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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 in the Treatment of Moderate-to-Severe Acne Vulgaris

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ABSTRACT

Background: Tazarotene has been extensively studied in clinical trials and is widely used to treat acne vulgaris (acne). Irritation potential has limited its use.

Objective: To compare efficacy, safety, and tolerability of a novel formulation tazarotene 0.045% lotion based on polymeric emulsion technology, and tazarotene 0.1% cream in patients with moderate-to-severe acne.

Methods: A total of 210 patients, 12 years and older were randomized to receive tazarotene 0.045% lotion, tazarotene 0.1% cream, or respective vehicle in double-blind, randomized, vehicle-controlled, 12-week study evaluating safety and efficacy (inflammatory and noninflammatory lesion counts and using Evaluator Global Severity Scores [EGSS]). In addition, patients completed a patient satisfaction survey (PSS), and acne-specific quality of life (QoL) questionnaire. Safety and cutaneous tolerability were assessed throughout.

Results: A novel tazarotene 0.045% lotion demonstrated statistically significant superiority to vehicle in reducing inflammatory and noninflammatory lesion counts (P=.006 and P<.001) and clearly more effective in treatment success at week 12. In addition, at less than half the concentration, tazarotene 0.045% lotion was numerically more effective than tazarotene 0.1% cream. Mean percent reductions in inflammatory and noninflammatory lesions were 63.8% and 56.9%, compared with 60.0% and 54.1% with tazarotene 0.1% cream at week 12. Treatment success assessed by the investigator or patients' self-assessment was also numerically greater with tazarotene 0.045% lotion. There were no significant differences in patient satisfaction or QoL between the two active treatments. Both were well-tolerated, however, there were more treatment-related adverse events with tazarotene 0.1% cream (5.6% versus 2.9%); most common being application site pain.

Limitations: This study was primarily designed to direct the phase 3 program and some of the results are post hoc analyses.

Conclusions: A novel tazarotene 0.045% lotion provides statistically significant greater efficacy than vehicle in terms of lesion reduction, and numerically better treatment success than tazarotene 0.1% cream; with a highly favorable safety and tolerability profile in moderate-to-severe acne patients.

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INTRODUCTION

Topical retinoids (eg, tazarotene, tretinoin, adapalene) have played an important role in the management of acne vulgaris (acne). They reduce visible lesions and inhibit the development of microcomedones and new lesions.[1-3] Retinoids normalize the abnormal desquamation process by reducing keratinocyte proliferation and promoting differentiation,[4] as well as modulating several important inflammatory pathways.[4-10] Extensive clinical data have shown retinoids to be highly effective in acne, and they are recommended as the cornerstone of topical therapy.[11] Comparative studies between tazarotene, tretinoin and adapalene have generally reported greater efficacy with tazarotene, but more irritation.[12-20]

A key aspect of acne management has been the ongoing evolution of topical treatments that use innovative delivery solutions and optimal formulations to help minimize irritation, without

compromising efficacy. A novel lotion formulation was developed using a polymeric emulsion, with the aim of improving both efficacy and tolerability. This polymeric emulsion technology provides a more uniform distribution of active and moisturizing excipients at the surface of the skin, which should enhance efficacy and minimize irritation.

In this report data from a comparative phase 2 clinical study where patients with moderate-to-severe acne were treated with tazarotene 0.045% lotion, tazarotene 0.1% cream, or vehicle are presented.

METHODS

Study Design

This was a multicenter, randomized, double-blind, vehicle-controlled, clinical study in patients with moderate-to-severe acne who met specific inclusion/exclusion criteria as described below. Protocol received approval from the appropriate institutional review board (IRB) for each center before patient enrollment and were conducted in accordance with the Declaration of Helsinki and Good Clinical Practices (GCP) and in compliance with local regulatory requirements. All patients were informed of the study details and provided written consent.

Patients were enrolled with an Evaluator Global Severity Score [EGSS] score of 3 (moderate) or 4 (severe). Treatments were randomized (2:2:1:1) to tazarotene 0.045% lotion, tazarotene 0.1% cream, and vehicle lotion or cream (to ensure blinding). Data on vehicle are combined in the result presented here. All patients applied study medication to the face once-daily in the evening for 12 weeks; after being instructed to gently washing their face with a non-medicated cleanser.

Study Population

Approximately 210 patients were planned for enrollment. Eligible patients were of any gender, race and ethnicity aged 12 years and older who presented with 20 to 40 inflammatory lesions (papules, pustules, and nodules), 20 to 100 noninflammatory lesions (open and closed comedones), and two nodules or less. Women of childbearing potential were required to have a negative urine pregnancy test result and to agree to use an effective form of contraception for the duration of the study. A washout period of up to 1 month was required for patients who used previous prescription and over-the-counter acne treatments (and six months for systemic retinoids). Investigator approved non-mediated facial cleanser, moisturizer, and sunscreen was allowed.

Efficacy Evaluation

Efficacy evaluations comprised inflammatory, and noninflammatory lesion counts and an EGSS at screening, baseline, and during treatment (at weeks 2,4, 8, and 12) performed by the investigator. Primary efficacy endpoints included mean absolute change from baseline to week 12 in inflammatory and noninflammatory lesion counts, and the proportion of patients who achieved at least a 2-grade reduction from baseline to week 12 in EGSS and were 'clear' or 'almost clear'. Other efficacy endpoints included mean percent change from baseline to week 12 in inflammatory and noninflammatory lesion counts. Data for vehicle lotion and cream were pooled for the efficacy analysis.

Additional analyses were performed to evaluate the impact of treatment on other patient outcomes. These included a Patient Satisfaction Survey (PSS) with scores ranging from 1-10 (where 10 was the most satisfied); a validated Acne-Specific Quality of Life (Acne-QoL) questionnaire (Merck & Co, Inc. Whitehouse, NJ); and a Subject Self-Assessment (SSA) scale (using a 7-point scale, where 0=worse and 6=clear). The SSA was assessed at baseline and weeks 2, 4, 8, and 12; PSS and Acne-QoL were completed at baseline and week 12.

Safety Evaluation

Cutaneous safety (erythema, scaling, hypopigmentation, and hyperpigmentation) and tolerability (itching, burning, and stinging) were assessed using a 4-point scale where 0=none, 1=mild, 2=moderate and 3=severe. The investigator assessed erythema, scaling, and hyper-/hypopigmentation at the time of the study visit. Itching, burning, and stinging were solicited from the patient and recorded as an average of the patient's symptoms during the period since the previous visit.

Safety was also evaluated through reported adverse events (AEs), which were summarized by treatment group, severity, and relationship to study medication.

Statistical Analysis

The intent-to-treat (ITT) population comprised all patients randomized and provided with study drug and vehicle. The safety population comprised all randomized patients who were presumed to have used the study medication or vehicle at least once and who provided at least one post baseline evaluation. The primary method of handling missing efficacy data in the ITT analysis set was last observation carried forward (LOCF). No imputations were made for missing safety data.

Reductions in lesion counts are presented as means and contrast p-values are from a ranked analysis of covariance with factor of treatment and the respective baseline lesion count as covariate. Significance of EGSS reductions were obtained from a Cochran-Mantel-Haenszel (CMH) test.

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. The frequency of patients with one or more AEs during the study was tabulated by treatment group.

RESULTS

Baseline Characteristics

Total of 210 patients were enrolled across 16 investigative sites in the United States, randomly assigned to tazarotene 0.045% lotion (N=69), tazarotene 0.1% cream (N=72), or vehicle (N=69) and included in the ITT analysis, see Figure 1. Patients were treated with vehicle lotion (N=34) or vehicle cream (N=35) to ensure blinding, however vehicle results are combined in these analyses. Overall, 189 patients (90%) completed the study, including 65 patients (94.2%) on tazarotene 0.045% lotion, 63 patients (87.5%) on tazarotene 0.1% cream, 61 patients (88.4%) on combined vehicle. The most common reasons for study discontinuation were 'lost to follow-up (N=12)' or 'subject request (N=5)'. One patient treated with tazarotene 0.1% cream discontinued due to adverse event. Four patients were excluded from the safety population due to no post-baseline safety assessment.

Demographic data (Table 1) was similar across the treatment groups. The mean age was 21.2 to 23.3 years. There was a slightly higher proportion of female patients overall (55.2%); 61.4% were Caucasian, with 28.6% Black or African American. There were no noticeable differences between treatment groups in regard to baseline lesion counts, or EGSS. At baseline, the mean number of inflammatory and noninflammatory lesions ranged from 27.2 to 28.3 and 36.6 to 37.6, respectively. At baseline, 92.4% of patients had moderate acne (EGSS=3).

Efficacy

Lesion Counts

Tazarotene 0.045% lotion resulted in statistically significant reductions in both inflammatory and noninflammatory lesion reductions compared to combined vehicle at week 12. Mean percentage change from baseline to week 12 in inflammatory lesion counts was 63.8% versus 51.4% with the combined vehicle (P=.006), and in noninflammatory lesion counts 56.9% versus 35.2% with vehicle (P<.001), see Figures 2 and 3. Tazarotene 0.045% lotion showed a greater reduction from baseline to week 12 in inflammatory and noninflammatory lesions when compared with tazarotene 0.1% cream, but differences were not significant (P=.680 and .612).

Median percent change from baseline to week 12 in inflammatory and noninflammatory lesion counts with tazarotene 0.045% lotion was 72.4% and 62.5% versus 66.7% and 56.4% with tazarotene 0.1% cream and 60.0% and 42.3% with vehicle, respectively.

FIGURE 1. Patient disposition ITT population (all randomized subjects, N=210).

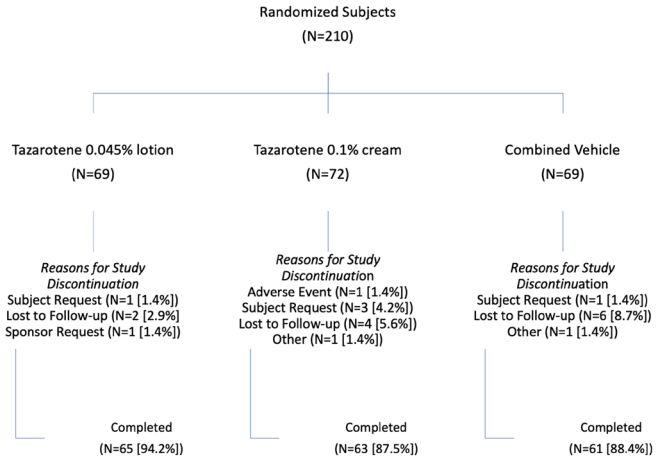


TABLE 1.

Demographics and Baseline Characteristics (ITT population)	Tazarotene 0.045% Lotion (N=69)	Tazarotene 0.1% Cream (N=72)	Combined Vehicle (N=69)
Age			
Mean years (SD)	23.3 (10.20)	22.0 (8.96)	21.2 (8.44)
Sex N (%)			
Male	32 (46.4%)	31 (43.1%)	31 (44.9%)
Female	37 (53.6%)	41 (56.9%)	38 (55.1%)
Ethnicity N (%)			
Hispanic or Latino	27 (39.1%)	29 (40.8%)	25 (36.2%)
Not Hispanic or Latino	42 (60.9%)	42 (59.2%)	44 (63.8%)
Race N (%)			
American Indian or Alaska Native	1 (1.4%)	0 (0.0%)	2 (2.9%)
Asian	4 (5.8%)	4 (5.6%)	2 (2.9%)
Black or African American	21 (30.4%)	16 (22.2%)	23 (33.3%)
Native Hawaiian or Other Pacific Islander	1 (1.4%)	0 (0.0%)	1 (1.4%)
White	41 (59.4%)	50 (69.4%)	38 (55.1%)
Other	1 (1.4%)	2 (2.8%)	3 (4.3%)
Evaluator's Global Severity Score N (%)			
3 – Moderate	64 (92.8%)	66 (91.7%)	64 (92.8%)
4 – Severe	5 (7.2%)	6 (8.3%)	5 (7.2%)
Inflammatory Lesion Count			
Mean (SD)	28.3 (6.00)	27.3 (5.95)	27.2 (5.49)
Noninflammatory Lesion Count			
Mean (SD)	37.6 (14.70)	36.6 (13.31)	36.6 (13.17)

FIGURE 2. Percent change in mean inflammatory lesions from baseline to week 12. (ITT population): Comparison of Tazarotene 0.045% lotion, Tazarotene 0.1% cream, and vehicle.

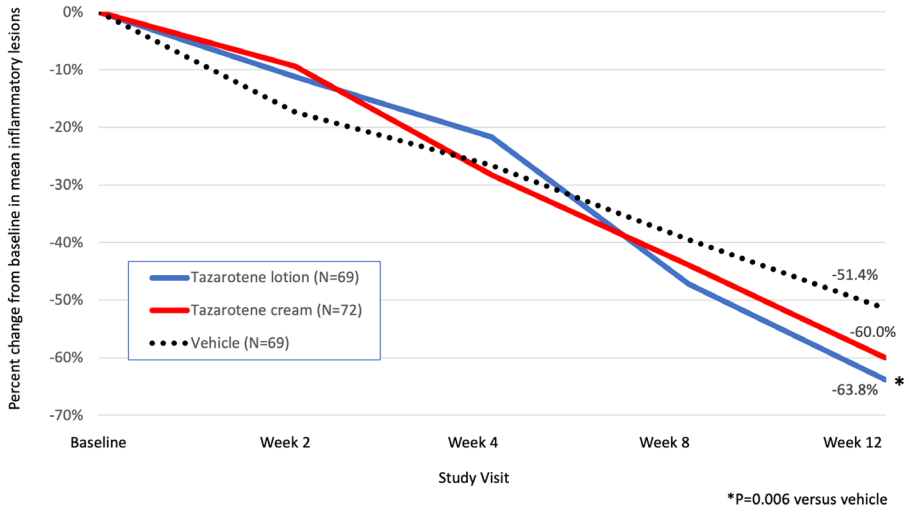
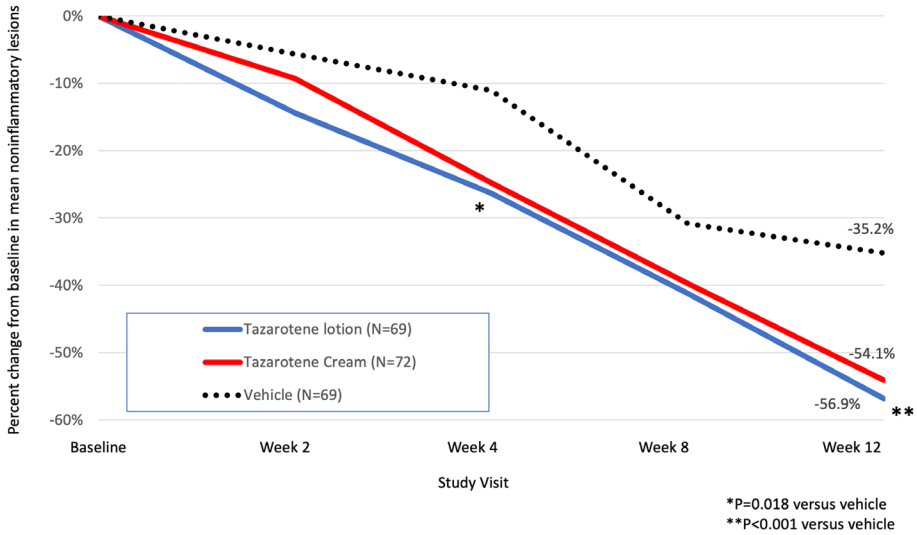


FIGURE 3. Percent change in mean noninflammatory lesions from baseline to week 12 (ITT population): Comparison of Tazarotene 0.045% lotion, Tazarotene 0.1% cream, and vehicle.



Treatment Success

Treatment success was defined as at least a 2-grade improvement in global severity by EGSS and 'clear' or 'almost clear'. At week 12, 18.8% of patients achieved treatment success with tazarotene 0.045% lotion compared to 10.1% with combined vehicle (*P*=.148; Figure 4). Tazarotene 0.045% lotion showed a greater treatment success at week 12 when compared with tazarotene 0.1% cream (16.7%), but differences were not significant.

Subject Self-Assessment (SSA)

Tazarotene 0.045% lotion showed a greater numerical treatment success ('clear' or 'almost clear') at week 12 in terms of SSA when compared with tazarotene 0.1% cream (*P*=.768). Treatment success was achieved in 38.5% of patients, compared with 35.9% and 24.6% (tazarotene 0.01% cream and combined vehicle [*P*=.096], respectively).

FIGURE 4. Treatment success based on Evaluator's Global Severity Scores (ITT population): Comparison of Tazarotene 0.045% lotion, Tazarotene 0.1% cream, and vehicle.

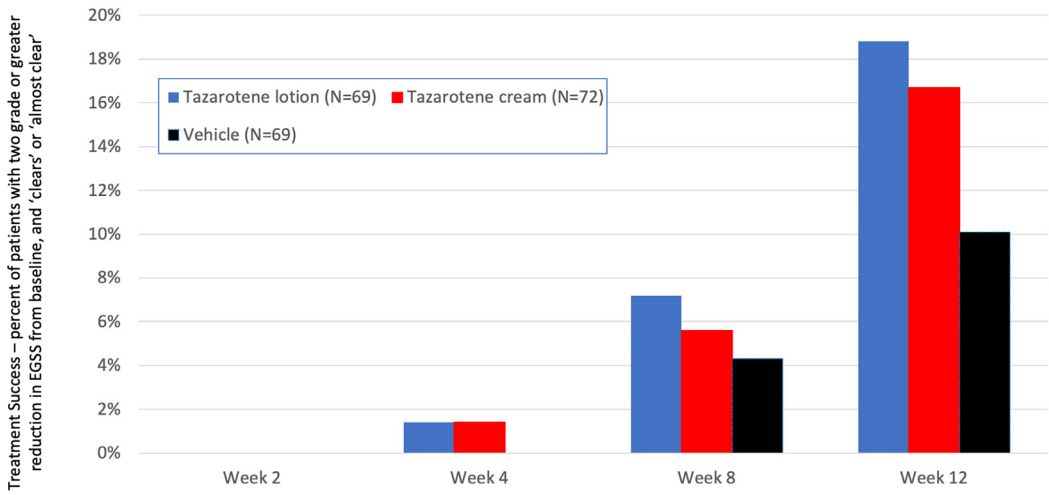
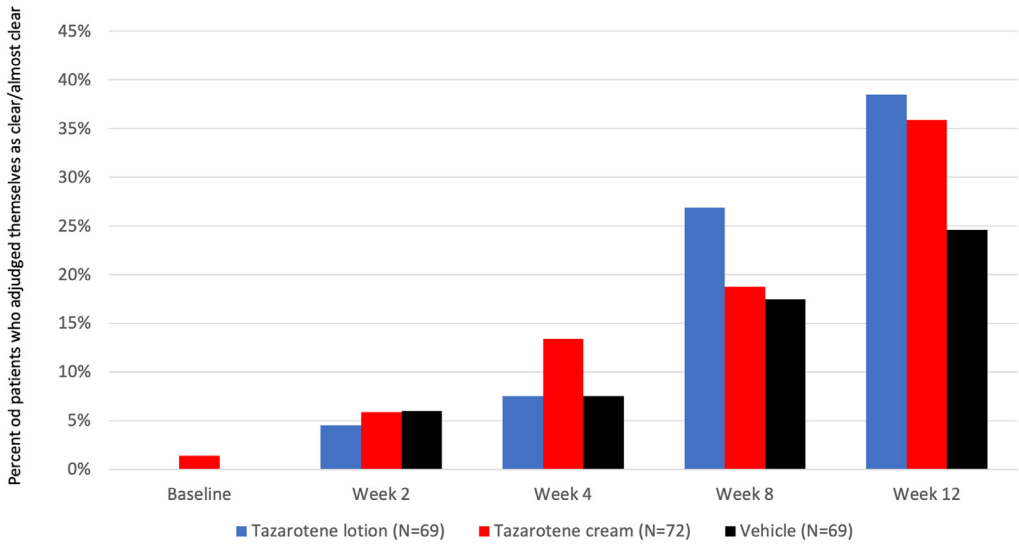


FIGURE 5. Subject Self-Assessment (SSA) at each evaluation (ITT Population 'Clear' or 'Almost Clear' [>=90%]): Comparison of Tazarotene 0.045% lotion, Tazarotene 0.1% cream, and vehicle.



Patient Satisfaction (PSS) and Quality of Life

There were no significant differences in PSS mean scores at week 12 between tazarotene 0.045% lotion and tazarotene 0.1% cream (P=.372) or combined vehicle (P=.242). Overall, patients treated with tazarotene 0.045% lotion assessed their treatment satisfaction higher than tazarotene 0.1% cream (mean score of 7.7 versus 7.4).

There were also no statistically significant differences in the improvement between treatment groups based on the mean Acne-QoL assessments in each of the 4 evaluated domains. Improvements in self-perception, role-emotional, and role-social were similar with tazarotene 0.045% lotion and tazarotene 0.1% cream, and markedly greater than those achieved in the combined vehicle groups. In terms of acne symptoms improvement, the absolute change from baseline with tazarotene 0.045% lotion was again greater than that achieved with the combined vehicle, however tazarotene 0.1% cream only demonstrated an improvement similar to that achieved with vehicle.

Safety

A higher proportion of patients treated with tazarotene 0.1% cream (26.8%) reported treatment-emergent AEs compared with tazarotene 0.045% lotion (14.7%) or combined vehicle (13.4%). TEAEs were mostly mild or moderate and unrelated to study drug (Table 2). Treatment-related AEs were more common with tazarotene 0.1% cream. There were two reports of application site pain (2.9%) with tazarotene 0.045% lotion; compared with three reports with tazarotene 0.1% cream (4.2%).

Cutaneous Safety and Tolerability

Each of the signs and symptoms of cutaneous safety and tolerability (scaling, erythema, hypopigmentation, hyperpigmentation, itching, burning, and stinging) showed improvements from baseline to week 12. There were slight increases in mean scores for scaling, burning and stinging at week 4, consistent with tazarotene's safety profile, but these reduced at subsequent study visits. All mean scores were ≤0.6 (where a score of 1=mild); scores being similar or slightly lower at interim study visits with tazarotene 0.045% lotion compared with tazarotene 0.1% cream, especially in terms of scaling, itching, burning, and stinging at weeks 2 and 4.

TABLE 2.

Treatment-Emergent and Related Adverse Event (AE) Characteristics through Week 12 (Safety population, N=206)

	Tazarotene Lotion (N=68)	Tazarotene Cream (N=71)	Combined Vehicle (N=67)
Patients reporting any TEAE	10 (14.7%)	19 (26.8%)	9 (13.4%)
Patients reporting any SAE	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patients who died	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patients who discontinued due to TEAE	0 (0.0%)	1 (1.4%)	0 (0.0%)
Severity of AEs reported			
Mild	6 (8.8%)	12 (16.9%)	9 (13.4%)
Moderate	2 (2.9%)	7 (9.9%)	0 (0.0%)
Severe	2 (2.9%)	0 (0.0%)	0 (0.0%)
Relationship to study drug			
Related	2 (2.9%)	4 (5.6%)	0 (0.0%)
Unrelated	8 (11.8%)	15 (21.1%)	9 (13.4%)
Treatment Related AEs reported by ≥1% patients			
Application site pain	2 (2.9%)	3 (4.2%)	0.(0.0%)
Application site erythema	0 (0.0%)	1 (1.4%)	0 (0.0%)
Application site exfoliation	0 (0.0%)	1 (1.4%)	0 (0.0%)
Application site dryness	0 (0.0%)	1 (1.4%)	0 (0.0%)
Erythema	0 (0.0%)	1 (1.4%)	0 (0.0%)

DISCUSSION

Despite recommendations to use retinoids as first-line acne treatment,[11,21] they remain underutilized.[22-24]The slow onset of action in the treatment of inflammatory lesions,[25] and the widely recognized irritation potential of these agents have somewhat limited their use. Consequently, several attempts have been made to alleviate these efficacy and tolerability issue using new delivery technology. The clinical benefits observed with tazarotene 0.1% foam,[26,27] 0.1% cream,[28] and 0.1% gel[29] appear similar, although no direct comparisons exist in the literature.

The rationale behind the development of a novel lotion formulation of tazarotene stemmed from its proven efficacy in acne and the fact that a lotion formulation is the easiest and most acceptable formulation for application to the face; but also the potential for tazarotene cream (and to a lesser extent foam[26]) to cause concentration dependent skin irritation and dryness, which had been shown to be both bothersome in many patients and may impact adherence and successful acne treatment. For example, pooled results from several clinical studies showed that 14% of patients treated with tazarotene 0.1% foam reported irritation and 7% dryness, compared with only 1% using vehicle.[30]

Tazarotene 0.045% lotion is a novel topical treatment for moderate-to-severe acne leveraging polymeric emulsion technology with the aim to improve both efficacy and tolerability. The polymeric emulsion technology affords more uniform deposition of active, excipients and moisturizers onto the skin surface. This phase 2 study is the first to compare a novel formulation of tazarotene 0.045% lotion with commercially available tazarotene 0.1% cream in patients with moderate-to-severe acne. Tazarotene 0.045% lotion was significantly superior to vehicle in reducing both inflammatory and noninflammatory lesions; and numerically more effective than tazarotene 0.1% cream despite the two-fold difference in tazarotene concentration. Median reductions in inflammatory and noninflammatory lesions with tazarotene 0.045% lotion were 72% and 63%, respectively, at 12 weeks.

The only treatment-related AE with tazarotene 0.045% lotion observed was application site pain (2.9%). Skin reactions (such as scaling, burning, and stinging) were infrequent, had onsets early in the treatment period, were mostly mild and appeared transient. Erythema and itching noted at baseline improved progressively with daily tazarotene 0.045% lotion treatment. Again, these data concur with those in other clinical trials of retinoids where the peak of cutaneous irritation typically occurs within the first 1-2 weeks and subsides.[31]

CONCLUSIONS

Tazarotene 0.045% lotion was developed using a polymeric emulsion technology. In this phase 2 study of patients with moderate-to-severe acne, tazarotene 0.045% lotion was as effective as the higher concentration tazarotene 0.1% cream, with fewer treatment-emergent adverse events.

DISCLOSURES

Drs Tanghetti, Kircik and Green were study investigators. Dr Kircik and Green are advisors to Ortho Dermatologics. Dr Guenin, Pillai, and Ms Harris and Martin are employees of Bausch Health Americas, Inc.

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