial nodules at the screening visit. Eligible patients were randomized (1:1) to receive tazarotene 0.045% lotion or vehicle lotion to be applied to the face once daily for 12 weeks. CeraVe® hydrating cleanser and moisturizing lotion (L'Oreal, NY) were provided as an option for optimal cleansing and moisturization of the skin.

All studies were conducted in accordance with the International Conference on Harmonization, the Declaration of Helsinki, Good Clinical Practice Guidelines, and local regulations. All participants or their legal guardians provided written informed consent. The studies were approved by the relevant independent ethics committee or institutional review board at each study site.

Efficacy and Safety Assessments

Efficacy assessments comprised investigator-assessed inflammatory and noninflammatory lesion counts and treatment success, defined as the proportion of participants achieving ≥2-grade reduction from baseline in EGSS and a score of 0 or 1; the EGSS is rated on a scale of 0 to 4, where 0=clear, 1=almost clear, 2=mild, 3=moderate, and 4=severe. Study visits included baseline and weeks 4, 8, and 12.

Investigator assessments of cutaneous safety (scaling, erythema, hypopigmentation, hyperpigmentation) were evaluated using a 4-point scale where 0=none; 1=mild; 2=moderate; and 3=severe. Participant evaluations of tolerability (itching, burning, stinging) were reported at all post-screening visits using the same 4-point scale. Adverse events (AEs) were monitored throughout the study.

Statistical Analysis

In each individual phase 3 trial, the co-primary efficacy endpoints were the absolute reductions from baseline to week 12 in inflammatory and noninflammatory lesion counts and the percentage of participants achieving treatment success at week 12. Secondary efficacy endpoints included the percent change in inflammatory and noninflammatory lesion count from baseline to week 12. The intent-to-treat (ITT) population comprised all participants who were randomized and provided with study drug. The safety population consisted of all randomized participants who used study drug or vehicle at least once with a minimum of 1 post-baseline evaluation.

For this pooled post hoc analysis, participants were grouped by sex. Analyses included the percent change from baseline in inflammatory and noninflammatory lesion counts by visit and the percentage of male and female participants achieving treatment success at week 12. For the mean percent changes in inflammatory and noninflammatory lesions, significant skewness was observed. Therefore, a nonparametric method was utilized in which data were rank transformed prior to the analysis of covariance (ANCOVA), with a factor of treatment and the respective baseline lesion count as a covariate. For differences between tazarotene-treated females and males, ranked ANCOVAs with factor of gender and baseline lesion counts as a covariate were used. Treatment success was evaluated via logistic regression using Firth's Penalized Likelihood, with a factor of treatment group. For all 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 for tazarotene 0.045% versus vehicle and female versus male were based on two-tailed tests of the null hypothesis resulting in $P \leq 0.05$.

Dosing compliance, defined as participants not missing more than 5 consecutive days of dosing and applying 80–120% of ex-

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pected applications while enrolled in the study, was summarized using descriptive statistics. Cutaneous safety and tolerability assessments were also 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

Participant Disposition and Demographics

A total of 1,614 participants were randomized in the two phase 3 studies. For the post hoc analysis, 1,064 females and 550 males were included in the ITT population; 1,032 females and 538 males comprised the safety population. In the randomized population, 86% of female participants and 91% of male participants completed the study. The most common reasons for discontinuation were lost to follow-up (females: n=77; males: n=24), participant request (females: n=40; males: n=17), or adverse event (females: n=21; males: n=2). Most participants (>88%) were compliant with tazarotene 0.045% or vehicle treatment. A higher percentage of male participants were compliant with vehicle relative to tazarotene (96.6% and 89.3%, respectively) while female participants had similar rates of compliance with both treatments (96.3% and 92.9%, respectively).

Baseline demographics and disease characteristics are presented in Table 1. Female participants were 4.5 years older than males on average. More than 85% of both female and male participants had moderate disease (EGSS=3) at baseline; a lower percentage of females reported severe disease (EGSS=4) compared with males.

Efficacy

At week 12, least-squares (LS) mean percent changes from baseline in inflammatory lesion counts were greater with tazarotene 0.045% lotion versus vehicle lotion in females (-60.1% vs -52.1%; $P<0.001$) and males (-53.6% vs -39.8%; $P<0.001$; Figure 1). Week 8 results were also statistically significant in both subgroups. At weeks 4 and 12, tazarotene-treated females had a significantly greater mean percent decrease in inflammatory lesions than tazarotene-treated males ($P<0.05$, both); no difference between the sexes was observed at week 8.

For noninflammatory lesions, results from week 12 indicated a significant difference between tazarotene 0.045% lotion and vehicle in females (-57.6% vs -44.9%; $P<0.001$) and males (-52.9% vs -36.5%; $P<0.001$), as did the results from weeks 4 and 8 (Figure 2). At weeks 4, 8, and 12, tazarotene-treated females had a significantly greater mean percent decrease in noninflammatory lesions than tazarotene-treated males ($P<0.05$, all).

The percentage of participants with treatment success at week 12 was significantly higher with tazarotene 0.045% lotion compared with vehicle lotion in females (33.1% vs 20.6%; $P<0.001$) and males (25.1% vs 12.8%; $P<0.001$; Figure 3). A significantly greater percentage of tazarotene-treated female participants achieved treatment success at week 12 versus tazarotene-treated male participants ($P<0.05$).

Safety

AEs and cutaneous safety and tolerability for the overall pooled population have been previously reported.[16] In this analysis, rates

TABLE 1.

Participant Demographics and Baseline Disease Characteristics (ITT population, pooled)

	Females		Males	
	Tazarotene 0.045% Lotion (n=531)	Vehicle Lotion (n=533)	Tazarotene 0.045% Lotion (n=268)	Vehicle Lotion (n=282)
Age, mean (SD), y	22.0 (7.3)	22.1 (7.4)	17.6 (5.0)	17.4 (4.2)
Race, n (%)				
White	382 (71.9)	371 (69.6)	209 (78.0)	229 (81.2)
Black	100 (18.8)	105 (19.7)	25 (9.3)	32 (11.3)
Asian	24 (4.5)	28 (5.3)	18 (6.7)	8 (2.8)
Other[a]	25 (4.7)	29 (5.4)	16 (6.0)	13 (4.6)
Ethnicity, n (%)				
Non-Hispanic/Latino	419 (78.9)	420 (78.8)	212 (79.1)	211 (74.8)
Hispanic/Latino	112 (21.1)	113 (21.2)	56 (20.9)	71 (25.2)
Inflammatory lesion count, mean (SD)	27.4 (6.8)	27.5 (6.8)	29.8 (7.7)	29.1 (7.4)
Noninflammatory lesion count, mean (SD)	40.3 (16.1)	40.0 (15.6)	43.7 (18.0)	42.0 (17.4)
Evaluator's Global Severity Score, n (%)				
3 – Moderate	490 (92.3)	497 (93.2)	236 (88.1)	244 (86.5)
4 – Severe	41 (7.7)	36 (6.8)	32 (11.9)	38 (13.5)

[a]Includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and other/multiple races.
ITT, intent to treat; SD, standard deviation.

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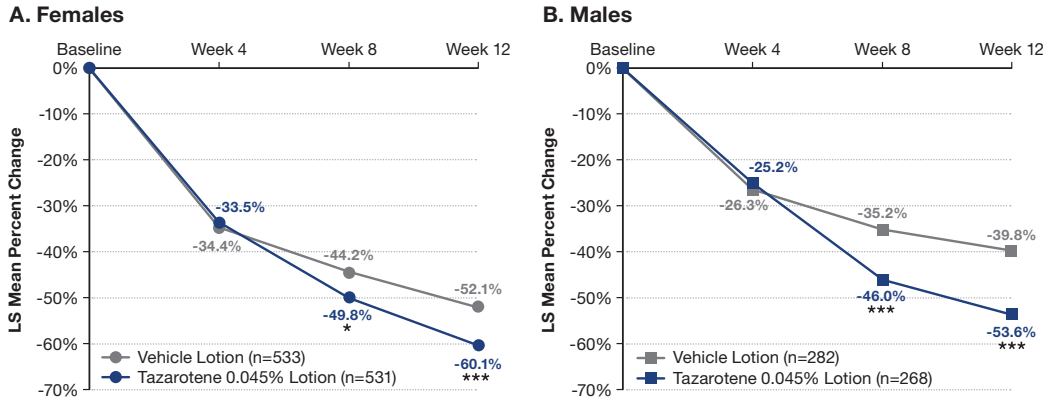
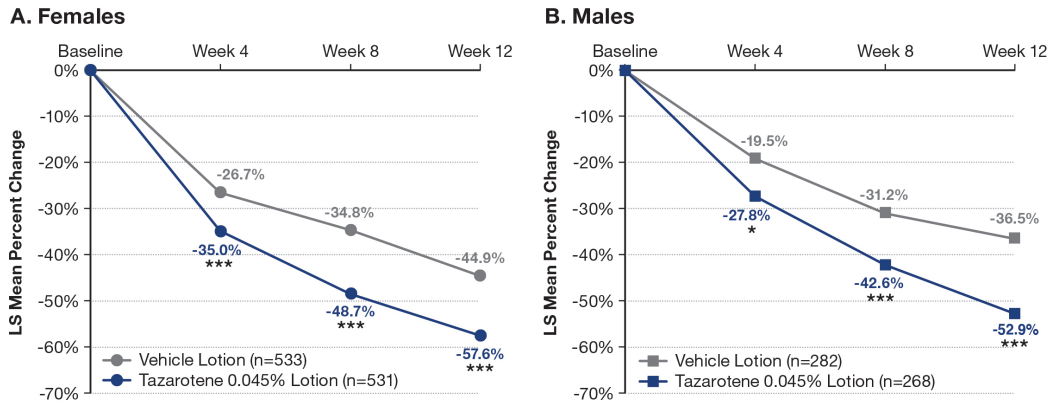
FIGURE 1. LS mean percent changes from baseline in inflammatory lesions by study visit in female and male participants (ITT population, pooled).



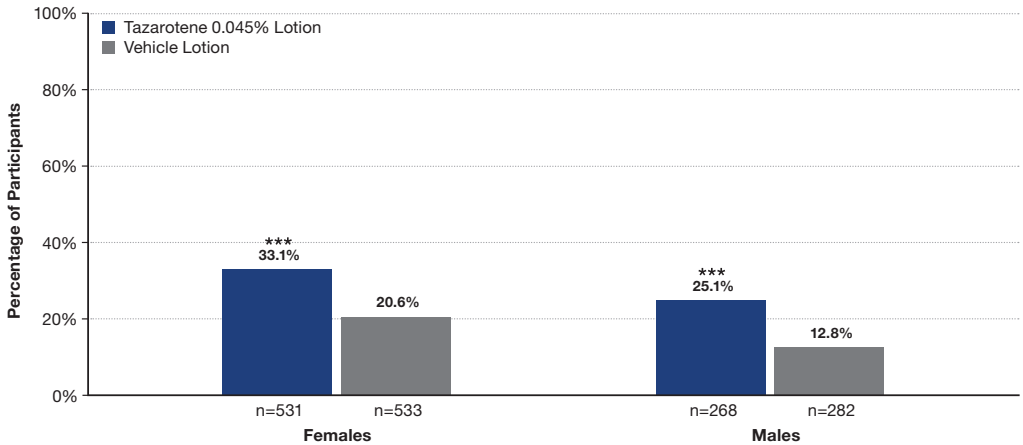
*P<0.05; ***P<0.001 versus vehicle.
Statistical analyses were also conducted between tazarotene-treated female and male participants, which demonstrated significant differences at weeks 4 and 12 (P<0.05, both).
ITT, intent to treat; LS, least squares.

FIGURE 2. LS mean percent changes from baseline in noninflammatory lesions by study visit in female and male participants (ITT population, pooled).



*P<0.05; ***P<0.001 versus vehicle.
Statistical analyses were also conducted between tazarotene-treated female and male participants, which demonstrated significant differences at weeks 4, 8, and 12 (P<0.05, all).
ITT, intent to treat; LS, least squares.

FIGURE 3. Treatment success at week 12 in female and male participants (ITT population, pooled).



***P<0.001 versus vehicle.
Treatment success was defined as ≥2-grade reduction from baseline and a rating of "clear" or "almost clear" on the Evaluator's Global Severity Score.
Statistical analysis was also conducted between tazarotene-treated female and male participants, which demonstrated a significant difference (P<0.05).
ITT, intent-to-treat

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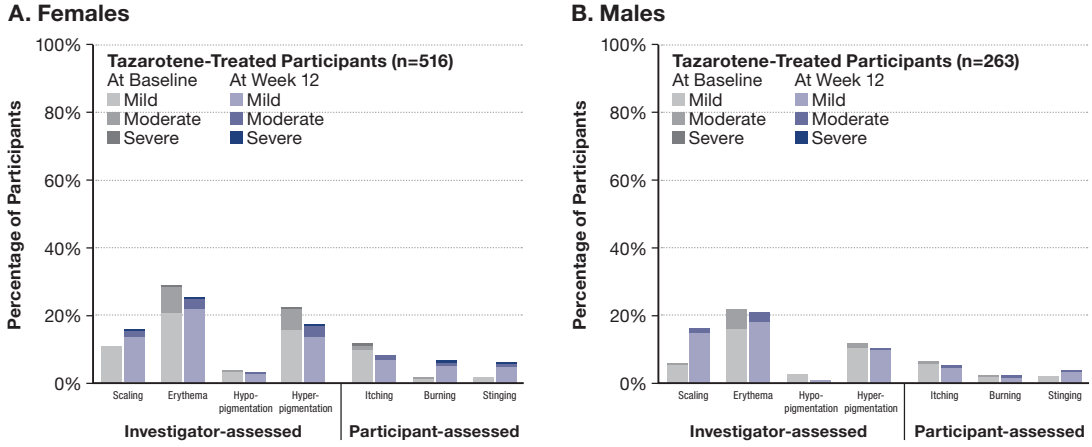
TABLE 2.

Treatment-emergent Adverse Events through Week 12 (safety population, pooled)				
	Females		Males	
n (%)	Tazarotene 0.045% Lotion (n=516)	Vehicle Lotion (n=516)	Tazarotene 0.045% Lotion (n=263)	Vehicle Lotion (n=275)
Participants reporting any TEAE	159 (30.8)	98 (19.0)	50 (19.0)	53 (19.3)
Participants reporting any serious TEAE[a]	3 (0.6)	3 (0.6)	1 (0.4)	1 (0.4)
Participants discontinuing due to TEAEs	19 (3.7)	4 (0.8)	3 (1.1)	0
Severity of TEAEs reported				
Mild	103 (20.0)	48 (9.3)	33 (12.5)	35 (12.7)
Moderate	48 (9.3)	47 (9.1)	15 (5.7)	17 (6.2)
Severe	8 (1.6)	3 (0.6)	2 (0.8)	1 (0.4)
Relationship to study drug				
Related	76 (14.7)	8 (1.6)	12 (4.6)	1 (0.4)
Unrelated	83 (16.1)	90 (17.4)	38 (14.4)	52 (18.9)
TEAEs reported in ≥5% of participants in any treatment group				
Application site pain	34 (6.6)	2 (0.4)	7 (2.7)	0
Application site dryness	28 (5.4)	1 (0.2)	2 (0.8)	0

[a]None of the participants had serious AEs that were considered by the investigator to be treatment related.
TEAE, treatment-emergent adverse event.

of TEAEs were similar between tazarotene- and vehicle-treated males (19.0% vs 19.3%; Table 2). TEAE rates for tazarotene-treated females, however, were greater than vehicle-treated females (30.8% vs 19.0%). Tazarotene-treated females also had higher TEAE rates than males treated with tazarotene (19.0%) or vehicle (19.3%). The majority of TEAEs were of mild to moderate severity and generally deemed unrelated to treatment, except in tazarotene-treated females who had similar incidences of related and unrelated TEAEs (14.7% and 16.1%, respectively). The most common TEAEs (≥5% of females or males in any treatment group) were application site pain and application site dryness; these were reported by a greater percentage of tazarotene-treated females than males. Discontinuations due to AEs were <4% with either treatment in both females and males, although rates were higher in females (3.7% tazarotene and 0.8% vehicle) than males (1.1% and 0%) in both treatment arms. None of the reported serious AEs were considered by the investigator to be related to treatment.

FIGURE 4. Cutaneous safety and tolerability at baseline and week 12 in tazarotene-treated female and male participants (safety population, pooled).



Data for "none" are not shown.

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At baseline and week 12, most (≥71%) tazarotene-treated female and male participants reported ratings of 0 (none) on cutaneous safety and tolerability evaluations; of participants that had any signs/symptoms, over 93% reported ratings of 1 (mild) or 2 (moderate; Figure 4). On most assessments, transient increases in severity (primarily mild or moderate) were found with tazarotene 0.045% at earlier visits (data not shown). By week 12, however, the percentage of participants reporting "none" were generally similar to baseline values for most assessments. At baseline and week 12, no tazarotene-treated male participants reported ratings of 3 (severe) on any safety or tolerability assessments. For tazarotene-treated females, a similar number of severe ratings were reported at baseline and week 12 (baseline, n=5 total: erythema [n=3], hyperpigmentation and itching [n=1 each]; week 12, n=6 total: burning [n=2], scaling, erythema, hyperpigmentation, and stinging [n=1 each]).

DISCUSSION

Topical retinoids are widely recommended as first line acne treatment in both men and non-pregnant women but can cause considerable dryness and irritation, limiting their use[1] and reducing treatment adherence.[17] Tazarotene 0.045% polymeric emulsion lotion was developed to provide a lower-concentration formulation to improve tolerability and penetration of active drug.[14] This is accomplished via encapsulation of tazarotene within oil droplets along with hydrating and moisturizing ingredients. The oil droplets are evenly distributed in an oil-and-water emulsion and are separated in a three-dimensional mesh matrix, allowing for uniform dispersion of the oil droplets on the skin.[14] In two identical phase 3 randomized studies in participants with moderate-to-severe acne, this lower concentration tazarotene 0.045% lotion was efficacious compared with vehicle and demonstrated a positive safety and tolerability profile.[16]

Although acne affects both female and male patients, there are differences in disease severity, acne onset (persistent, new, or recurrent), and skin physiology which may impact treatment efficacy, tolerability, or adherence.[3,5] As such, the present post hoc analysis was conducted to further explore the efficacy and safety of tazarotene 0.045% lotion by sex. Results demonstrated that tazarotene 0.045% was effective in reducing inflammatory and noninflammatory lesion counts versus vehicle at week 12 in females and males. Significant reductions were observed as early as weeks 4 and 8 in noninflammatory and inflammatory lesion counts, respectively, in both sexes.

While tazarotene 0.045% was efficacious in both females and males, there were some observed differences between the sexes in the present analysis. Reductions in inflammatory and noninflammatory lesions following tazarotene treatment were significantly greater in females than males at nearly all monthly assessments. A greater percentage of tazarotene-treated females also achieved treatment success at week 12 than tazarotene-treated males. Though females had higher responses to tazarotene than males, the separation between tazarotene and vehicle was numerically larger in males at week 12 for both inflammatory and noninflammatory lesion types. The reasons for these results cannot be explained by the current analysis, but differences in terms of compliance (active treatment and/or vehicle) and baseline disease severity may be contributing factors. In addition to being efficacious, tazarotene 0.045% lotion was generally well tolerated in both female and male participants. Although tazarotene-treated females had higher rates of TEAEs compared with tazarotene-treated males, rates of discontinuation due to AEs were low (<4%) in both females and males in either treatment group. The majority of female and male participants reported AE severity as mild. At baseline and week 12, few tazarotene-treated females reported any "severe" ratings for cutaneous safety or tolerability. This may be due to a variety of reasons, including improvement in these ratings over time or a result of participants with moderate or severe ratings dropping out of the study or being less compliant with treatment over time.

The higher TEAE rates and more severe tolerability ratings observed in female participants in this analysis may be due to age differences. On average, the female participants were almost 5 years older than the male participants, with an age range of 10–65 years versus 10–44 for males. Female patients commonly experience dry and sensitive skin,[6] especially at older ages when sebum production decreases.[5] In addition, older, menopausal females are more likely to experience erythema and hyper- or hypo-pigmentation.[6] Even though tazarotene-treated females in the current analysis had higher TEAE rates than males, these rates were similar to those reported in the tazarotene-treated overall population pooled from the two pivotal phase 3 studies (females in current analysis 30.8%; overall pooled population: 26.8%).[16] This may be a result of the larger number of female than male participants in the current analysis. Furthermore, rates of application site pain and dryness observed in tazarotene-treated females in this analysis were similar to those seen in the tazarotene-treated overall pooled population (pain, females in the present analysis versus overall population: 6.6% versus 5.3%; dryness: 5.4% versus 3.9%).[16]

Results from the present analysis demonstrate that the moisturizing, lower-concentration polymeric tazarotene 0.045% lotion was efficacious, safe, and well tolerated for the treatment of moderate-to-severe acne in both female and male participants. Safety and tolerability were more favorable in tazarotene-treated males, although TEAE rates were comparable to rates in the overall population in the two phase 3 trials of tazarotene 0.045% lotion. The females in this analysis were older than the males on average, which may have impacted tolerability due to the changes in skin physiology that occur with aging. Future studies should examine the effects of age and gender on tolerability to better understand the treatment needs of this population.

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CONCLUSION

Results from this pooled post hoc analysis from two identical phase 3 studies demonstrate that tazarotene 0.045% lotion significantly reduced acne lesions and led to higher rates of treatment success versus vehicle in female and male participants with moderate-to-severe acne. Overall AE rates were low, with favorable tolerability in both sexes. Together, these data demonstrate this hydrating polymeric lotion formulation of tazarotene is both an efficacious and well tolerated treatment for acne in females and males.

DISCLOSURES

Leon Kircik has acted as an investigator, advisor, speaker, and consultant for Ortho Dermatologics. Linda Stein Gold has served as investigator/consultant or speaker for Ortho Dermatologics, LEO, Dermavant, Incyte, Novartis, AbbVie, Galderma, Sol-Gel, Foamix, and Lilly. Kenneth Beer has received funding from Allergan, Galderma, Evolus, and Revance. Jerry Tan has served as an advisor, investigator/consultant or speaker for Bausch Health and Ortho Dermatologics. Hilary Baldwin has served as advisor, investigator, and on speakers' bureaus for Almiral, Cassiopea, Foamix, Galderma, Ortho Dermatologics, Sol Gel, and Sun Pharmaceuticals. Eric Guenin is an employee of Ortho Dermatologics and may hold stock and/or stock options in its parent company. Robert Kang and Johnson Varughese are employees of Bausch Health US, LLC and may hold stock and/or stock options in its parent company.

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