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 ORIGINAL ARTICLE

Novel Polymeric Lotion Formulation of Once-Daily Tazarotene (0.045%) for Moderate-to-Severe Acne: Pooled Phase 3 Analysis

Emil A. Tanghetti MD,[a] William Philip Werschler MD,[b] Edward Lain MD MBA,[c] Eric Guenin PharmD PhD MPH,[d] Susan Harris MS,[e] Anya Loncaric MS,[e] Radhakrishnan Pillai PhD[e]

[a]Center for Dermatology and Laser Surgery, Sacramento, CA
[b]University of Washington, School of Medicine, Seattle, WA
[c]Austin Institute for Clinical Research, Austin, TX
[d]Ortho Dermatologics, Bridgewater, NJ
[e]Bausch Health US, LLC, Petaluma, CA

ABSTRACT

Background: As current tazarotene formulations indicated for acne (0.1%) can cause irritation, a new tazarotene 0.045% lotion formulation was developed using polymeric emulsion technology. The objective was to assess efficacy, safety, and tolerability of tazarotene 0.045% lotion in patients with moderate-to-severe acne in a pooled analysis of data from two identical phase 3, double-blind, randomized, vehicle-controlled 12-week clinical studies.

Methods: Patients aged ≥9 years with moderate-to-severe acne were randomized (1:1) to tazarotene 0.045% lotion or vehicle lotion applied once daily. Inflammatory and noninflammatory lesion counts and Evaluator's Global Severity Score (EGSS) were assessed. Treatment success was defined as a ≥2-grade improvement in EGSS and a score of 'clear'/'almost clear'. Adverse events (AEs) and cutaneous safety and tolerability were also assessed.

Results: In total, 1614 patients (mean age: 20.5 years) were randomized to tazarotene 0.045% lotion (n=799) or vehicle (n=815). At week 12, tazarotene 0.045% lotion demonstrated statistically significant superiority versus vehicle in reducing inflammatory and noninflammatory lesion counts (least-squares mean percent changes from baseline: inflammatory, -57.9% vs -47.8% [P<0.001]; noninflammatory, -56.0% vs -42.0% [P<0.001]). Treatment success at week 12 was also greater with tazarotene 0.045% lotion versus vehicle (30.4% vs 17.9%; P<0.001). The most frequent treatment-emergent AEs related to tazarotene treatment were application site pain (5.3%), dryness (3.6%), and exfoliation (2.1%).

Conclusions: The new tazarotene 0.045% lotion formulated with polymeric emulsion technology demonstrated statistically significantly superior efficacy versus vehicle and was well tolerated in pediatric and adult patients with moderate-to-severe acne in this pooled analysis of 2 vehicle-controlled phase 3 studies.

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INTRODUCTION

Topical retinoids remain the mainstay of therapy for acne vulgaris.[1] They are, however, associated with skin irritation during the initial weeks of application. Erythema, scaling, dryness, burning, and pruritis of varying severities can occur, depending on the retinoid, dose, and vehicle. These unwanted effects, along with unpleasantly greasy or sticky-feeling formulations,[2] can potentially affect comfort and treatment adherence. More importantly, traditional semisolid formulations—such as creams, lotions, and ointments—may not provide an even dispersion of drug onto the skin.[2]

Among topical retinoids, tazarotene 0.1% has proven to be highly effective both as monotherapy and in combination with other agents. A number of studies have reported that tazarotene markedly reduces both comedonal and inflammatory facial acne lesions.[3-15] Although tazarotene may be more effective than other topical retinoids in treating acne,[11,16] problems with skin irritation continue to exist with the current approved formulations (gel, foam, cream),[17] which may limit its usefulness. The application of tazarotene with a moisturizer appears to improve tolerability without affecting efficacy;[18] however, there continues to be an unmet need for a highly effective topical acne medication that has a lower irritability profile than the currently available treatment options.

Polymeric emulsion technology represents a novel approach to developing dermatological products. This technology provides simultaneous delivery of the active ingredient along with solvents, emollients, and humectants—which allows for lower drug concentrations compared to conventional formulations,

potentially minimizing irritation. With polymeric emulsion technology, the active ingredient and moisturizing/hydrating ingredients are encapsulated within oil droplets, which are uniformly dispersed within an oil-in-water emulsion separated by a three-dimensional mesh matrix. Once applied to the skin, the mesh instantly breaks apart, ensuring rapid, uniform, and simultaneous release of ingredients, thus improving delivery and clinical efficacy.[2] This technology has the potential to overcome several limitations of conventional topical drug delivery, including limited skin delivery and local cutaneous irritation, the latter which is known to be associated with poor patient adherence.[19,20] Polymeric emulsion technology has been applied to tazarotene, resulting in a 0.045% lotion which may afford similar efficacy to the higher concentration tazarotene formulations indicated for acne (0.1%) while reducing the potential for skin irritation.

In a phase 2 study comparing tazarotene 0.045% lotion with tazarotene 0.1% cream and vehicle lotion or cream (to ensure blinding), tazarotene 0.045% lotion demonstrated statistically significant superiority to vehicle in reducing lesion counts at week 12 (P=0.013 for inflammatory; P<0.001 for noninflammatory lesions).[21] At less than half the active concentration, tazarotene 0.045% lotion was also more effective than the 0.1% cream in reducing lesion counts and in achievement of treatment success, defined as having ≥2-grade improvement from baseline in the Evaluator's Global Severity Score (EGSS), and an EGSS score equating to 'clear' or 'almost clear'. Treatment-related adverse events AEs were more common for the 0.1% cream (5.6% versus 2.9% for the 0.045% lotion), the most common being application site pain (4.2% versus 2.9% for 0.045% lotion).

Subsequently, two identical phase 3 double-blind, randomized, vehicle-controlled 12-week clinical studies confirmed the efficacy and safety of tazarotene 0.045% lotion versus vehicle lotion in patients with moderate-to-severe acne.[22] In both studies, tazarotene 0.045% lotion demonstrated statistically significant reductions in inflammatory and noninflammatory lesions, with a greater percentage of patients achieving treatment success at week 12 than those receiving vehicle (P<0.001, all). The data from these two studies were pooled to examine the safety and efficacy of tazarotene 0.045% lotion in patients with moderate-to-severe acne.

METHODS

Study Design and Patients

Detailed methods for the studies (NCT03168334 and NCT03168321) have been reported.[22] In brief, each of the two identical multicenter, double-blind, randomized, vehicle-controlled, parallel-group phase 3 studies enrolled patients 9 years of age or older with moderate (EGSS 3) or severe (EGSS 4) acne at 89 study centers. Eligible participants also must have had 20-50 facial inflammatory lesions (papules, pustules, and nodules), 25-100 noninflammatory lesions (open and closed comedones), and two or less facial nodules.

Patients were randomized 1:1 to receive tazarotene 0.045% lotion or vehicle to be applied to the face once daily for 12 weeks. The study protocol was approved by institutional review boards or ethics committees at all investigational sites. Studies were carried out in accordance with principles of Good Clinical Practice (GCP) and the Declaration of Helsinki. All patients provided written informed consent.

Study Assessments

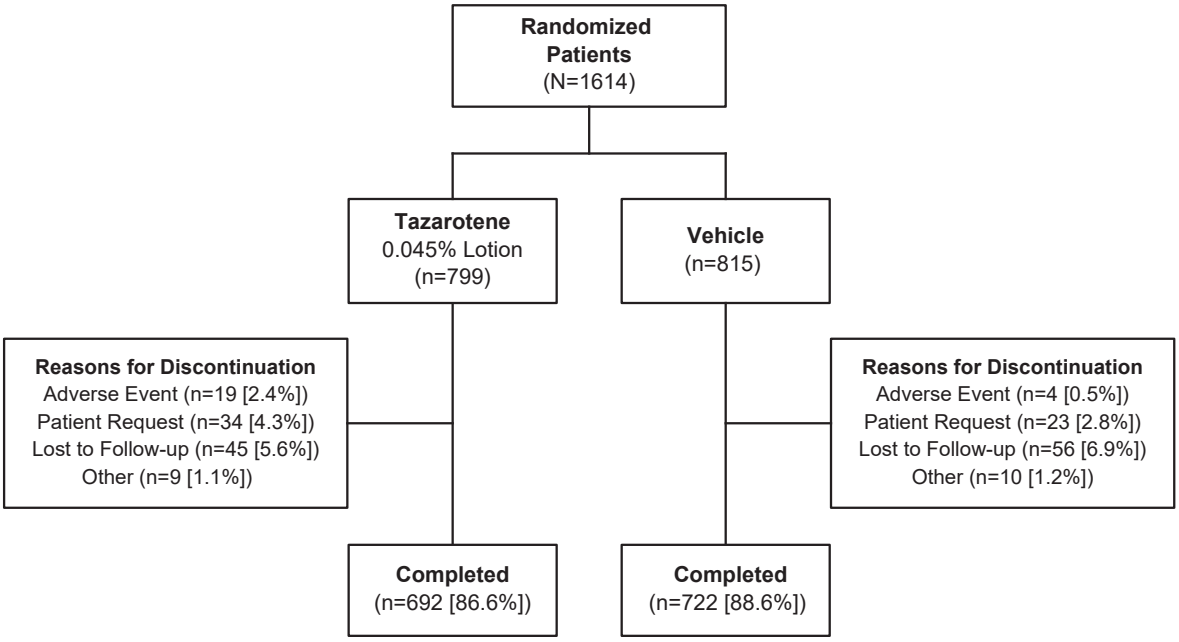
Efficacy evaluations included inflammatory and noninflammatory lesion counts and treatment success, defined as the proportion of patients achieving ≥2-grade reduction from baseline in EGSS and a score of 'clear' (0) or 'almost clear' (1). Assessments were performed at screening, baseline, and weeks 2, 4, 8, and 12 (end of treatment). At baseline and week 12, patients also completed an Acne Specific Quality of Life (Acne-QoL) questionnaire covering four different domains (self-perception, role-emotional, role-social, and acne symptoms); higher scores for each domain reflect improved health-related QoL. Cutaneous safety (scaling, erythema, hypopigmentation, hyperpigmentation) was evaluated by investigators using a 4-point scale where 0=none and 3=severe. Tolerability (itching, burning, stinging) was reported by patients at all post-screening visits. AEs were evaluated throughout the study.

Statistical Analysis

The co-primary endpoints for the individual studies were the percentage of patients achieving treatment success at week 12 and absolute reductions from baseline to week 12 in inflammatory and noninflammatory lesion counts. The intent-to-treat (ITT) population consisted of all patients who were randomized and provided with study drug. The safety population was defined as all randomized patients who were presumed to have used study medication or vehicle at least once and who had at least one post-baseline evaluation.

For pooled study analyses of the mean percent changes from baseline in noninflammatory and inflammatory lesion counts, significant skewness was observed; as such, a nonparametric method was used in which the data were rank transformed prior to the analysis of covariance (ANCOVA), with factor of treatment and the respective baseline lesion count as a covariate. EGSS reductions were analyzed via logistic regression using Firth's Penalized Likelihood with a factor of treatment group. Values were adjusted for multiple imputations. Missing efficacy data was handled based on estimation using the Markov Chain Monte Carlo multiple imputation method. Results of the Acne-QoL questionnaire were summarized using descriptive statistics with no imputation of missing values.

FIGURE 1. Patient disposition.



Statistical analyses were conducted using SAS® software, version 9.3 or later. AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA) terminology for the safety population.

RESULTS

Patient Disposition and Demographics

In this pooled analysis, a total of 1614 patients were randomized to tazarotene 0.045% lotion (n=799) or tazarotene lotion vehicle (n=815; Figure 1). Of these, 692 (86.6%) and 722 (88.6%) completed the study, respectively. The most common reasons for study discontinuation were lost to follow up (45, 5.6%) and patient request (34, 4.3%) in the tazarotene 0.045% lotion arm, and lost to follow up (56, 6.9%) and patient request (23, 2.8%) in the vehicle arm. AEs led to study discontinuation in 19 (2.4%) and 4 (0.5%) of patients in the tazarotene and vehicle arms, respectively. The safety population consisted of 1570 patients (tazarotene n=779; vehicle n=791), with 44 patients not included due to lack of any post-baseline safety evaluation.

Patient demographics and disease characteristics at baseline are shown in Table 1 and baseline QoL scores in Table 2. Characteristics were well matched between the two arms. The mean age overall was 20.5 years (standard deviation [SD] 6.9) and the majority of patients (65.9%) were female. All patients had moderate (EGSS 3) or severe (EGSS 4) disease, the latter comprising 9.1% and 9.1% of the tazarotene and vehicle arms, respectively.

Efficacy Evaluations

Significantly more patients in the tazarotene 0.045% arm than in the vehicle arm achieved the co-primary endpoint of treatment success, defined as achieving at least a 2-grade improvement in EGSS with a final score of clear or almost clear (30.4% vs 17.9%, $P<0.001$; Figure 2).

Tazarotene 0.045% lotion was associated with significant reductions in inflammatory lesion counts (Figure 3) as well as noninflammatory lesion counts (Figure 4) compared with vehicle. Mean inflammatory lesion counts were reduced 57.9% and 47.8% in the tazarotene and vehicle arms, respectively ($P<0.001$) at week 12; significant differences between tazarotene and vehicle were observed by week 8 (Figure 3). Significant reductions in noninflammatory lesion counts were observed as early as week 4 (32.6% vs 24.2%; $P<0.001$) and were further reduced at week 8 (46.6% vs 33.6%; $P<0.001$) and week 12 (56.0% vs 42.0%; $P<0.001$; Figure 4).

Improvements in Acne-Specific QoL scores at week 12 were numerically greater for the tazarotene 0.045% cohort versus vehicle in all 4 domains (self-perception: 7.5 vs 6.7; role emotional: 6.0 vs 5.5; role-social: 4.7 vs 4.1; acne symptoms: 6.4 vs 5.3; Table 2).

Safety Evaluations

Safety results for the pooled studies have been reported.[22] Treatment-emergent AEs (TEAEs) were reported by 209 patients

TABLE 1.

Demographics and Baseline Characteristics (ITT population, pooled)			
	IDP-123 Lotion (n=799)	Vehicle Lotion (n=815)	Total (N=1614)
Age, mean (SD), y	20.5 (6.9)	20.4 (6.9)	20.5 (6.9)
Range	10-54	10-65	10-65
Sex, n (%)			
Male	268 (33.5)	282 (34.6)	550 (34.1)
Female	531 (66.5)	533 (65.4)	1064 (65.9)
Ethnicity, n (%)			
Not Hispanic or Latino	631 (79.0)	631 (77.4)	1262 (78.2)
Hispanic or Latino	168 (21.0)	184 (22.6)	352 (21.8)
Race, n (%)			
White	591 (74.0)	600 (73.6)	1191 (73.8)
Black or African American	125 (15.6)	137 (16.8)	262 (16.2)
Asian	42 (5.3)	36 (4.4)	78 (4.8)
American Indian or Alaska Native	9 (1.1)	6 (0.7)	15 (0.9)
Native Hawaiian or Other Pacific Islander	0	4 (0.5)	4 (0.2)
Other/Multiple	32 (4.0)	32 (3.9)	64 (4.0)
Evaluator's Global Severity Score, n (%)			
3 – Moderate	726 (90.9)	741 (90.9)	1467 (90.9)
4 – Severe	73 (9.1)	74 (9.1)	147 (9.1)
Inflammatory lesion count, mean (SD)	28.2 (7.2)	28.0 (7.1)	28.1 (7.1)
Noninflammatory lesion count, mean (SD)	41.5 (16.8)	40.7 (16.3)	41.1 (16.5)

SD, standard deviation.

TABLE 2.

Summary of Acne-QoL Questionnaire Responses (ITT population, pooled)						
Domain	IDP-123 Lotion			Vehicle Lotion		
	N	Mean	SD	N	Mean	SD
Self-Perception						
Baseline	796	19.9	8.91	814	20.2	8.74
Change from BL at week 12	690	7.5	8.06	723	6.7	8.07
Role-Emotional						
Baseline	796	20.6	8.25	814	20.5	8.27
Change from BL at week 12	690	6.0	8.32	723	5.5	8.09
Role-Social						
Baseline	796	19.2	7.26	813	19.3	7.10
Change from BL at week 12	690	4.7	6.60	722	4.1	6.43
Acne Symptoms						
Baseline	796	19.3	5.69	814	19.4	5.74
Change from BL at week 12	690	6.4	6.29	723	5.3	6.13

Higher scores for each domain reflect improved health-related QoL.
Self-perception domain assesses the extent facial acne has affected a particular area of self-perception. Role-emotional domain assesses the emotional effect or impact of facial acne. Role-social domain assesses the impact of facial acne on a respondent's intersocial relationships. Acne symptoms assesses the physical symptoms experienced with facial acne; the acne symptom domain score correlates inversely with acne severity.
BL, baseline; ITT, intent-to-treat; QoL, quality of life; SD, standard deviation.

FIGURE 2. Percentage of patients achieving treatment success, by week (ITT population, pooled). Treatment success = percentage of patients with at least a 2-grade reduction in EGSS relative to baseline and 'clear' or 'almost clear'. EGSS, Evaluator's Global Severity Score. *P<0.05 versus vehicle; ***P<0.001 versus vehicle.

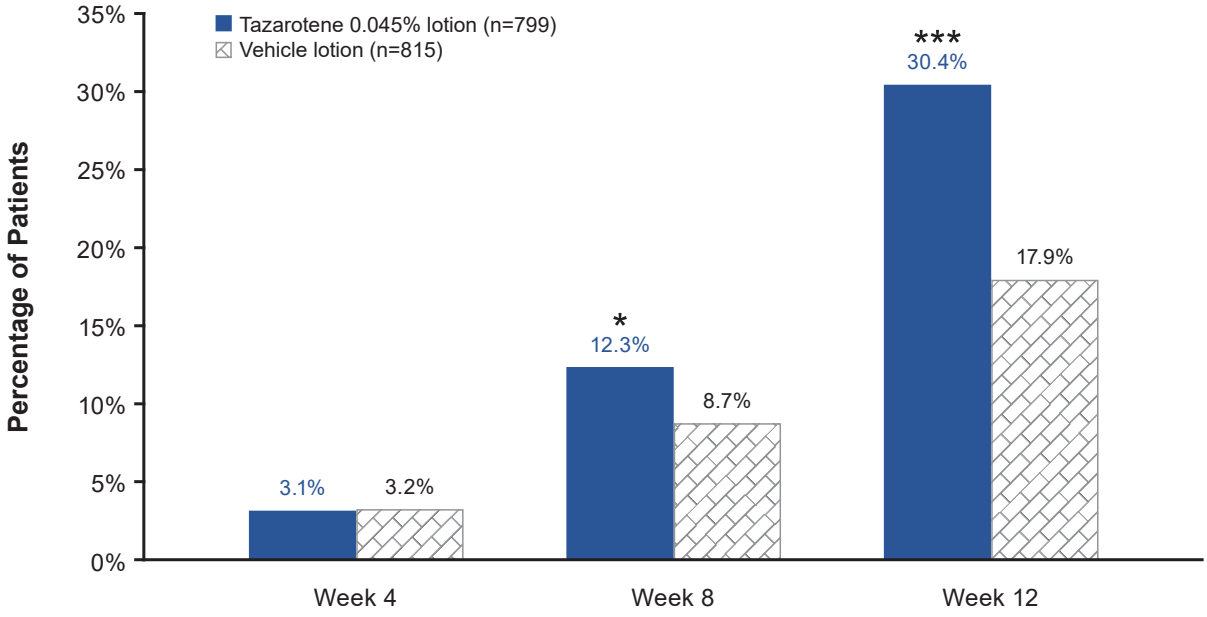


FIGURE 3. Mean percent change from baseline in inflammatory lesions, by week (ITT population, pooled). LS, least squares. ***P<0.001 versus vehicle.

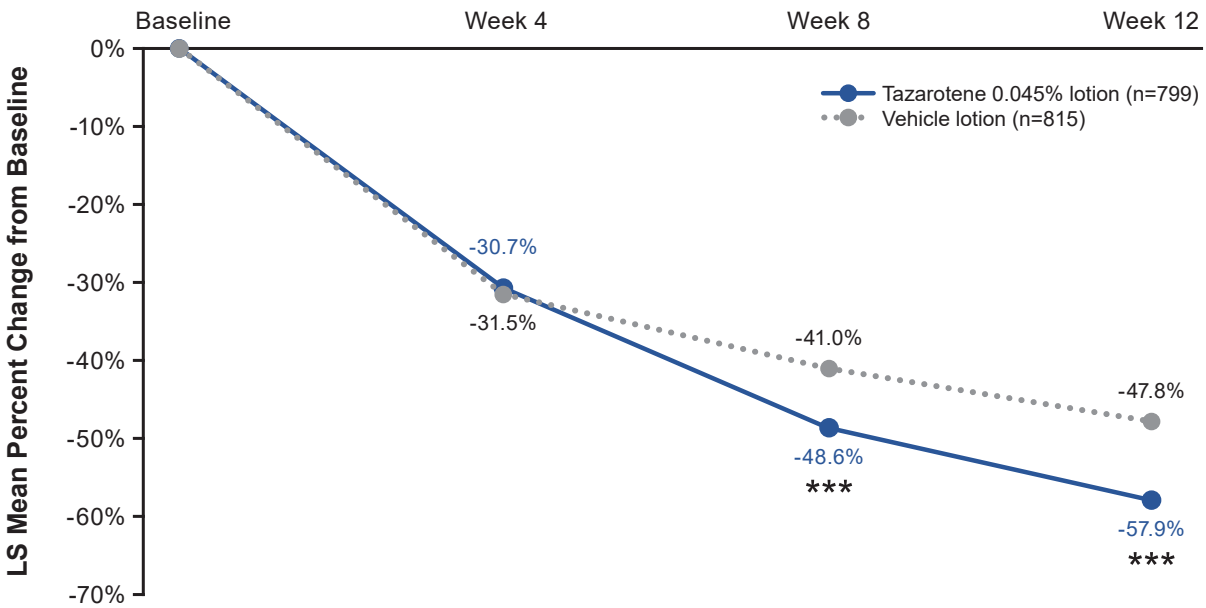


FIGURE 4. Mean percent change from baseline in noninflammatory lesions, by week (ITT population, pooled). LS, least squares. *** *P*<0.001 versus vehicle.

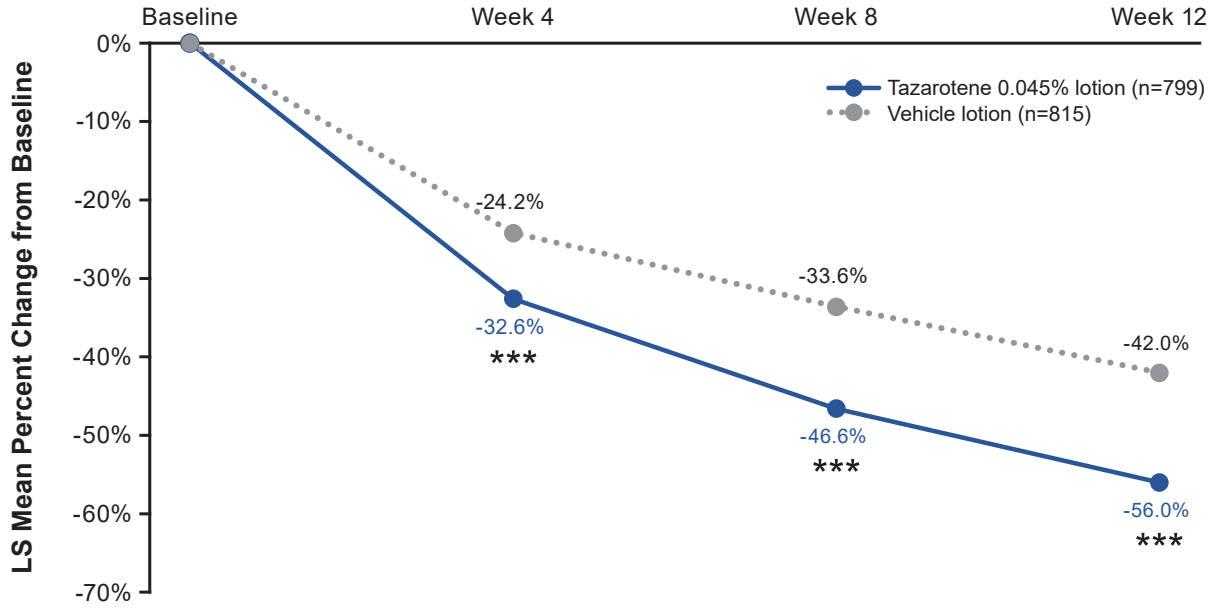
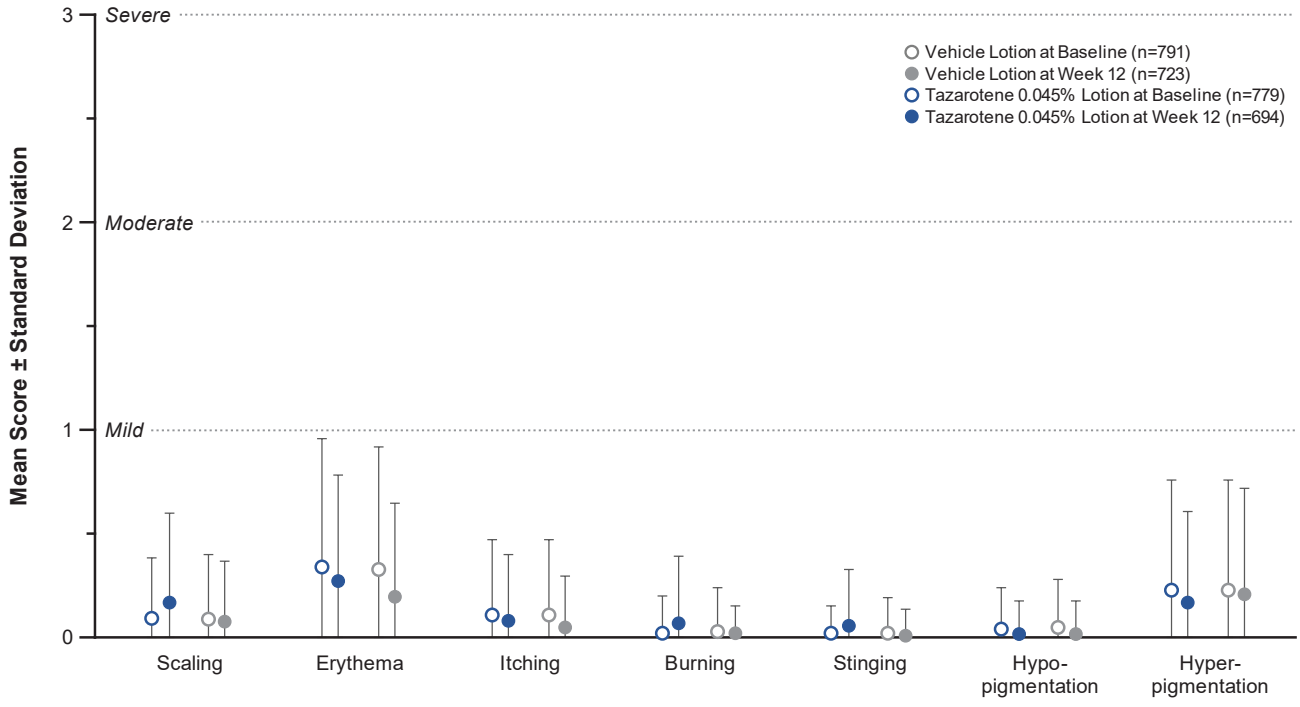


FIGURE 5. Mean cutaneous safety and tolerability ratings at baseline and week 12 (Safety population, pooled data). n = number of participants with available data.



(26.8%) and 151 patients (19.1%) in the 0.045% tazarotene and vehicle groups, respectively. Of the patients who reported any TEAE, more than 95% reported only AEs of mild or moderate severity (tazarotene, 95.2%; vehicle, 97.4%). In the tazarotene arm, 88 patients (11.3%) reported AEs that were deemed treatment-related; the most common were application site pain (5.3%), dryness (3.6%), exfoliation (2.1%), and erythema (1.8%). Of the 8 participants who reported serious AEs during the study (n=4 in each treatment group), none were deemed related to treatment. Among AEs leading to study discontinuation in the tazarotene arm, the most common were application site pain (13 [1.7%]) and application site erythema (6 [0.8%]). Details regarding cutaneous safety and tolerability have been reported.[22] Briefly, in the tazarotene-treated group, mean cutaneous safety and tolerability ratings were all between none (0) and mild (1) at weeks 4, 8, and 12. By week 12, any slight, transient increases in cutaneous safety and tolerability had returned to baseline values or improved (Figure 5).

DISCUSSION

Based on decades of clinical experience, multiple consensus guidelines recommend topical retinoids, either as monotherapy or in combination with other agents, for treating acne vulgaris.[23,24] However, irritating side effects—which may vary depending on the type and dosage of the active ingredient, as well as vehicle characteristics—can limit their use and negatively impact patient adherence.[25,26] To alleviate these bothersome side effects, patients may try to apply a moisturizer along with their topical retinoid, but this approach does not guarantee that active ingredient(s) will be evenly dispersed onto the skin.

Studies to date suggest that tazarotene 0.1% in gel, foam, or cream formulation may have the greatest efficacy among topical retinoids and appears effective in reducing postinflammatory hyperpigmentation.[11,16] Unfortunately, tazarotene 0.1% formulations may also have the potential for the greatest cutaneous irritation.[27] Among these various formulations, the 0.1% foam may have some advantages over gels and creams, which have been reported to leave a sticky residue and can be difficult to apply evenly.[28] Patient preference data for this formulation is lacking, and clinical benefits appear similar to those of other randomized, double-blind studies of tazarotene 0.1% cream and gel,[9,29] with treatment emergent AEs including application site irritation, dryness, and erythema still common, particularly in the first four weeks of treatment.

To maintain the proven efficacy of tazarotene while improving its irritability profile, a unique formulation of tazarotene 0.045% lotion was developed utilizing a new polymeric matrix technology. This is the first acne treatment with a reduced tazarotene concentration relative to standard 0.1% formulations. With polymeric matrix technology, uniform and simultaneous distribution of tazarotene, humectants, and emollients can be delivered in a lightly moisturizing and aesthetically pleasing lotion formulation. As a result, this new lower-dose formulation provides optimal delivery of tazarotene into epidermal layers, thereby maintaining efficacy while reducing local irritation.[21]

In the current pooled analysis, tazarotene 0.045% lotion significantly reduced both inflammatory and noninflammatory lesions relative to vehicle at week 12. Treatment success was achieved in 30.4% of patients at that time point. Notably, tazarotene 0.045% lotion was also well tolerated, with the most common treatment-related AEs being application site pain (5.3%), dryness (3.6%), and exfoliation (2.1%). These rates compare favorably with those previously reported for tazarotene 0.1% cream and gel formulations (irritation: 3.5% to 13%;[7-9,13-15] burning: 1% to 14%;[7-10,14,15] dryness, 1% to 27%;[7-11,13-15] exfoliation, 1% to 29%).[5,7-10,12,14,15] Application site reactions were generally less frequent than those previously reported for tazarotene 0.1% gel, cream, or foam, possibly as a result of the novel formulation and/or lower tazarotene concentration, although these data are difficult to compare in the absence of head-to-head trials. Overall AE rates were also low, with favorable tolerability, which may improve patient adherence.

CONCLUSION

Utilizing polymeric emulsion technology, a novel tazarotene formulation—with less than half the concentration of other available tazarotene products for acne—is effective and well tolerated in this pooled analysis of two phase 3 studies. Compared to other tazarotene formulations approved for treatment of moderate-to-severe acne, this new formulation offers significant tolerability benefits (without sacrificing efficacy) by allowing simultaneous delivery of tazarotene, humectants, and moisturizers.

DISCLOSURES

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. William Philip Werschler has served as an investigator for Ortho Dermatologics. Dr. Edward Lain has served as an investigator/consultant or speaker for Ortho Dermatologics. Dr. Eric Guenin is an employee of Ortho Dermatologics and may hold stock and/or stock options in its parent company. Dr. Radhakrishnan Pillai, Susan Harris, and Anya Loncaric are employees of Bausch Health US, LLC and may hold stock and/or stock options in its parent company. Bausch Health US, LLC is an affiliate of Bausch Health Companies Inc. Ortho Dermatologics is a division of Bausch Health US, LLC.

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AUTHOR CORRESPONDENCE

Emil A. Tanghetti MD

E-mail:..... et@dermatologyandlasersurgery.com