doi:10.36849/JDD.2020.3977

Tazarotene 0.045% Lotion for Once-Daily Treatment of Moderate-to-Severe Acne Vulgaris: Results from Two Phase 3 Trials

Emil A. Tanghetti MD,[a] William P. Werschler MD,[b] Terry Lain MD,[c] Eric Guenin PharmD PhD MPH,[d] Gina Martin MOT,[e] Radhakrishnan Pillai PhD[e]

[a]Center for Dermatology and Laser Surgery, Sacramento, CA
[b]University of Washington, School of Medicine, Seattle, WA
[c]University of Texas MD Anderson Cancer Center, Houston, TX
[d]Ortho Dermatologics, Bridgewater, NJ
[e]Bausch Health Americas, Inc., Petaluma, CA

ABSTRACT

Background: Tazarotene has been extensively studied in clinical trials and is widely used to treat acne vulgaris (acne), with data suggesting that is one of the most potent topical retinoids. Irritation from the cream, foam, and gel formulations has limited its use in clinical practice.

Objective: To assess the efficacy, safety, and tolerability of a unique tazarotene 0.045% lotion formulation based on polymeric emulsion technology in subjects with moderate or severe acne.

Methods: A total of 1614 subjects, 9 years and older were randomized to receive tazarotene 0.045% lotion or vehicle in two identical double-blind, randomized, vehicle-controlled 12-week studies evaluating safety and efficacy (inflammatory [papules and pustules] and noninflammatory [comedonal] lesion counts and using Evaluator Global Severity Scores [EGSS]). Treatment success was defined as at least a 2-grade improvement in EGSS and 'clear'/'almost clear' and efficacy assessed through reduction in lesion counts. In addition, patients completed a validated Acne-Specific Quality of Life (Acne-QoL) questionnaire. Safety, adverse events (AEs), and cutaneous tolerability were assessed throughout.

Results: Tazarotene 0.045% lotion demonstrated statistically significant superiority to vehicle in reducing inflammatory and noninflammatory lesion counts at week 12. Mean percent reductions in inflammatory and noninflammatory lesions were 55.5% and 51.4% (Study 1, both $P<0.001$ versus vehicle [45.7% and 41.5%, respectively]) and 59.5% and 60.0% (Study 2, both $P<0.001$ versus vehicle [49.0% and 41.6%, respectively]), with tazarotene 0.1% cream at week 12. Treatment success was achieved by 25.5% (Study 1) and 29.6% (Study 2) of subjects treated with tazarotene 0.045% lotion (both $P<0.001$ versus vehicle [13.0% and 17.3%, respectively]). Improvements in QoL domain scores were consistently greater with tazarotene. Tazarotene 0.045% lotion was well-tolerated. The most common treatment-related AEs were application site pain (5.3%), dryness (3.6%), and exfoliation (2.1%).

Conclusions: Tazarotene 0.045% lotion provides statistically significant greater efficacy than vehicle in terms of lesion reduction and treatment success, with a highly favorable safety and tolerability profile in moderate-to-severe acne patients.

J Drugs Dermatol. 2020;19(1):70-77. doi:10.36849/JDD.2020.3977

INTRODUCTION

Topical tazarotene 0.1% gel, foam and cream have been shown to be highly effective for the treatment of acne vulgaris (acne), both as monotherapy and in combination with other agents. Several studies have shown tazarotene to markedly reduce both comedonal and inflammatory facial acne lesions.[1-13]

All topical retinoids can produce irritant contact dermatitis during the first few weeks of application; with many patients experiencing erythema, scaling, dryness, burning, and pruritus that can vary in severity, that appear to be compound, quantity applied and vehicle dependent, and can be sufficiently symptomatic to reduce adherence with treatment.[14] Although tazarotene is an effective topical retinoid to treat acne, as true with all retinoids, skin irritation can limit its usefulness.[14]

A new approach utilizing polymeric emulsion technology has been applied to the development of dermatological products. Upon topical application, the polymeric emulsion helps a uniform release of humectants, moisturizing/hydrating ingredients, and uniform distribution of micronized oil droplets containing active ingredient which helps control the delivery

into skin, thus resulting in an efficient and clinically effective delivery system. This formulation approach has been used to develop tazarotene 0.045% lotion, providing uniform distribution of tazarotene onto the skin and providing a more efficient delivery into the epidermis; which may afford similar efficacy to the higher concentrations of tazarotene formulations currently available (gel, foam, and cream) while reducing the irritation potential.

In a phase 2 comparative study with tazarotene 0.045% lotion versus tazarotene 0.1% cream, tazarotene 0.045% lotion demonstrated statistically significant superiority to vehicle in reducing inflammatory and noninflammatory lesion counts (P=0.013 and P<.001) at week 12.[15] At less than half the concentration, tazarotene 0.045% lotion was numerically more effective than tazarotene 0.1% cream in terms of reduction in lesion counts and treatment success. Treatment Emergent Adverse Events (TEAEs) were twice as common with tazarotene 0.1% cream (26.8% versus 14.7% with tazarotene 0.045% lotion and 13.4% with vehicle) and there were also more treatment-related AEs with tazarotene 0.1% cream (5.6% versus 2.9%); most common being application site pain (4.2%) which is likely a manifestation of irritation.

Here we present data from two large multicentred, double-blind vehicle-controlled studies of tazarotene 0.045% lotion in subjects with moderate or severe acne.

METHODS

Study Design

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]). Treatment was topically applied once-daily to the face, excluding mouth, eyes, inside the nose, and lips. Power calculations were computed using the results from the phase 2 study.[15] Active and vehicle were identical formulations, with the absence of tazarotene in the vehicle comparator, with identical physical appearance and packaging to ensure blinding.

Studies were registered on clinicaltrials.gov NCT03168334 and NCT03168321, conducted at 89 clinical sites in the United States and Canada from June 2017 to July 2018.

Subjects and Randomization

Key inclusion criteria included subjects of either gender, 9 years or older 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.

A washout period of up to 1 month was required for patients who used previous prescription and over-the-counter acne treatments longer for systemic retinoids. Specifically, the following mandatory washout periods and restrictions applied to these topical and systemic 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). Approximately 1600 subjects (800 in each study) were planned for enrollment.

Study drug kits were assigned based on a randomization code. Subjects were randomized (1:1) to receive tazarotene 0.045% lotion or vehicle applied topically to the face once daily for 12 weeks. The initial topical application was made at the investigational center. Subjects were asked to apply their daily treatment in the evening at home. During the studies, each subject was permitted to use only approved cleansers, moisturizers, and sunscreens, and noncomedogenic makeup and shaving products. Investigators were trained thoroughly to ensure consistency in the evaluation of the subjects for lesion count and EGSS. Assessments were carried out at screening, baseline, weeks 2, 4, 8, and 12 (end of treatment). The EGSS was determined prior to performing lesion counts. Subjects also completed an Acne-Specific Quality of Life (Acne-QoL) questionnaire and were asked to answer questions pertaining to their QoL as it related to their facial acne at baseline and at week 12.

Study Oversight

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.

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. Percent of 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 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, 1614 subjects were randomized to tazarotene 0.045% lotion or vehicle lotion and included in the ITT population (Figure 1). Across the two studies, 86.6% (N=799) and 88.6% (N=815) of subjects treated with tazarotene 0.045% lotion or vehicle completed. Main reasons for study discontinuation with tazarotene 0.045% lotion were lost to follow-up (5.6%, N=45), subject request (4.3%, N=34), or adverse events (2.4%, N=19). Lost to follow-up (6.9%, N=56) and subject request (2.8%, N=23) were also the main reasons for discontinuation in the vehicle arms.
A total of 1570 subjects were included in the safety population, (44 subjects were not included due to no post baseline safety evaluation).

Demographics and Baseline Characteristics

Demographic data were comparable across the two studies (Table 1). Mean age was 20.6 (SD 7.11) in Study 1 and 20.3 (SD 6.65) in Study 2. Overall, the majority of subjects were female (65.9%, N=1064) and Caucasian (73.8%, N=1191).

FIGURE 1. Patient disposition showing percent completion and reasons for discontinuation (All Randomized Subjects Study 1 and Study 2).

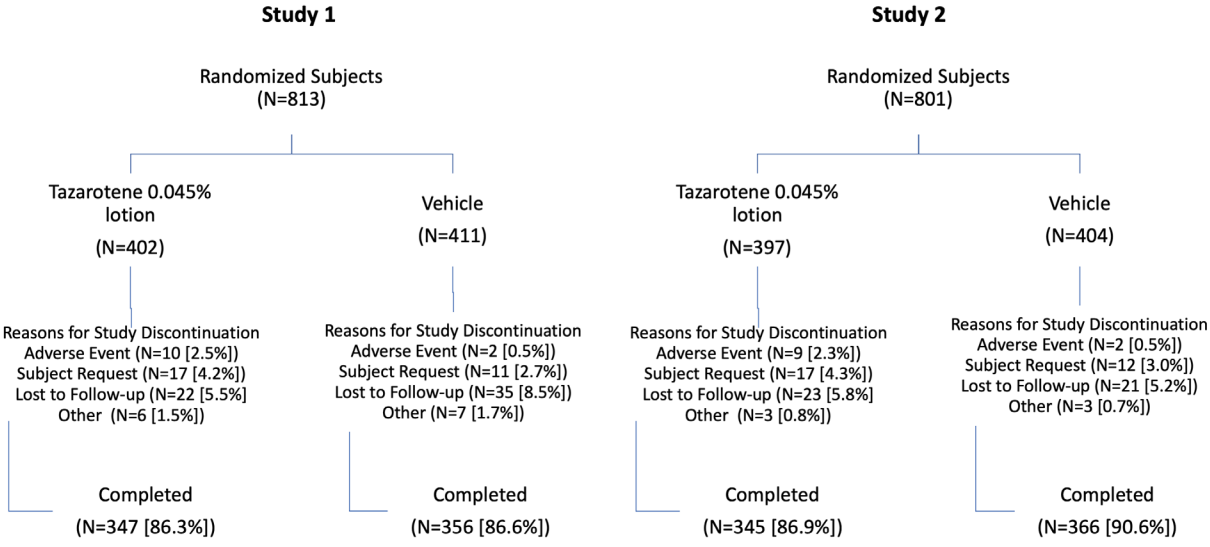


TABLE 1.

Demographics and Baseline Characteristics (ITT population Study 1 and Study 2)						
	Study 1			Study 2		
	Tazarotene 0.04% (N=402)	Vehicle (N=411)	Total (N=813)	Tazarotene 0.04% (N=397)	Vehicle (N=404)	Total (N=801)
Age- Mean years (SD)	20.8 (7.29)	20.4 (6.94)	20.6 (7.11)	20.1 (6.48)	20.5 (6.81)	20.3 (6.65)
Range	10-50	10-65	10-65	10-54	10-53	10-54
Sex N (%)						
Male	122 (30.3%)	140 (34.1%)	262 (32.2%)	146 (36.8%)	142 (35.1%)	288 (36.0%)
Female	280 (69.7%)	271 (65.9%)	551 (67.8%)	251 (63.2%)	262 (64.9%)	513 (64.0%)
Ethnicity N (%)						
Hispanic or Latino	67 (16.7%)	76 (18.5%)	143 (17.6%)	101 (25.4%)	108 (26.7%)	209 (26.1%)
Not Hispanic or Latino	335 (83.3%)	335 (81.5%)	670 (82.4%)	296 (74.6%)	296 (73.3%)	592 (73.9%)
Race N (%)						
American Indian or Alaska Native	3 (0.7%)	3 (0.7%)	6 (0.7%)	6 (1.5%)	3 (0.7%)	9 (1.1%)
Asian	15 (3.7%)	13 (3.2%)	28 (3.4%)	27 (6.8%)	23 (5.7%)	50 (6.2%)
Black or African American	76 (18.9%)	83 (20.2%)	159 (19.6%)	49 (12.3%)	54 (13.4%)	103 (12.9%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	2 (0.5%)	2 (0.2%)	0 (0.0%)	2 (0.5%)	2 (0.2%)
White	293 (72.9%)	297 (72.3%)	590 (72.6%)	298 (75.1%)	303 (75.0%)	601 (75.0%)
Other	15 (3.7%)	13 (3.2%)	28 (3.4%)	17 (4.3%)	19 (4.7%)	36 (4.5%)
Evaluator's Global Severity Score N (%)						
3 – Moderate	368 (91.5%)	384 (93.4%)	752 (92.5%)	358 (90.2%)	357 (88.4%)	715 (89.3%)
4 – Severe	34 (8.5%)	27 (6.6%)	61 (7.5%)	39 (9.8%)	47 (11.6%)	86 (10.7%)
Inflammatory Lesion Count- Mean (SD)	28.5 (7.04)	28.1 (7.04)	28.3 (7.04)	28.0 (7.32)	27.9 (7.10)	28.0 (7.21)

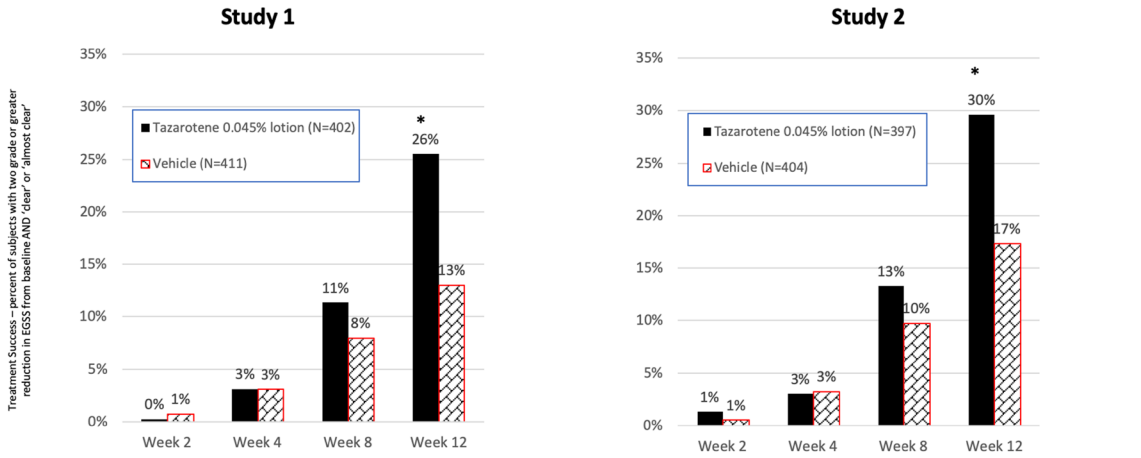
Baseline disease characteristics were comparable (Table 1). Subjects had a baseline EGSS of 3 - moderate (90.9%, N=1467) or 4 - severe (9.1%, N=147). Mean (SD) inflammatory and noninflammatory lesion counts were 28.1 (7.12) and 41.1 (16.54).

Efficacy Evaluation

Evaluator's Global Severity Score (EGSS)

Tazarotene 0.045% lotion was significantly more effective than vehicle in achieving treatment success (Figure 2), defined as at least a 2-grade improvement in EGSS and 'clear'/'almost clear'. By week 12, 25.5%, and 29.6% (Study 1 and 2) of subjects in the tazarotene 0.045% lotion groups achieved this co-primary efficacy outcome compared with 13.0% and 17.3% with vehicle (both $P<0.001$). In addition, 28.3% and 34.5% (Study 1 and 2)

FIGURE 2. Treatment success. Subjects with at least a 2-grade improvement and 'clear' or 'almost clear at each study visit (ITT population, Study 1 and Study 2).



*P<0.001 versus vehicle. P-value from a logistic regression (using Firth's Penalized Likelihood) with factors of treatment group and analysis center. Values have been adjusted for multiple imputation. Summary statistics for Weeks 2, 4, and 8 represent average values, obtained from averaging the summary statistics generated from each imputed dataset.

TABLE 2.

Treatment-Emergent and Related Adverse Event (AE) Characteristics through Week 12 (Safety population, pooled data)		
	Pooled Data (Study 1 and Study 2)	
	Tazarotene 0.045% Lotion (N=779)	Vehicle Lotion (N=791)
Subjects reporting any TEAE	209 (26.8%)	151 (19.1%)
Subjects reporting any SAE	4 (0.5%)	4 (0.5%)
Subjects who died	0 (0.0%)	0 (0.0%)
Subjects who discontinued due to TEAE	22 (2.8%)	4 (0.5%)
Severity of AEs reported		
Mild	136 (17.5%)	83 (10.5%)
Moderate	63 (8.1%)	64 (8.1%)
Severe	10 (1.3%)	4 (0.5%)
Relationship to study drug		
Related	88 (11.3%)	9 (1.1%)
Unrelated	121 (15.5%)	142(18.0%)
Treatment Related AEs reported by ≥1% subjects		
Application site pain	41 (5.3%)	2 (0.3%)
Application site dryness	28 (3.6%)	1 (0.1%)
Application site erythema	14 (1.8%)	0 (0.0%)
Application site exfoliation	16 (2.1%)	0 (0.0%)

of subjects in the tazarotene 0.045% lotion groups achieved at least a 2-grade improvement in EGSS at week 12 compared with 15.2% and 20.9% with vehicle (both $P<0.001$).

Lesion Counts

Tazarotene 0.045% lotion was significantly more effective than vehicle in achieving a reduction in lesion counts (Figure 3 and 4). At week 12, the absolute reduction (15.6, Study 1 and 16.7, Study 2) in inflammatory lesion count relative to baseline for the tazarotene 0.045% lotion group was significantly greater than for vehicle (12.4, Study 1 and 13.4, Study 2, $P<0.001$ both studies). Correspondingly, the absolute reduction (21.0, Study 1 and 24.6, Study 2) in noninflammatory lesion count relative to baseline for the tazarotene 0.045% lotion group was significantly greater than for vehicle (16.4, Study 1 and 16.6, Study 2, $P<0.001$ both studies).

By week 12, there was a 55.5% and 51.4% (Study 1) change in inflammatory and noninflammatory lesion counts from baseline (LS mean), and a 59.5% and 60.0% change in Study 2, respectively, compared with 45.7% and 41.5% (Study 1, both $P<0.001$) and 49.0% and 41.6% (Study 2, both $P<0.001$) with vehicle.

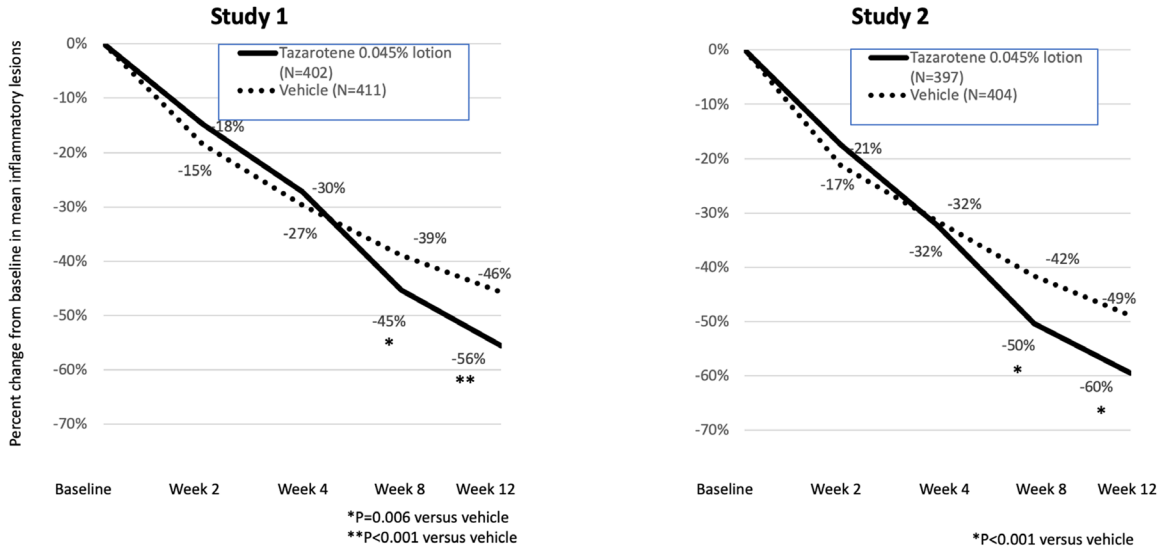
Percent changes in noninflammatory lesions were statistically significant compared with vehicle from week 2 (Study 2, $P=0.018$) or week 4 (Study 1, $P=0.004$) and changes in inflammatory lesions statistically significantly greater at week 8 ($P\leq0.006$) Acne-Specific QoL

At baseline, the mean scores for each domain were similar. By Week 12 improvements in QoL (mean absolute changes) were consistently greater in the groups treated with tazarotene 0.045% lotion. Absolute change from baseline in Self-Perception, Role-Emotional, Role-Social and Acne Symptom domains were 7.5, 6.0, 4.7, and 6.4, respectively, compared with 6.7, 5.5, 4.1, and 5.3 for subjects treated with vehicle.

Safety Evaluation

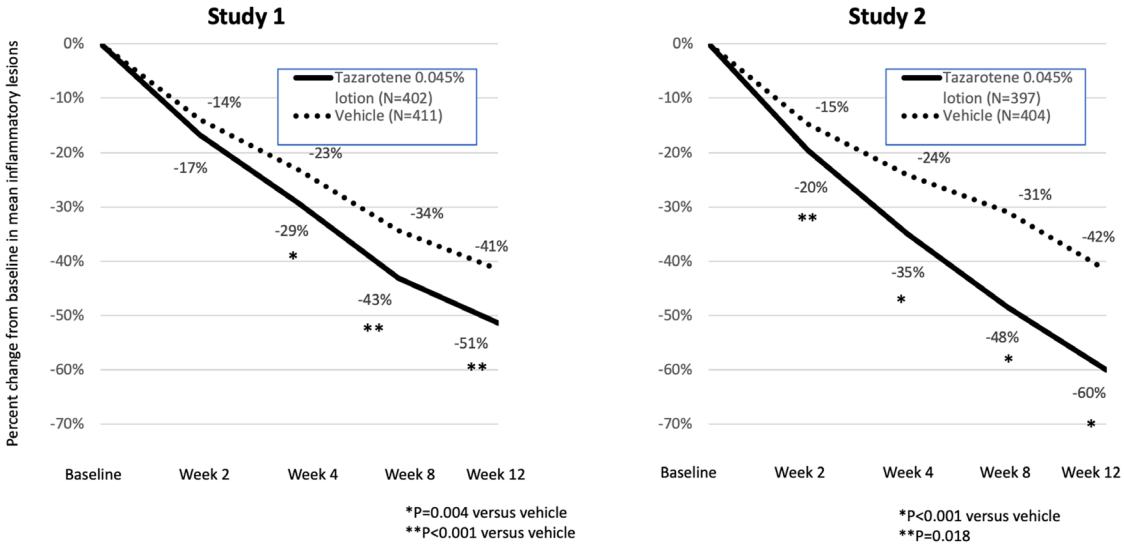
Overall, 26.8% (N=209) of subjects treated with tazarotene 0.045% lotion reported AEs compared with 19.1% (N=151) with

FIGURE 3. Percent change in inflammatory lesions from baseline to week 12 (ITT population, Study 1 and Study 2, LS Mean).



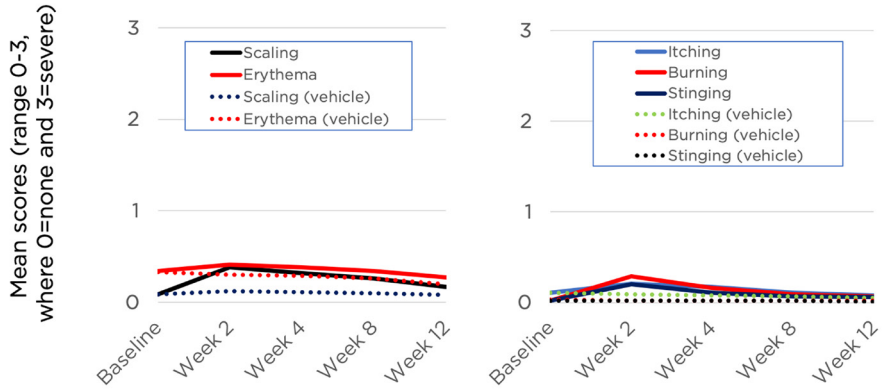
The LS means, SDs, and p-values were obtained from an analysis of covariance (ANCOVA) with factors of treatment group and analysis center, and the respective Baseline lesion count as a covariate. Values have been adjusted for multiple imputation. Negative LS mean values represent a decrease from Baseline.

FIGURE 4. Percent change in noninflammatory lesions from baseline to week 12 (ITT population, Study 1 and Study 2, LS Mean).



The LS means, SDs, and p-values were obtained from an analysis of covariance (ANCOVA) with factors of treatment group and analysis center, and the respective Baseline lesion count as a covariate. Values have been adjusted for multiple imputation. Negative LS mean values represent a decrease from Baseline.

FIGURE 5. Cutaneous safety and tolerability assessment from baseline to week 12 (Safety population, pooled data).



vehicle; the majority (98.7%) were mild or moderate (Table 2). There were an equal number of SAEs with tazarotene 0.045% lotion and vehicle (N=4). Less than half of the tazarotene 0.045% lotion AEs were treatment-related AEs (88/209). Most common were application site pain (5.3%), dryness (3.6%), exfoliation (2.1%) and erythema (1.8%). Only four subjects reported serious AEs (SAEs) following tazarotene 0.045% lotion treatment; none were treatment-related (abortion induced [2], abortion spontaneous, suicidal ideation). There was no death reported in either study.

Cutaneous Safety and Tolerability

At baseline, there were few reports of itching (N=75, 9.6%), burning (N=14, 1.8%), or stinging (N=13, 1.7%) in the tazarotene 0.045% lotion treatment groups. There were slight transient increases in these reports following treatment, peaking at week 2 (N=137, 18.1%; N=165, 21.7%; and N=114, 15.0%).

The severity of itching, burning and stinging was very low over the course of the studies (Figure 5). Mean scores for itching, burning and stinging at baseline (0.11, 0.02, and 0.02, respectively) increased slightly all peaking at week 2 (0.21, 0.29, and 0.20, respectively, where 1=mild) following tazarotene 0.045% lotion treatment, returning to below, or similar to baseline levels by week 12.

Reports of scaling (N=71, 9.1%) or erythema (N=207, 26.6%) were more common at baseline, although in most instances these were mild. Again, following treatment with tazarotene 0.045% lotion there were transient increases in mean scores,

from baseline (0.09 and 0.34) peaking at week 2 (0.38 and 0.41, respectively, where 1=mild), returning to below, or similar to baseline levels by week 12. Again, mean scores were low (where 1=mild) over the course of the studies.

Hyperpigmentation (N=145, 18.6%) was more commonly reported than hypopigmentation (N=26, 3.4%) at baseline. There were no increases in severity (mean scores) with treatment.

DISCUSSION

Topical retinoids provide the mainstay of acne treatment. While they have been shown to be very effective either as monotherapy or in combination, they are capable of producing cutaneous irritancy during the first few weeks of application. These side effects vary in severity and duration, appear to be compound and vehicle dependent, and can both limit treatment and reduce patient adherence. Studies suggest tazarotene 0.1% (gel, foam, or cream) may be the most effective retinoid, but its potential for cutaneous irritation is also the greatest. While tazarotene 0.1% foam may overcome some of the aesthetic disadvantages of gels and creams (they have been reported to leave a greasy, sticky residue and can be difficult to apply evenly[16]), no data are available on patient preferences and clinical benefits[17] are similar to those reported in other randomized, double-blind studies of tazarotene 0.1% cream[2] and gel.[18] Treatment-emergent AEs such as application site irritation (18% and 11%, study 1 and 2 respectively), dryness (6% and 8%), and erythema (9% and 4%) were still common, especially over the first four weeks treatment.

The rationale behind the novel formulation of tazarotene 0.045% lotion was to develop a topical treatment for moderate or severe acne; providing optimal efficacy and minimizing the tazarotene irritant effects in a light and aesthetically pleasing lotion formulation, where lotion is the preferred formulation for facial application. The formulation process utilized new polymeric emulsion technology to ensure uniform distribution of tazarotene and moisturizing ingredients onto the skin surface and efficient delivery into the epidermal layers. A comparative study of tazarotene 0.045% lotion and tazarotene 0.1% cream in moderate-to-severe acne reported numerically greater efficacy with tazarotene 0.045% lotion at 12 weeks despite half the concentration of tazarotene and fewer treatment-related AEs.[15]

Following the promising phase 2 results, we further investigated the safety and efficacy of tazarotene 0.045% lotion, reporting on two phase 3 clinical studies in moderate-to-severe acne in subjects 9 years and older. Treatment success was achieved in close to 30% of subjects by week 12; with significant reductions in both inflammatory and comedonal lesions, compared with vehicle (P<0.001). Tazarotene 0.045% lotion was also well-tolerated. Most common treatment-related AEs were application site pain (5.3%), dryness (3.6%), and exfoliation (2.1%). Application site reactions were less common than those reported previously with tazarotene 0.1% gel, cream or foam and may be as a result of formulation benefits as well as the lower concentration of tazarotene. Overall cutaneous tolerability and safety scores were also low. There were slight transient increases peaking at week 2 with scores returning to below or similar to baseline levels by week 12.

CONCLUSIONS

Tazarotene 0.045% lotion utilizes new polymeric emulsion technology with moisturizing excipients to provide a topical treatment for moderate-to-severe acne that is effective and well-tolerated. With half the concentration of other marketed formulation (gel, foam, or cream) it appears to be at least as effective and demonstrates a better safety and tolerability profile.

DISCLOSURES

Drs Tanghetti, Werschler, and Lain are investigators and/or advisors to Ortho Dermatologics. Drs Guenin and Pillai and Ms Martin are employees of Bausch Health.

ACKNOWLEDGMENTS

We thank Brian Bulley, MSc (Konic Limited, UK) for assistance with the preparation of the manuscript. Valeant Pharmaceuticals, funded Konic's activities pertaining to this manuscript.

REFERENCES

1. Leyden JJ, Shalita A, Thiboutot D, et al. Topical retinoids in inflammatory acne: a retrospective, investigator-blinded, vehicle-controlled, photographic assessment. *Clin Ther.* 2005;27(2):216-224.
2. Shalita AR, Berson DS, Thiboutot DM, et al. Effects of tazarotene 0.1 % cream in the treatment of facial acne vulgaris: pooled results from two multicenter, double-blind, randomized, vehicle-controlled, parallel-group trials. *Clin Ther.* 2004;26(11):1865-1873.
3. Leyden J, Thiboutot DM, Shalita AR, et al. Comparison of tazarotene and minocycline maintenance therapies in acne vulgaris: a multicenter, double-blind, randomized, parallel-group study. *Arch Dermatol.* 2006;142(5):605-612
4. Draelos ZD, Tanghetti EA. Optimizing the use of tazarotene for the treatment of facial acne vulgaris through combination therapy. *Cutis.* 2002;69(2 Suppl):20-29.
5. Tanghetti E, Abramovits W, Solomon B, et al. Tazarotene versus tazarotene plus clindamycin/benzoyl peroxide in the treatment of acne vulgaris: a multicenter, double-blind, randomized parallel-group trial. *J Drugs Dermatol.* 2006;5(3):256-261
6. Leyden JJ, Tanghetti EA, Miller B, et al. Once-daily tazarotene 0.1 % gel versus once-daily tretinoin 0.1 % microsponge gel for the treatment of facial acne vulgaris: a double-blind randomized trial. *Cutis.* 2002;69(2 Suppl):12-19.
7. Webster GF, Guenther L, Poulin YP, et al. A multicenter, double-blind,randomized comparison study of the efficacy and tolerability of once-daily tazarotene 0.1% gel and adapalene 0.1% gel for the treatment of facial acne vulgaris. *Cutis.* 2002;69(2 Suppl):4-11.
8. Webster GF, Berson D, Stein LF, et al. Efficacy and tolerability of once-daily tazarotene 0.1% gel versus once-daily tretinoin 0.025% gel in the treatment of facial acne vulgaris: a randomized trial. *Cutis.* 2001;67(6 Suppl):4-9.
9. Leyden J, Lowe N, Kakita L, et al. Comparison of treatment of acne vulgaris with alternate-day applications of tazarotene 0.1% gel and once-daily applications of adapalene 0.1% gel: a randomized trial. *Cutis.* 2001;67(6 Suppl):10-16.
10. Shalita A, Miller B, Menter A, et al. Tazarotene cream versus adapalene cream in the treatment of facial acne vulgaris: a multicenter, double-blind, randomized, parallel-group study. *J Drugs Dermatol.* 2005;4(2):153-158.
11. Tanghetti E, Dhawan S, Green L, et al. Randomized comparison of the safety and efficacy of tazarotene 0.1% cream and adapalene 0.3% gel in the treat-

doi:10.36849/JDD.2020.3977

ment of patients with at least moderate facial acne vulgaris. *J Drugs Dermatol.* 2010;9(5):549-558.
12. Tanghetti E, Dhawan S, Green L, et al. Clinical evidence for the role of a topical anti-inflammatory agent in comedonal acne: findings from a randomized study of dapsone gel 5% in combination with tazarotene cream 0.1% in patients with acne vulgaris. *J Drugs Dermatol.* 2011;10(7):783-792.
13. Thiboutot D, Arsonnaud S, Soto P. Efficacy and tolerability of adapalene 0.3% gel compared to tazarotene 0.1% gel in the treatment of acne vulgaris. *J Drugs Dermatol.* 2008 ;7(6 Suppl):S3-S10.
14. Del Rosso JQ, Tanghetti E. A status report on topical tazarotene in the management of acne vulgaris. *J Drugs Dermatol.* 2013;12(3):S53-S58.
15. Tanghetti EA, Kircik LH, Green LJ, et al. A Phase 2, Multicenter, Double-Blind, Randomized, Vehicle-Controlled Clinical Study to Compare the Safety and Efficacy of a Novel Tazarotene 0.045% Lotion and Tazarotene 0.1% Cream (Tazorac®) in the Treatment of Moderate-to-Severe Acne Vulgaris. *J Drugs Dermatol.* 2019 in press.
16. Zhao Y, Jones SA , Brown MB. Dynamic foams in topical drug delivery. *J Pharm Pharmacol.* 2010;62:678-684
17. Shalita AR, Chalker DK, Griffith RF, et al. Tazarotene gel is safe and effective in the treatment of acne vulgaris: a multicenter, double-blind, vehicle-controlled study. *Cutis.* 1999;63:349-354.
18. Feldman SR, Werner CP, Alio Saenz, AB. The Efficacy and Tolerability of Tazarotene Foam, 0.1%, in the Treatment of Acne Vulgaris in 2 Multicenter, Randomized, Vehicle-Controlled, Double-Blind Studies. *J Drugs Dermatol.* 2013;12(4):438-446.

AUTHOR CORRESPONDENCE

Emil Tanghetti MD
E-mail:.....et@dermatologyandlasersurgery.com