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# Supplement

## Managing Acne With Adapalene 0.1% and 0.3% Gels

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# Original Articles



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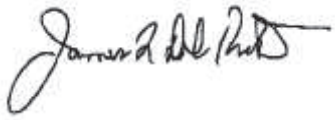
# Introduction

When I was asked to author the introduction to this supplement of the *Journal of Drugs in Dermatology*, I accepted without hesitation. The opportunity to review, evaluate, and discuss new clinical information about treatment of the most common disorder encountered in dermatology practice, acne vulgaris, is one that I could not pass up. Clinical research evaluating the efficacy and safety of topical acne therapies has evolved significantly over the past decade, beyond the conventional determinations of inflammatory, noninflammatory, and total lesion counts, which still remain as important primary and/or secondary efficacy parameters. Well-designed studies of treatments for acne vulgaris now commonly include parameters such as static global assessments, definitions of treatment "success" and "failure," intent-to-treat population analyses, detailed assessments of tolerability profiles, patient satisfaction surveys, and validated quality-of-life (QoL) evaluations, including disease-specific QoL instruments.

As acne vulgaris is a very common chronic dermatologic disorder affecting up to 85% of adolescents, and much attention has been given to researching acne therapy and developing rational guidelines related to its management. Combination therapy is fundamental to the medical management of acne vulgaris. Topical retinoid therapy is well-established as a fundamental component of both initial treatment and maintenance therapy for acne vulgaris, exhibiting both anticomedonal and anti-inflammatory effects. At present, there are 3 topical retinoid compounds available for treatment of acne vulgaris, tretinoin, adapalene, and tazarotene; with various vehicles formulations developed over time to improve skin tolerability and sustain efficacy. This supplement includes 4 articles, which discuss results from clinical trials completed with adapalene 0.1% gel and adapalene 0.3% gel, including comparisons of efficacy and safety compared to a topical tazarotene.

The studies published in this supplement support the efficacy and safety of both adapalene 0.3% gel and adapalene 0.1% gel in the management of acne vulgaris. Importantly, data also support the value of continued application of a topical retinoid in the management of acne vulgaris and the importance of not changing therapy prematurely. I anticipate that you will find the information presented in this supplement to be clinically relevant and useful to both dermatologists and their patients.



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# Efficacy and Tolerability of Adapalene 0.3% Gel Compared to Tazarotene 0.1% Gel in the Treatment of Acne Vulgaris

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## Abstract

Treatment of acne vulgaris can be challenging for both patients and physicians. Topical retinoids are often considered first-line therapy for the treatment of all but the most severe forms of acne. A variety of formulations of topical retinoids, including adapalene and tazarotene, are available but tazarotene 0.1% gel is widely perceived to be the most efficacious. The goal of this study was to evaluate the efficacy and tolerability of a new, higher concentration of adapalene, adapalene 0.3% gel, compared to tazarotene 0.1% gel in the treatment of acne vulgaris. The primary efficacy outcome was the percent reduction in total lesion count at week 12. Subjects 12 to 35 years of age with acne vulgaris (N=172) participated in a 12-week, randomized, evaluator-blinded, noninferiority study of once-daily therapy with adapalene 0.3% gel or tazarotene 0.1% gel. Subjects in each group achieved clinically significant reductions in total lesion counts at week 12 (61% and 57% median reductions for adapalene and tazarotene, respectively); adapalene 0.3% gel was noninferior to tazarotene 0.1% gel (95% confidence interval [CI]: -5.2-9.6). The adapalene arm was also therapeutically similar to the tazarotene arm in terms of the percent reduction in inflammatory and noninflammatory lesion counts at week 12, as well as in the assessments of acne severity and improvement. Mean tolerability scores for erythema, dryness, scaling, and stinging/burning were consistently lower in the adapalene arm compared to patients treated with tazarotene (P<.014 at week 12, Cochran-Mantel-Haenszel [CMH] test). The worst score for any tolerability parameter in the treatment phase in the adapalene arm was less than 1 (mild). Adapalene was also associated with a lower incidence of treatment-related adverse events when compared to tazarotene (3.5% versus 14%, respectively). Once daily therapy with adapalene 0.3% gel provided similar efficacy (noninferior) to tazarotene 0.1% gel in the treatment of acne vulgaris, but demonstrated a superior tolerability profile.

## Introduction

Acne vulgaris is a chronic skin disease affecting approximately 80% of young adults and adolescents.[1-4] Management of acne can be challenging due to the variability in a patient's response to treatment and the need for long-term therapy. If not appropriately treated, acne can have a significant negative impact on a patient's quality of life.[5] A variety of topical and systemic therapies are available for the treatment of acne, including retinoids, antibiotics, benzoyl peroxide, and hormone therapy. Topical retinoids, such as tretinoin, adapalene, and tazarotene, are an integral part of acne therapy and considered appropriate first-line therapy, either alone or in combination with antimicrobials, for all but the most severe cases of acne.[5,6]

Adapalene is a synthetic naphthoic acid derivative with retinoid activity that has been shown to reverse the abnormal follicular desquamation and inflammatory responses involved in the pathogenesis of acne as observed with other topical retinoids such as tretinoin and tazarotene.[7-10]

Tazarotene is a synthetic acetylenic retinoid that penetrates the skin and is converted to an active metabolite, tazarotenic acid. Like adapalene, tazarotene is effective in reducing acne lesions,[11-14] however the tolerability profile of the 0.1% gel formulation may decrease its routine use for mild to moderate acne. The tolerability of a topical retinoid is of importance as it can significantly influence a patient's adherence to an acne treatment regimen, including combination therapy and long-term topical therapy for acne.[5,15]

To address the need for an efficacious, well-tolerated treatment, a higher concentration of adapalene (0.3%) in a gel formulation has been developed. A comparison of adapalene 0.3% gel to adapalene 0.1% gel, and to the vehicle in a recent pivotal trial demonstrated superior clinical responses for the 0.3% concentration, while maintaining a low incidence of severe skin irritation comparable to the 0.1% gel formulation.[16] The objective of the current study was to compare the efficacy and safety of adapalene 0.3% gel to that of tazarotene 0.1% gel, which is perceived to be the most efficacious retinoid for patients with acne vulgaris.

## Methods

The study was a phase 3b, randomized, controlled, evaluator-blinded, parallel-arm, multicenter trial designed to evaluate the efficacy and tolerability of adapalene 0.3% gel (Differin® 0.3% gel) compared to tazarotene 0.1% gel (Tazorac® 0.1% gel), each applied daily for 12 weeks for the treatment of acne vulgaris.

The target enrollment was 160 male and female subjects between 12 and 35 years of age with 15 to 100 noninflammatory lesions, at least 20 inflammatory lesions, and not more than 3 nodules on the face. Exclusion criteria included subjects with severe nodulocystic acne, female subjects that

**Table 1.** Subject baseline demographics (n=86 for both treatment arms; n (%) unless otherwise stated).

| | Adapalene 0.3% gel: n (%) | Tazarotene 0.1% gel: n (%) |
|---|---|---|
| **Gender** | | |
| Male | 52 (60.5) | 45 (52.3) |
| Female | 34 (39.5) | 41 (47.7) |
| **Race** | | |
| Caucasian | 53 (61.6) | 51 (59.3) |
| Black | 10 (11.6) | 9 (10.5) |
| Asian | 2 (2.3) | 3 (3.5) |
| Hispanic | 19 (22.1) | 22 (25.6) |
| Other | 2 (2.3) | 1 (1.2) |
| **Mean age (±SD)** | 18.1 (±5.9) | 17.8 (±4.8) |
| **Baseline lesion counts (range)** | | |
| Inflammatory lesions median | 28 (20-81) | 27 (20-50) |
| Noninflammatory lesions median | 39 (15-106) | 41 (15-95) |
| Total lesions median | 69 (35-140) | 71 (35-118) |
| **Baseline disease severity** | | |
| Mild | 16 (18.6) | 16 (18.6) |
| Moderate | 62 (72.1) | 64 (74.4) |
| Severe | 8 (9.3) | 6 (7.0) |

were pregnant, nursing, or planning a pregnancy during the study, subjects with facial hair that would impair study assessments, or subjects with other dermatologic conditions requiring interfering treatment. The specific washout period was 2 weeks for topical acne treatments, 4 weeks for systemic antibiotics, and the required washout period for systemic acne therapies (ie, isotretinoin) was 6 months.

Subjects were randomized in a 1:1 ratio to receive a once-daily evening application of either adapalene 0.3% gel or tazarotene 0.1% gel. The randomization schedule remained blinded from those involved in the clinical conduct of the study. The integrity of the blinding was ensured by requiring a third party, other than the investigator/evaluator, to dispense the medication. Subjects were provided with a moisturizer (Cetaphil® Daily Facial Moisturizer, SPF 15) to use as needed

**Figure 1.** Patient population from enrollment to completion in study.

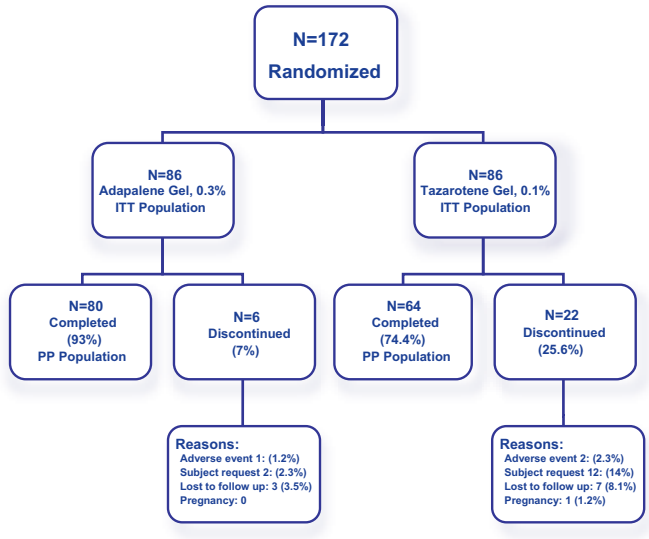
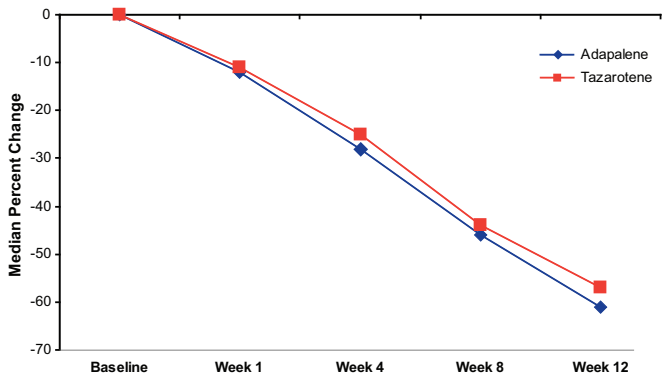



**Figure 2.** Median percent change from baseline in total lesion counts through week 12 in the adapalene 0.3% gel (n=86) and tazarotene 0.1% gel (n=86) treatment arms (ITT-LOCF).




for the symptomatic relief of skin dryness or irritation as well as a mild cleanser (Cetaphil® Gentle Skin Cleanser). Evaluations were performed at baseline and weeks 1, 4, 8, and 12.

This study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and Good Clinical Practice, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, and in compliance with local regulatory requirements. This study was reviewed and approved by an institutional review board. All patients provided a written informed consent prior to entering the study.

### *Efficacy*

The percent of change in total lesion counts from baseline at week 12 was the primary efficacy outcome. Inflammatory and noninflammatory lesions were counted and added together to form the total lesion count. Secondary outcomes included: percent of change from baseline in inflammatory

**Figure 3.** Median percent reduction from baseline in inflammatory lesion counts through week 12 in the adapalene 0.3% gel (n=86) and tazarotene 0.1% gel (n=86) treatment arms (ITT-LOCF).

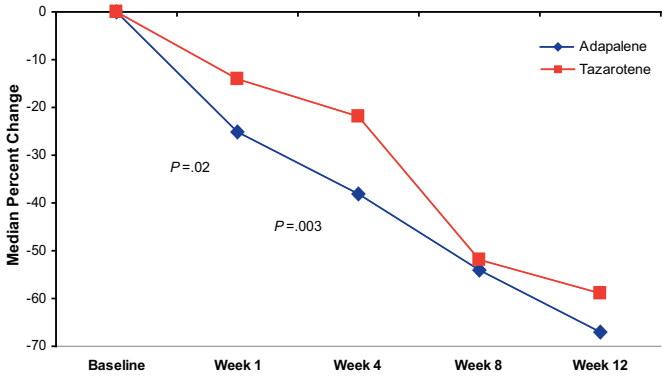



**Figure 4.** Median percent reduction from baseline in noninflammatory lesion counts through week 12 in the adapalene 0.3% gel (n=86) and tazarotene 0.1% gel (n=86) treatment arms (ITT-LOCF).

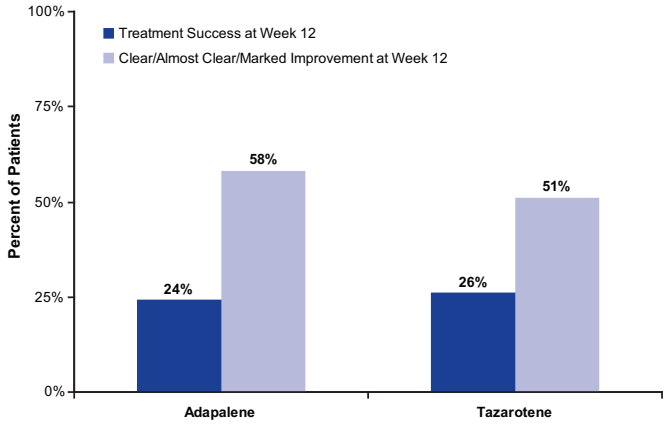
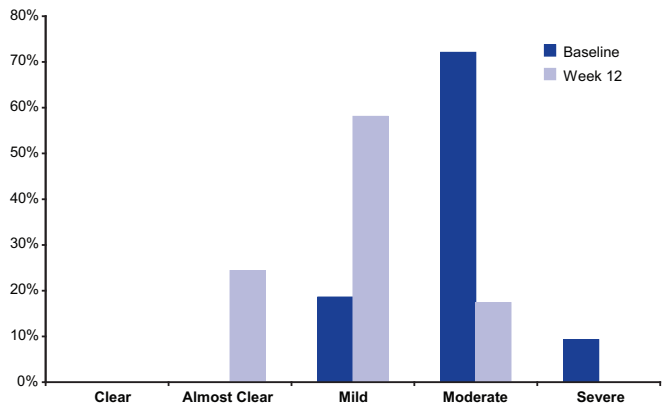
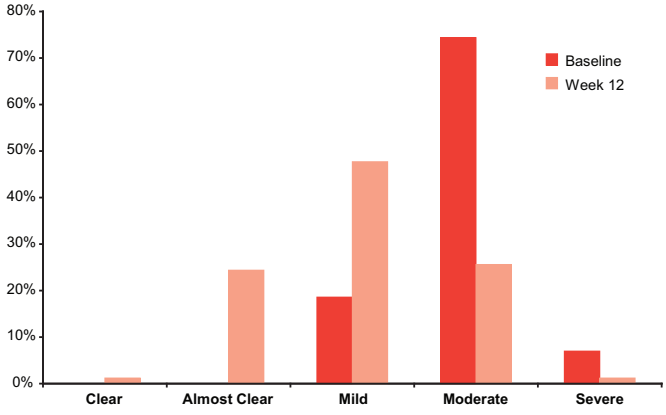



**Figure 5.** Distribution of acne severity at baseline and week 12 for adapalene **(left)** and tazarotene **(right)** (n=86 for each treatment arm).




lesion counts at each visit, percent of change from baseline in noninflammatory lesion counts at each visit, global severity assessment at full scale at each visit, global severity assessment on a dichotomous scale (success or failure) at each visit, and investigator global assessment of improvement at week 12.

The global severity assessment of acne at baseline and each visit was a static assessment based on a scale of 0 (clear) to 5 (very severe). Success on the dichotomous scale was defined as a score of either 0 (clear) or 1 (almost clear). Global assessment of improvement was performed by comparing the patient's acne at week 12 (or early termination) to baseline using a scale of 0 (clear) to 6 (worse).

### *Tolerability and Safety*

Tolerability, as measured by the degree of erythema, scaling, dryness, and stinging/burning, was evaluated at each visit based on a scale of 0 (none) to 3 (severe). All adverse events and serious adverse events were monitored and reported. Mean scores at each treatment visit and worst score (worst observation recorded for a subject during the postbaseline period) were recorded.

### *Subject Satisfaction Questionnaire*

At week 12 or early termination, each subject was asked to complete a brief questionnaire to assess subject satisfaction with the study treatment.

### *Statistical Analyses*

All efficacy variables were to be analyzed at each postbaseline visit using the Cochran-Mantel-Haenszel (CMH) test controlling for analysis center. Due to the skewed distributions, the percent reduction in lesion counts was estimated using medians. The 95% confidence interval (CI) of the median difference in total lesion counts at week 12 was calculated using a nonparametric method equivalent to the Wilcoxon rank sum test. Noninferiority was established if the 95% CI excluded a 15% inferiority margin. Three study populations were analyzed. The safety population was defined as all patients randomized and treated at least once. The intent-to-treat (ITT) population included all randomized subjects who were dispensed study medication. The per-protocol (PP)

**Table 2.** Subject satisfaction survey.

| | Adapalene 0.3% gel: n (%) | Tazarotene 0.1% gel: n (%) | *P* value* |
|---|---|---|---|
| **Are you satisfied with the treatment?** | | | |
| Very satisfied | 33 (39.8) | 28 (35.9) | .082 |
| Satisfied | 38 (45.8) | 26 (33.3) | |
| Somewhat satisfied | 12 (14.5) | 14 (17.9) | |
| Not satisfied | 0 (0) | 10 (12.8) | |
| **How bothered were you by the treatment side effects?** | | | |
| Not bothered at all | 46 (55.4) | 19 (24.4) | <.001 |
| Bothered somewhat | 34 (41.0) | 38 (48.7) | |
| Bothered | 3 (3.6) | 11 (14.1) | |
| Bothered a great deal | 0 (0) | 10 (12.8) | |
| **How do you feel since the treatment started?** | | | |
| A lot better | 41 (49.4) | 36 (46.2) | .321 |
| A little better | 32 (38.6) | 27 (34.6) | |
| No change | 10 (12.0) | 12 (15.4) | |
| Worse | 0 (0) | 3 (3.8) | |
| **How satisfied are you with the cosmetic properties of the treatment?** | | | |
| Very satisfied | 38 (45.8) | 18 (23.1) | <.001 |
| Satisfied | 39 (47.0) | 38 (48.7) | |
| Somewhat satisfied | 6 (7.2) | 19 (24.4) | |
| Not satisfied | 0 (0) | 3 (3.8) | |
| **How satisfied are you with the effectiveness of the treatment?** | | | |
| Very satisfied | 23 (27.7) | 24 (30.8) | .614 |
| Satisfied | 34 (41.0) | 28 (35.9) | |
| Somewhat satisfied | 26 (31.3) | 18 (23.1) | |
| Not satisfied | 0 (0) | 8 (10.3) | |

**P* value for between treatment differences, by Cochran-Mantel-Haenszel test based on ridit scores stratified by psuedo-center.

population included all randomized subjects without any major protocol deviations. This analysis was conducted for both the ITT and PP populations. The last observation carried forward (LOCF) method was used to impute missing values. Tolerability signs and symptoms were analyzed for worst response using the CMH statistic and adverse events were summarized using descriptive statistics. SAS® software version 8.2 (SAS Institute, Cary, NC) was used for all data analyses and tabulations, unless otherwise stated.

**Figure 6.** Subject photos at baseline **(a and c)** and week 12 **(b and d)** for adapalene 0.3% gel.

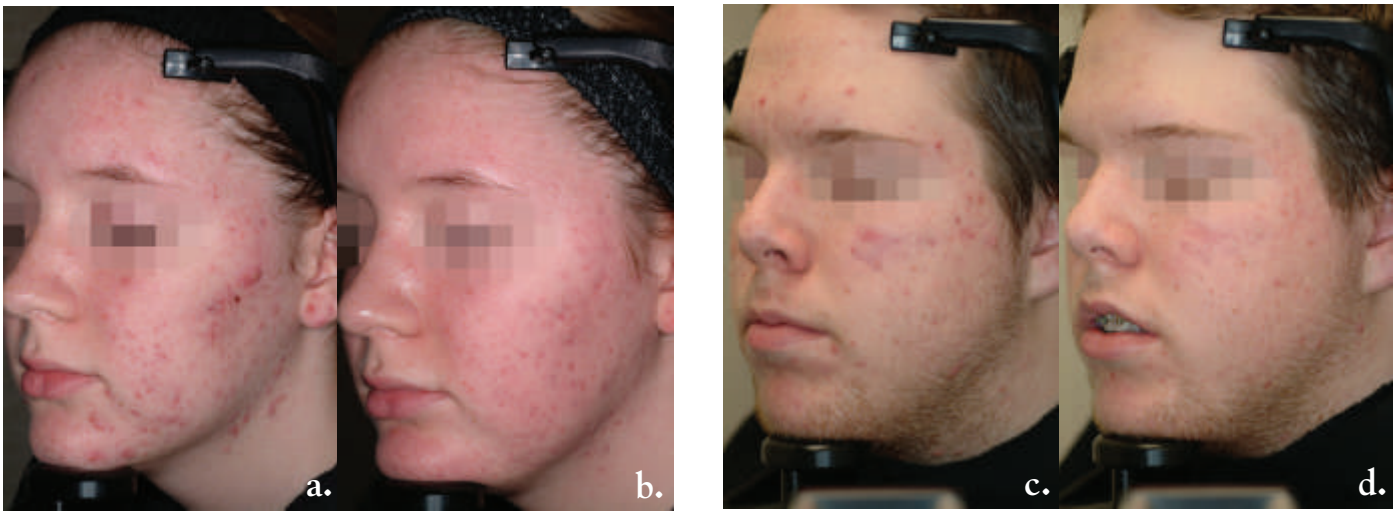
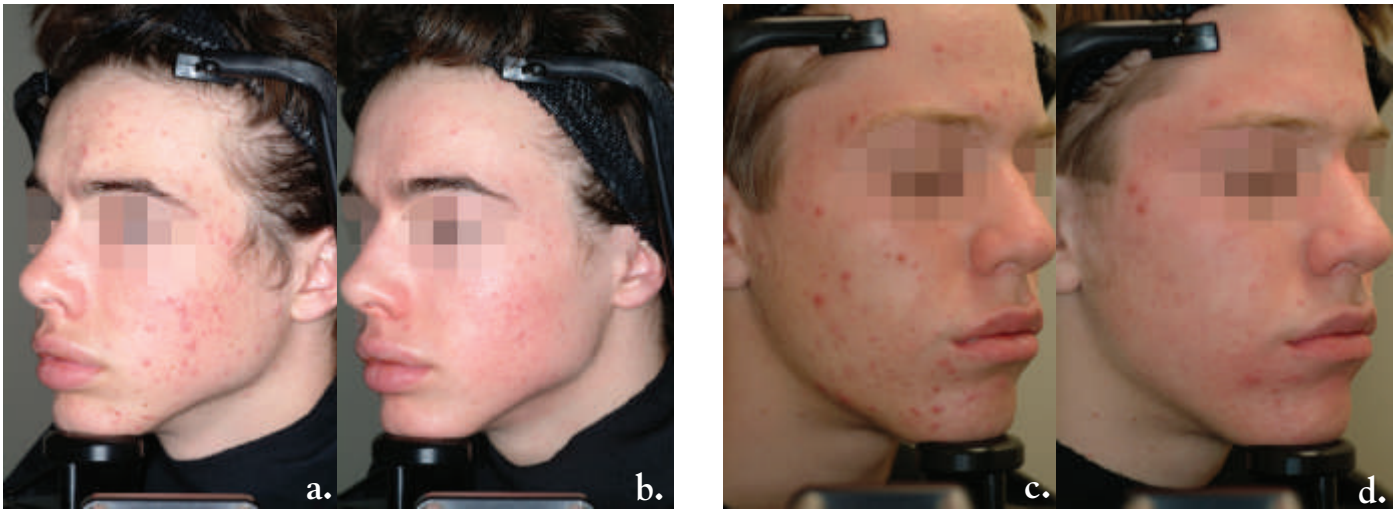



**Figure 7.** Subject photos at baseline **(a and c)** and week 12 **(b and d)** for tazarotene 0.1% gel.



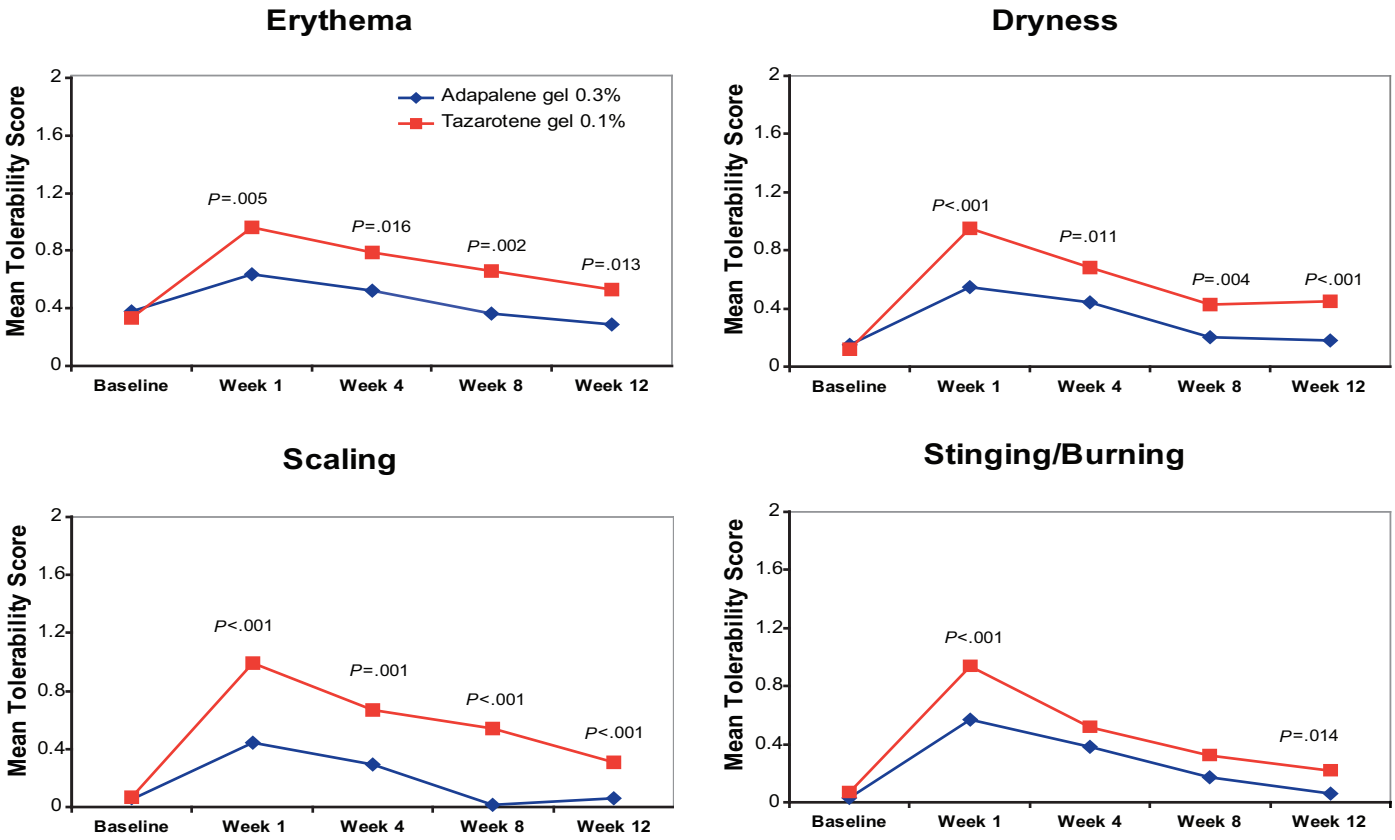

## Results

A total of 172 subjects was enrolled and randomized to the adapalene (n=86) or tazarotene (n=86) treatment arms. A total of 8 investigative sites participated. The safety population (all subjects who took at least 1 dose of study medication) had 172 subjects and the PP population had 141 subjects. More subjects discontinued the study from the tazarotene arm compared to the adapalene arm (25.6% versus 7.0%, respectively). Reasons given for not completing the study included adverse events (adapalene, 1.2%; tazarotene, 2.3%), subject request (adapalene, 2.3%; tazarotene, 14.0%), and loss to follow-up (adapalene, 3.5%; tazarotene, 8.1%). One subject in the tazarotene arm discontinued due to pregnancy (Figure 1). The average age of subjects was 18 years. A detailed description of subject demographics is given in Table 1. The treatment arms had comparable numbers of inflammatory, noninflammatory, and total lesion counts at baseline, and the majority of subjects presented with moderate acne (72.1% in the adapalene arm and 74.4% in the tazarotene arm).

The primary efficacy outcome was the percent change from baseline in total lesion counts. Both treatment arms had therapeutically similar efficacy results and showed improvements in lesion counts from baseline to week 12. Adapalene 0.3% gel was shown to be noninferior within a 15% margin to tazarotene 0.1% gel with median reductions in total lesion counts by week 12 of 61% and 57%, respectively ($P$=.515; 95% CI: -5.2-9.6) (Figure 2).

The adapalene and tazarotene arms also had similar percent reductions in inflammatory lesions (67% versus 59%, respectively; $P$=.066) and noninflammatory lesions (55% in each arm; $P$=.307) at week 12 (Figures 3 and 4). However, at weeks 1 and 4, adapalene-treated subjects had significantly greater reductions in inflammatory lesions ($P$=.020 and $P$=.003, respectively) whereas tazarotene-treated subjects had significantly greater reductions in noninflammatory lesions ($P$=.047 and $P$=.003, respectively). The tazarotene arm had a statistically significantly greater noninflammatory lesion reduction at weeks 1 and 4. The adapalene arm had a

**Figure 8.** Mean tolerability scores (scale of 0 [none] to 3 [moderate]) for erythema, dryness, scaling, and stinging/burning. Mean scores are for all subjects treated (safety population).




statistically significantly greater inflammatory lesion reduction at weeks 1 and 4.

Results of the dichotomous global severity assessment and the global assessment of improvement from baseline also showed comparable efficacy between the 2 study treatments. By week 12, 24.4% of subjects in the adapalene arm had treatment successes compared with 25.6% in the tazarotene arm ($P$=.790). The results for the worst case analysis, in which all missing data were considered treatment failures, were identical to the LOCF analysis at week 12 ($P$=.790). Static global assessments revealed a shift in severity distributions for both treatments (Figure 5). In the adapalene arm, 81.4% of subjects had moderate or severe acne at baseline which was reduced to 17.4% of subjects with moderate acne at week 12. In the tazarotene arm, 81.4% of subjects had moderate or severe acne at baseline which was reduced to 25.6% of subjects with moderate acne and 1.2% of subjects with severe acne at week 12. Acne improvement from baseline was comparable in each group. In the adapalene arm, 58% of patients had marked improvement or were almost cleared of their acne at week 12 compared to 51% of patients in the tazarotene arm. Photos of representative subjects at baseline and week 12 for each treatment arm are shown in Figures 6 and 7.

Cutaneous tolerability scores were markedly better (lower) in the adapalene arm compared to the tazarotene arm for all parameters assessed. The mean tolerability scores for each parameter generally peaked at week 1 and then resolved over the remainder of the study for both arms; however, the scores were lower (statistically significant) in the adapalene arm at most time points evaluated ($P$<0.05) (Figure 8) with the exception of stinging and burning which showed statistically significant differences in favor of adapalene at weeks 1 and 12. Worst postbaseline severity tolerability scores also favored adapalene with statistically significant lower mean scores for adapalene-treated versus tazarotene-treated subjects for erythema (0.84 versus 1.15, $P$=.005), dryness (0.72 versus 1.07, $P$<.001), scaling (0.59 versus 1.17, $P$<.001), and stinging/burning (0.75 versus 1.1, $P$=.001).

The proportion of subjects reporting adverse events was 31% in the adapalene arm and 42% in the tazarotene arm. Fewer subjects in the adapalene arm, compared to the tazarotene arm, experienced adverse events that were "possibly," "probably," or "definitely" related to study treatment compared to the tazarotene arm (3 [3.5%] subjects in the adapalene arm compared to 12 [14.0%] subjects in the tazarotene arm). The most common treatment-related adverse event for the patients receiving adapalene was skin irritation (2.3%) while the most common treatment-related adverse events for patients receiving tazarotene were skin discomfort (5.8%), skin irritation (3.5%), dry skin (3.5%), and pruritus (2.3%). Moreover, 5.8% of all tazarotene subjects experienced treat-

ment-related adverse events of severe intensity compared to only 1.2% among all adapalene subjects.

On the last visit, each subject was asked to complete a 5-question survey regarding their satisfaction with the treatment. Overall, 85.6% of subjects were satisfied or very satisfied with adapalene 0.3% gel compared to 69.2% of subjects treated with tazarotene 0.1% gel. No subject reported being not satisfied with adapalene, while 12.8% of subjects reported being not satisfied with tazarotene. Significantly more patients were not bothered by side effects from adapalene (55.4%) than from tazarotene (24.4%) ($P<.001$). Significantly more subjects were satisfied or very satisfied with the cosmetic properties of adapalene (92.8%) than subjects who were satisfied or very satisfied with the cosmetic properties of tazarotene (71.8%, $P<.001$). Satisfaction with treatment effectiveness and "feeling better" was similar between the 2 treatment groups (Table 2).

## Discussion

Adapalene and tazarotene are topical retinoids indicated for the treatment of acne vulgaris. Both retinoids are available in gel and cream formulations at this time, the highest concentration available for either product was 0.1%. Tazarotene 0.1% gel is perceived by US dermatologists to be the most effective topical retinoid currently available and a study by Webster et al demonstrated a greater percent reduction in total lesion counts at week 12 for tazarotene 0.1% gel compared to adapalene 0.1% gel.[17,18] The purpose of this study was to evaluate the efficacy and safety of a new, higher concentration (0.3%) of adapalene gel compared to tazarotene 0.1% gel for the treatment of acne. Results from the present study demonstrate that adapalene 0.3% gel has similar efficacy but better safety and tolerability compared to tazarotene 0.1% gel.

After 12 weeks of treatment, subjects in the adapalene and tazarotene arms had similar median percent reductions in total lesion counts. Comparable median percent reductions in inflammatory lesions and noninflammatory lesions were also observed at week 12. It is interesting that at early time points in the study, noninflammatory lesions decreased to a greater extent in the tazarotene arm whereas inflammatory lesions decreased to a greater extent in the adapalene arm. This observation is consistent with results from a previous study comparing adapalene 0.3% gel to adapalene 0.1% gel, in which the 0.3% gel concentration produced a greater percent reduction in inflammatory lesions relative to noninflammatory lesions.[19] The authors speculated that the greater impact of adapalene on inflammatory lesions compared to noninflammatory lesions may be connected to the anti-inflammatory activity observed in *in vitro* and animal models tested with adapalene.[20] In previous comparisons of adapalene and tazarotene, differential effects of the 2 treatments on inflammatory and noninflammatory lesions were also noted. Depending upon the progression of acne severity in individual patients, having both the 0.1% and 0.3% concentrations of adapalene available may provide physicians with more treatment options for patients with acne.

Results of the global assessments of acne severity and improvement also showed comparable efficacy between adapalene 0.3% gel and tazarotene 0.1% gel. Similar proportions of subjects had treatment success at 12 weeks and there was no difference between the treatment arms in subjects who had at least marked improvement in their acne relative to baseline. The success rate observed in adapalene-treated subjects is similar to that observed in a previous study of adapalene 0.3% gel further confirming the clinical benefit of this higher concentration.[18]

Tolerability is important for topical retinoids, particularly when they are used in combination therapy or in long-term maintenance therapy.[5,21,22] Results from the present study are encouraging in that the higher concentration of adapalene (0.3%) has a better tolerability profile compare to tazarotene 0.1% gel. Mean cutaneous tolerability scores at each time point were lower in the adapalene arm compared to the tazarotene arm for all parameters assessed (erythema, dryness, scaling, and stinging/burning), especially at week 1, when tolerability scores peaked in each arm. The adapalene arm also had significantly lower postbaseline scores for each of the 4 assessments, with all mean scores below 1 (mild). Likewise, adverse events were experienced to a lesser extent in the adapalene arm (31% of subjects) compared to the tazarotene arm (42% of subjects). Treatment-related adverse events were infrequent in this study, however the incidence was higher in the tazarotene arm (14%) than the adapalene arm (3.5%).

## Conclusion

The results of this study help establish adapalene 0.3% gel as an effective and well-tolerated alternative to tazarotene 0.1% gel for the treatment of acne. The availability of 2 concentrations of adapalene may provide physicians with greater flexibility in addressing the efficacy and tolerability needs of individual patients and will possibly enable greater overall treatment success due to better treatment adherence.

## Disclosure

Stephanie Arsonnaud and Pascale Soto are employees of Galderma Research & Development. None of the authors have a financial interest in the company.

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# Is Switching Retinoids a Sound Strategy for the Treatment of Acne Vulgaris?

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## Abstract

Topical retinoids, such as adapalene gel and tazarotene cream, are considered first-line therapy for the treatment of acne vulgaris. Dermatologists often initiate adapalene gel treatment first, due to its good tolerability, followed by a switch to tazarotene cream in an effort to improve or hasten efficacy outcomes. The goal of this study was to compare the efficacy and safety of 2 daily regimens for the treatment of acne: adapalene 0.1% gel for 12 weeks and adapalene 0.1% gel for 6 weeks followed by tazarotene 0.1% cream for 6 weeks. The primary efficacy outcome was the percent of reduction in total lesion counts posttreatment. Subjects ages 12 to 35 years with acne vulgaris were selected to participate in a 12-week, randomized, evaluator-blind study of once-daily therapy with adapalene 0.1% gel (n=101) or "switch therapy," adapalene 0.1% gel followed by tazarotene 0.1% cream (n=100). Adapalene-treated subjects achieved similar percent reductions in total lesion counts at week 12 compared to subjects receiving switch therapy, demonstrating the noninferiority of adapalene gel treatment (median difference: -3.57%; lower confidence limit [LCL]: -11.25). Adapalene gel was associated with fewer reports of cutaneous irritation, particularly for scaling and stinging/burning, and fewer treatment-related adverse events compared to switch therapy. The results of this study indicate that daily therapy with adapalene 0.1% gel for 12 weeks was noninferior to switch therapy.

## Introduction

Acne vulgaris is a chronic skin disease affecting approximately 80% of young adults and adolescents.[1] The management of acne can be challenging due to the variability in response to treatment and the need for long-term therapy.[2,3] If not appropriately treated, acne may cause serious physical and emotional scarring and can significantly impact the quality of life of those affected by the disease.[4-8]

The Global Alliance to Improve Outcomes in Acne published practice guidelines for the treatment of acne in 2005.[4] According to these guidelines, topical retinoids, either alone or in combination with other medications, should be considered first-line therapies for acne. Guidelines from the American Academy of Dermatology (AAD) also emphasize the strong level of evidence for the use of topical retinoids in acne management.[9] Adapalene gel and tazarotene cream are topical retinoids that have been an integral part of topical acne treatment strategies for many years.[10-12] Efficacy profiles for adapalene gel and tazarotene cream are similar, however adapalene gel is generally associated with better cutaneous tolerability.[2,10,13,14]

Many physicians initiate retinoid therapy with adapalene gel because of its favorable tolerability profile; however, in many cases, patients are switched to a retinoid perceived to be more efficacious at follow-up visits. Reasons given for the switch in retinoids typically involve impatience on the part of patients for the treatment to produce visible results quickly. The physicians reported that by switching treatments patients have a renewed hope for acne clearance. Improvement in the latter half of the treatment course may be due to the new medication or simply a cumulative effect from several weeks of retinoid therapy.

In order to test the theory that switching retinoid therapy improves outcomes, a randomized multicenter, 3-arm study was designed to analyze a switch therapy (6 weeks of adapalene gel followed by 6 weeks of tazarotene cream) to compare 12 weeks of consistent therapy of adapalene gel or tazarotene cream. Endpoints for the switch arm included evaluating effectiveness in reducing total acne lesion counts at week 12 and cutaneous tolerability over the course of the 3 different treatment regimens. Subjects were randomized to 1 of 3 treatment arms. The results of 2 of these arms, the adapalene and switch arms, were compiled and then compared for efficacy and tolerability of treatment.

## Methods

The study was a phase 4, randomized, controlled, evaluator-blind, parallel-arm, multicenter trial designed to evaluate and compare the efficacy and safety of 2 acne regimens: adapalene 0.1% gel daily for 12 weeks (adapalene arm) and adapalene 0.1% gel daily for 6 weeks followed by tazarotene 0.1% cream daily for 6 weeks (switch arm). The target enrollment was 100 male or female subjects per treatment arm. Eligible subjects were between 12 and 35 years of age, with 15 to 100 noninflammatory lesions, at least 20 inflammatory lesions, and no more than 3 nodules. Exclusion criteria included subjects with severe nodulocystic acne; female subjects who were pregnant, nursing, or planning a pregnancy during the study; subjects with facial hair that would impair study assessments; subjects with washout periods less than 4 weeks for topical acne treatments or less than 6 months for systemic therapy; or subjects with other dermatologic conditions re-

**Table 1.** Subject demographics and baseline characteristics of the intent-to-treat population (adapalene arm: n=101; switch arm: n=100).

| | Adapalene 0.1% gel: n (%) | Switch*: n (%) |
|---|---|---|
| **Mean age (years)** | 18.5 | 19.4 |
| **Gender** | | |
| Male | 64 (63) | 55 (55) |
| Female | 37 (37) | 45 (45) |
| **Race** | | |
| Caucasian | 65 (64) | 64 (64) |
| Black | 16 (16) | 23 (23) |
| Asian | 3 (3) | 2 (2) |
| American Indian or Alaska Native | 0 (0) | 0 (0) |
| Hispanic or Latino | 6 (6) | 8 (8) |
| Native Hawaiian or Pacific Islander | 2 (2) | 0 (0) |
| Other or Mixed | 9 (9) | 3 (3) |
| **Fitzpatrick skin type** | | |
| I | 4 (4) | 3 (3) |
| II | 23 (23) | 16 (16) |
| III | 39 (39) | 40 (40) |
| IV | 16 (16) | 21 (21) |
| V | 11 (11) | 11 (11) |
| VI | 8 (8) | 9 (9) |

*Switch=12 week daily therapy with adapalene 0.1% gel for the first 6 weeks followed by a switch to tazarotene 0.1% cream for the remaining 6 weeks.

quiring interfering treatment. Subjects were randomized to 1 of 2 treatment arms and evaluations were performed at weeks 0 (baseline), 2, 6, 8, and 12.

### *Efficacy*

The primary efficacy outcome was measured by the percent of change in total lesion counts from baseline to week 12. Inflammatory and noninflammatory lesions were counted and added together to form the total lesion count. Secondary outcomes included: percent of change from baseline in total lesion counts at week 6, percent of change from baseline in inflammatory lesion counts at weeks 6 and 12, percent of change from baseline in noninflammatory lesion counts at weeks 6 and 12, global severity assessment at weeks 6 and 12, global severity assessment on a dichotomous scale (success or failure) at weeks 6 and 12, and global assessment of improvement from baseline at week 12. The global severity assessment of acne at baseline and at each postbaseline visit was a static assessment based on a scale of 0 (clear) to 5 (very severe). The evaluator was not to refer to baseline or other previous visits when evaluating the subject's facial acne. Success on the dichotomous scale was defined as a score of either 0 (clear) or 1 (almost clear). Global assessment of improvement was performed by comparing facial skin condition at week 12 (or early termination) to baseline on a scale of 0 (clear) to 6 (worse).

### *Tolerability and Safety*

Cutaneous tolerability, as measured by the degree of erythema, scaling, dryness, and stinging/burning was evaluated at each visit based on a scale of 0 (none) to 3 (severe). All adverse events were monitored and reported without omitting any requested and known information. Descriptions of adverse events included the date of onset, date the adverse event ended, severity of the adverse event, outcome, and whether any intervening medications were prescribed. All reported adverse events were summarized by the number of subjects reporting adverse events, system organ class, preferred term, severity, seriousness, and relationship to study medication.

### *Statistical Analyses*

Ninety-five percent confidence intervals (CIs) were computed for the primary and secondary analyses for each of the treatment pairs to test for noninferiority and superiority. Noninferiority was established if the lower confidence limit (LCL) of the 95% CI was between 0% and -15% and superiority was established if the LCL of the 95% CI was greater than 0. These analyses were conducted for both the intent-to-treat (ITT) and per-protocol (PP) populations.

Due to the non-normal distribution of the primary efficacy results, the Cochran-Mantel-Haenszel (CMH) statistic (stratified on analysis center after ridit transformation) was used. For the global assessment of acne severity, noninferiority was established if the LCL of the 1-sided 97.5% CI for the difference in success rates was between 0% and 15% using Wald's confidence interval with Yates' continuity correction.

The clinical study was conducted under a common protocol for each investigational site with the intention of pooling the data for analysis. The consistency of treatment response was investigated across the analysis centers to identify possible treatment by center interactions at an alpha level of .10. A sensitivity analysis (excluding analysis center(s) with extreme efficacy results) was performed to determine the robustness of the treatment effect.

**Table 2.** Summary of adverse events by seriousness, severity, and relationship to study medication (adapalene arm: n=98; switch arm: n=100).

| | Adapalene 0.1% gel: n (%) | Switch*: n (%) |
|---|---|---|
| **Number of adverse events reported** | 55 | 66 |
| **Subjects reporting adverse events** | 35 (35) | 36 (36) |
| **Serious*** | | |
| No | 52 (95) | 64 (97) |
| Yes | 3 (5) | 2 (3) |
| **Severity*** | | |
| Mild | 29 (55) | 33 (50) |
| Moderate | 21 (40) | 26 (39) |
| Severe | 3 (6) | 7 (11) |
| Not reported† | 2 | 0 |
| **Relationship to Study Medication§** | | |
| Definitely unrelated | 22 (40) | 25 (38) |
| Unlikely | 13 (24) | 10 (15) |
| Possible | 6 (11) | 7 (11) |
| Probably | 3 (5) | 11 (17) |
| Definitely related | 11 (20) | 13 (20) |

*Switch=12 week daily therapy with adapalene 0.1% gel for the first 6 weeks followed by a switch to tazarotene 0.1% cream for the remaining 6 weeks. †Proportion based on number of events. §Pregnancies reported on the serious adverse event case report form did not report severity.

Other efficacy endpoints were summarized using descriptive statistics. For adverse events, the Fisher's exact test was used to compare the proportion of subjects in each treatment arm who reported any adverse event at a significance level of .05.

The last observation carried forward (LOCF) method was used to extrapolate missing lesion counts and global severity data for subjects who prematurely discontinued from the study. SAS® software, version 8.2 (SAS Institute, Cary, NC) was used for all data analyses and tabulations, unless otherwise stated.

The study was conducted in accordance with the World Medical Association's Declaration of Helsinki and its amendments, and Good Clinical Practice guidelines. Protocols were approved by institutional review boards and subjects provided written informed consent prior to the start of the study.

## Results

A total of 201 subjects were enrolled during the period from February 7, 2006 to September 5, 2006 and were randomized to either the adapalene 0.1% gel arm (n=101) or the switch therapy arm (n=100). The safety population (all subjects who took at least 1 dose of study medication) had 198 subjects, the ITT population included randomized subjects for whom medication was dispensed (N=201), and the PP population (all subjects who completed the entire treatment course as described in the protocol) had 170 subjects. More than 90% of subjects in the treatment arms adhered to the assigned treatment regimens, as reported in subject diaries. The average age of subjects was 19 years and the majority of subjects were male (63% in the adapalene gel arm and 55% in the switch arm). A detailed description of subject demographics is provided in Table 1. There were no significant differences between the treatment arms for baseline acne severity as determined by static global severity scoring, total lesion counts, and inflammatory lesion counts; however, the switch arm had more noninflammatory lesions at baseline (mean: 48) compared to the adapalene gel arm (mean: 41), and the mean difference was found statistically significant (*P*=.028).

### *Efficacy*

The primary efficacy outcome was the percent of change from baseline in total lesion counts. The adapalene arm was shown to be noninferior to the switch arm for the percent of change in total lesion counts at week 12 (median difference: -3.57%; LCL: -11.25) (Figure 1). Results from the PP population were similar to the ITT population. The adapalene arm was also shown to be noninferior to the switch arm for secondary efficacy outcomes of percent reduction in total lesion counts at week 6 (median difference: 1.12%; LCL: -5.89), the percent of reduction in inflammatory lesion counts at week 6 (median difference: 6.90%; LCL: -1.94) and week 12 (median difference: 6.79%; LCL: -1.17), and the percent of reduction in noninflammatory lesion counts at week 6 (median difference: -4.72%; LCL: -13.98). For percent reduction in noninflammatory lesion counts at week 12, the adapalene gel arm was not noninferior to the switch arm (median difference: -11.06%; LCL: -20.46); however, superiority testing did not reveal that switch therapy was superior to adapalene gel alone.

A preplanned analysis of the primary endpoint was designed to detect significant treatment effects by investigational site interaction and revealed a single center that contributed outlying data to the percent of change from baseline in total lesion counts (*P*=.037). Exclusion of subjects treated at this site (n=10 in both treatment arms) did not affect the outcome of the primary efficacy results in that the adapalene gel arm was still shown to be noninferior to the switch arm (median difference: -0.64; LCL: -8.37) in the percent of reduction in total lesion counts at week 12. Superiority testing

**Table 3.** Treatment-related* adverse events (adapalene arm: n=98; switch arm: n=100).

| | Adapalene 0.1% gel: n (%) | Switch†: n (%) |
|---|---|---|
| **Number of events reported§** | 20 | 31 |
| **Application site** | | |
| Exfoliation | 4 (4) | 7 (7) |
| Dryness | 4 (4) | 2 (2) |
| Irritation | 6 (6) | 8 (8) |
| Erythema | 1 (1) | 4 (4) |
| Pruritus | 1 (1) | 1 (1) |
| Burn | 1 (1) | 0 |
| Photosensitivity | 0 | 1 (1) |
| Paraesthesia | 0 | 1 (1) |
| Swelling | 0 | 1 (1) |
| **Sunburn** | 1 (1) | 1 (1) |
| **Skin irritation** | 1 (1) | 0 |
| **Burning sensation** | 1 (1) | 1 (1) |
| **Dry lip** | 0 | 1 (1) |

*Related=possibly, probably, or definitely related. †Switch=12 week daily therapy with adapalene 0.1% gel for the first 6 weeks followed by a switch to tazarotene 0.1% cream for the remaining 6 weeks. §Subjects with at least 1 event; subjects may have reported more than 1 event.

under these conditions did not reveal either treatment arm to be superior to the other.

Assessments of acne severity and improvement also were used to evaluate efficacy. On the static global assessment of acne severity, 27% of subjects in the adapalene gel arm and 26% of subjects in the switch arm had treatment success at week 12. Adapalene gel was noninferior on this assessment (median difference: 0.7; LCL: -12.44), as well as on the week 6 assessment (median difference: -5.1; LCL: -14.13). On the global assessment of acne improvement at week 12, similar efficacy results relative to baseline were observed: with 48 of 101 of the adapalene arm subjects rated as clear, almost clear or markedly improved, and 41 of 100 of the switch arm subjects (Figure 2).

### *Tolerability*

In the adapalene arm, the percentage of subjects reporting cutaneous irritation (erythema, scaling, stinging/burning, or dryness) of any severity generally peaked at week 2 (except for erythema, which peaked at week 6) and then resolved over the remainder of the study period (Figure 3). In the switch arm, the proportion of subjects reporting cutaneous irritation peaked at week 2 (2 weeks after initiation of adapalene gel) and week 8 (2 weeks after initiation of tazarotene cream). The tolerability results reported in the switch arm are consistent with the increases in cutaneous irritation parameters observed with each treatment separately. This pattern was similar for all cutaneous irritation parameters evaluated.

**Figure 1.** Efficacy of adapalene gel compared to switch therapy in reducing total lesion counts in the intent-to-treat population.

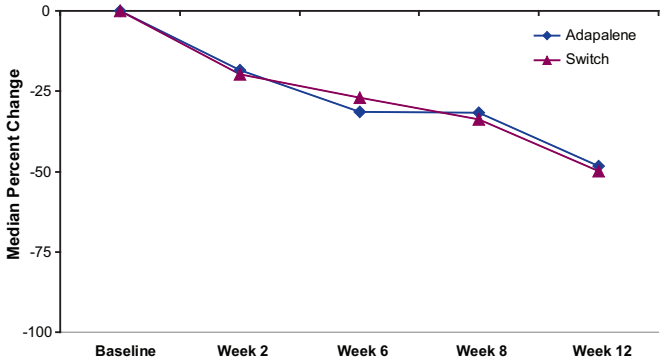
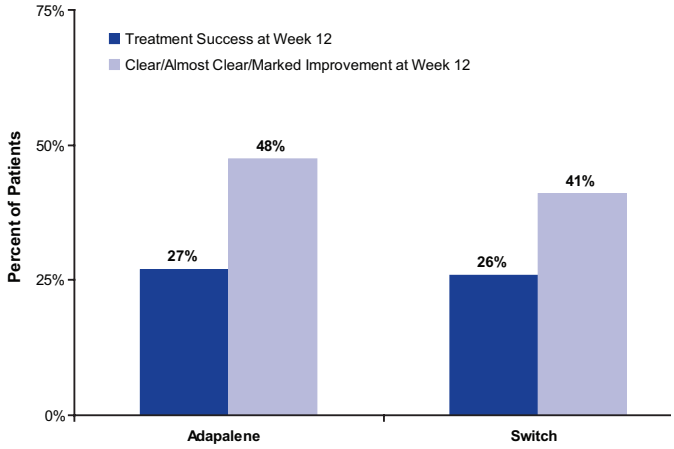



**Figure 2.** Treatment success and global improvement at week 12 in the intent-to-treat population.

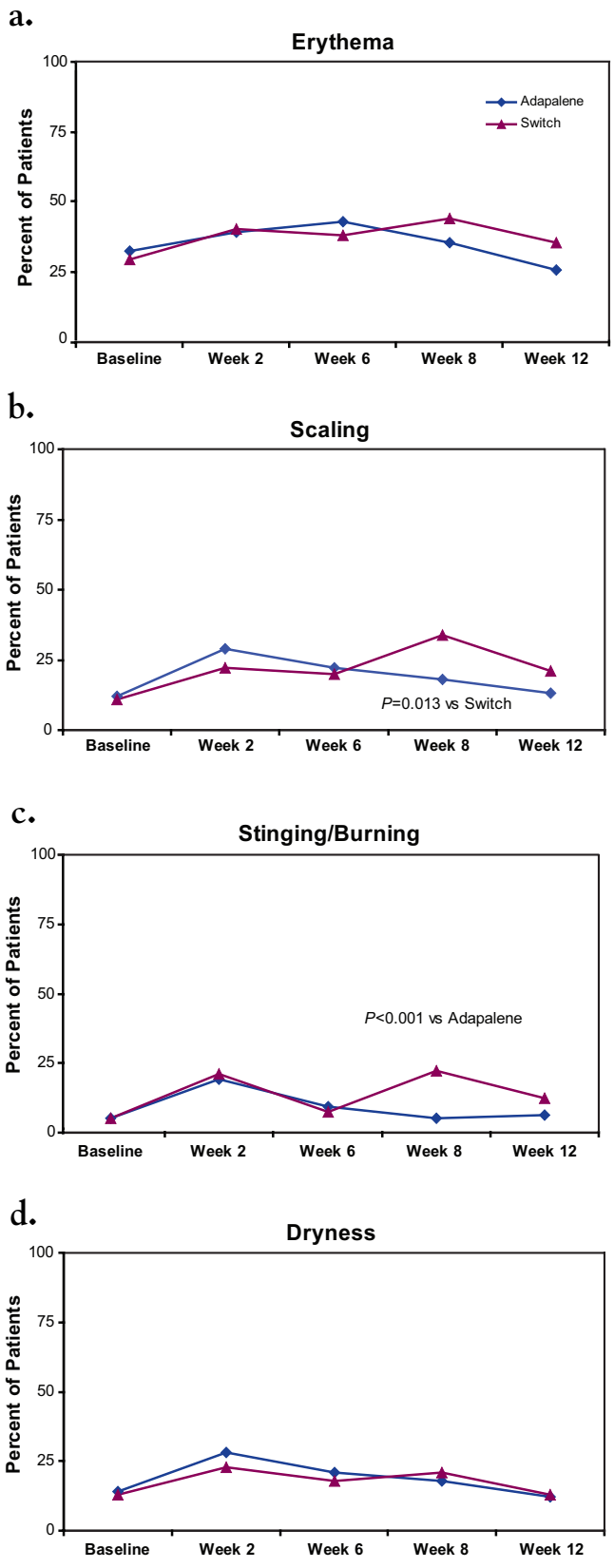



Treatment success was defined as clear or almost clear on the global assessment of acne severity.

### *Erythema*

The incidence of erythema was similar between the treatment arms with most subjects reporting no erythema or mild erythema as the worst response. Forty percent of adapalene gel subjects experienced erythema at week 2 compared to 41% of switch subjects at the end of week 2 of treatment. At week 8 (second peak for the switch arm), 36% of adapalene gel subjects reported erythema compared to 45% of switch subjects (Figure 3a). With respect to scaling, at week 2, 29% of adapalene gel subjects reported mild to moderate scaling compared to 22% of switch subjects (Figure 3b) whereas at week 8, data demonstrate a statistically significant increase

**Figure 3**. Tolerability assessments of **a)** erythema, **b)** scaling, **c)** stinging/burning, and **d)** dryness in the safety population.




of subjects in the switch arm (34%) who experienced scaling compared to the adapalene gel arm at this same evaluation point (18%, *P*=.013). Overall, a small percentage of subjects reported stinging and burning, with 19% of adapalene gel and switch subjects reporting stinging and burning at week 2 (both adapalene therapy). At week 8, statistically significantly more switch subjects (20%) than adapalene gel subjects (4%) reported stinging and burning, and the difference was also statistically significant (*P*=.001) (Figure 3c). Dryness was generally reported infrequently, and the numbers of subjects reporting dryness were similar between the treatment arms at all time points evaluated (Figure 3d).

### *Adverse Events*

The percentage of subjects reporting any adverse event was 35% in the adapalene gel arm and 36% in the switch arm (Table 2). More than 85% of adverse events were mild or moderate in severity. Among the reported events, 36% of the events in the adapalene gel arm and 47% of the events in the switch arm were related (possibly, probably, or definitely related) to study treatment. The treatment-related adverse events reported by the most subjects in the adapalene gel arm were exfoliation (scaling) (4%), dryness (4%), and irritation (6%), while the treatment-related adverse events reported by the most subjects in the switch arm were irritation (8%), exfoliation (7%), erythema (4%), and dryness (2%) (Table 3). For the adapalene gel arm, there were 2 pregnancies and 1 case of acute appendicitis. For the switch arm, 1 subject had surgery for endometriosis and another subject was hospitalized for biliary colic. None of these serious adverse events was related to either treatment regimen.

## Discussion

Acne affects more than 50 million Americans.[15] Treatment goals for acne mainly include reductions in total lesions and prevention of new lesions with minimal irritation to the skin. Adapalene 0.1% gel is a topical retinoid whose efficacy for lesion reduction has been well studied in clinical trials.[10] Adapalene 0.1% gel has a low adverse event profile, demonstrating similar efficacy and better tolerability to other available topical retinoids for the treatment of acne vulgaris.[10,13] It is interesting that subjects' perceptions of efficacy during early weeks of treatment may be negatively influenced by the lack of accompanying tolerability problems. In fact, it was originally believed that erythema and irritation were necessary components of the comedolytic activity of topical retinoids, a notion that was later disproved based on mechanism of action of adapalene.[16,17] Many online message boards and websites actually suggest that stinging is an indication that the remedy or treatment is working.[18-21]

Results from the adapalene gel and switch arms of the current study demonstrate that 12 weeks of treatment with adapalene gel alone leads to a considerable reduction in total acne lesions and that switching retinoids in the middle of the treatment course does not result in a statistically significant difference in lesion reduction.

Additional analyses of efficacy, including reduction in total lesions at week 6, reduction in inflammatory lesions at weeks 6 and 12, as well as global assessments of acne severity and improvement at week 12 also demonstrated noninferiority of adapalene 0.1% gel compared to switch therapy. Adapalene 0.1% gel was noninferior for reduction in noninflammatory lesion counts at week 6 but not at week 12. Superiority testing failed to show that either adapalene gel or switch therapy was superior at treating inflammatory lesions. These results, which failed to show noninferiority or superiority, suggest that a much larger sample size will be needed to determine the optimal treatment approach for noninflammatory lesions.

Although patients may confuse a lack of skin irritation with a lack of efficacy, tolerability is still an important aspect of patients' adherence to treatment, and therefore to overall treatment success.[10] In the present study, the overall tolerability of adapalene 0.1% gel and tazarotene 0.1% cream was generally good, with only transient increases in tolerability problems observed in the first few weeks of treatment. Signs and symptoms of cutaneous irritation such as erythema, scaling, stinging/burning, and dryness generally peaked 2 weeks after the initiation of adapalene treatment and resolved over the remainder of the treatment period. The tolerability profile of switch therapy was characterized by 2 peaks (at weeks 2 and 8) in which a greater percentage of patients reported tolerability problems. This observation suggests that when retinoids are switched in a treatment period, patients may experience an increase in irritation with the new retinoid, suggesting 1 retinoid may not offer protection from the "retinizing" effect of another. This phenomenon of a transient second rise in cutaneous irritation that must be balanced against no significant increase in efficacy over a 12-week period.

The incidence of adverse events in the adapalene gel arm was low, with only 11% of the reported events possibly related, 5% probably related, and 20% definitely related to the study drug. The percentage of subjects reporting treatment-related adverse events in the switch arm was also low, with 11% of the reported events possibly related, 17% probably related, and 20% definitely related, to the study drug. However a higher percentage of adverse events in the switch arm (31/66, 47%) compared to the adapalene gel arm (20/55, 36%) were possibly, probably, or definitely related to study drug.

In summary, the results of this study do not support the idea that switching from adapalene gel to tazarotene cream after 6 weeks of treatment will necessarily lead to better patient outcomes. Similar efficacy results, combined with high safety and a strong tolerability profile, suggest that treatment with adapalene 0.1% gel is as beneficial to patients for the treatment of acne vulgaris as the switch strategy without increasing cutaneous irritation. Furthermore, the risk/benefit ratio is in favor of staying on the initial retinoid rather than switching since cutaneous irritation seems to worsen after the switch in retinoid therapy. This information should be helpful in avoiding causing the patient to experience an extra adjustment period that is not necessary if the initial retinoid is continued throughout the treatment period.

**Disclosure**: Luz E. Colón MS, Lori A. Johnson PhD, and Ronald W. Gottschalk MD FRCPC are employees of Galderma Laboratories LP. None of the authors has a financial interest in the company.

An overview of some of the results (Table 1, Figures 1-3) was included in a scientific poster presented at the winter 2007 meeting of the American Academy of Dermatology.

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# Adapalene 0.1% Gel Compared to Tazarotene 0.1% Cream in the Treatment of Acne Vulgaris

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## Abstract

A variety of topical retinoids is available for the treatment of acne vulgaris. Selection of the appropriate treatment depends not only on efficacy but also on how well the patient can tolerate different formulations. The goal of this study was to evaluate the efficacy and tolerability of daily adapalene 0.1% gel compared to daily tazarotene 0.1% cream and to demonstrate the noninferiority of adapalene 0.1% gel when compared to tazarotene 0.1% cream in treating acne. This represents 2 arms of a 3-arm study. Subjects 12 to 35 years of age with acne vulgaris (N=202) participated in a 12-week, randomized, evaluator-blinded study of once-daily therapy with adapalene 0.1% gel versus tazarotene 0.1% cream. The primary measure of efficacy was the reduction in total lesion counts posttreatment. Subjects treated with adapalene 0.1% gel achieved similar reductions in total lesion counts at week 12 compared to the subjects treated with the tazarotene cream, which demonstrates the noninferiority of adapalene treatment compared to tazarotene (median difference: -1.18%; lower confidence limit [LCL]: -9.26). At week 2, the number of patients that experienced erythema and scaling with tazarotene 0.1% cream was greater when compared to adapalene 0.1% gel and statistically significant. By week 12, the percentage of subjects reporting cutaneous irritation had returned to or near baseline levels and was similar between treatment arms for all parameters assessed. Adapalene gel was associated with fewer treatment-related adverse events than tazarotene cream (36% versus 58%, respectively), and less than half as many adverse events that were "definitely" related to study treatment than tazarotene cream (20% versus 45%, respectively). Daily therapy with adapalene 0.1% gel was shown to be noninferior to tazarotene 0.1% cream in total acne lesion reductions, and during initial stages of treatment, demonstrated better tolerability with respect to erythema and scaling.

## Introduction

Acne vulgaris is the most common skin condition seen by physicians and one of the main reasons young people consult a physician.[1,2] The pathogenesis of acne is complex and involves at least 4 distinct events within pilosebaceous hair follicles, namely increased sebum production, increased epithelial cell turnover, colonization by *Propionibacterium acnes* (*P acnes*), and release of inflammatory mediators into the follicle and surrounding dermis.[3,4] Treatment strategies that simultaneously target more than one of these mechanisms are believed to be the most effective for clearing existing lesions and preventing recurring lesions.[5]

For all forms of acne except the most severe, recommended treatment strategies include topical retinoids, either alone or in combination with other medications, as first-line therapies.[5-7] Topical retinoids are thought to reverse abnormal desquamation in the follicle by reducing epithelial turnover and also may exert anti-inflammatory effects by modulating the skin's immune response.[6] It has been theorized that topical retinoids may also facilitate the penetration of other compounds, such as benzoyl peroxide and topical antibiotics, to reduce *P acnes* proliferation.[8]

Topical retinoids, such as adapalene and tazarotene, are available in both cream and gel formulations. Many dermatologists believe that minimizing skin irritation is key to maintaining patient compliance and thus the choice of a gel or cream formulation is important.[5] Comparisons of the efficacy and tolerability of the gel formulations of adapalene and tazarotene have been previously reported[9,10] but a direct comparison of adapalene 0.1% gel to tazarotene 0.1% cream has not been performed. This comparison is important since according to Wolters Kluwer Health, 37.5% of all dispensed tazarotene prescriptions in 2006 were for the 0.1% cream formulation, compared to 15.9% for the 0.1% gel formulation.[11]

A randomized multicenter study was designed to analyze adapalene 0.1% gel compared to tazarotene 0.1% cream for effectiveness and tolerability in reducing total acne lesion counts following 12 weeks of daily treatment. Subjects were randomized to 1 of 3 treatment arms and treated with adapalene 0.1% gel, tazarotene 0.1% cream, or adapalene 0.1% gel for 6 weeks followed by tazarotene 0.1% cream for 6 weeks (switch arm). Data from the noninferiority comparison between 2 of the 3 arms, adapalene 0.1% gel arm and tazarotene 0.1% cream arm, were analyzed.

## Methods

The study was a phase 4, randomized, controlled, evaluator-blind, parallel-arm, multicenter trial designed to evaluate and compare the efficacy and safety of adapalene 0.1% gel once daily for 12 weeks (adapalene 0.1% gel arm) to tazarotene 0.1% cream once daily for 12 weeks (tazarotene 0.1% cream arm) for the treatment of acne vulgaris.

The target enrollment was 100 male and female subjects per treatment arm. For inclusion, subjects had to be between 12 and 35 years of age, with 15 to 100 noninflammatory lesions, at least 20 inflammatory lesions, and not more than 3 nodu-

**Table 1.** Subject demographics and baseline characteristics of the intent-to-treat population (n=101 for both treatment arms).

| | Adapalene 0.1% gel: n (%) | Tazarotene 0.1% cream: n (%) |
|---|---|---|
| **Mean age (years)** | 18.5 | 18.5 |
| **Gender** | | |
| Male | 64 (63) | 65 (64) |
| Female | 37 (37) | 36 (36) |
| **Race** | | |
| Caucasian | 65 (64) | 58 (57) |
| Black | 16 (16) | 27 (27) |
| Asian | 3 (3) | 4 (4) |
| American Indian or Alaska Native | 0 (0) | 1 (1) |
| Hispanic or Latino | 6 (6) | 6 (6) |
| Native Hawaiian or Pacific Islander | 2 (2) | 0 (0) |
| Other or mixed | 9 (9) | 5 (5) |
| **Fitzpatrick skin type** | | |
| I | 4 (4) | 4 (4) |
| II | 23 (23) | 20 (20) |
| III | 39 (39) | 27 (27) |
| IV | 16 (16) | 19 (19) |
| V | 11 (11) | 18 (18) |
| VI | 8 (8) | 13 (13) |

**Table 2.** Summary of adverse events by seriousness, severity, and relationship to study medication (adapalene arm: n=98; tazarotene arm: n=99).*

| | Adapalene 0.1% gel: n (%) | Tazarotene 0.1% cream: n (%) |
|---|---|---|
| **Number of adverse events reported, n** | 55 | 64 |
| **Subjects reporting adverse events** | 35 (36) | 33 (33) |
| **Serious*** | | |
| No | 52 (95) | 62 (97) |
| Yes | 3 (5) | 2 (3) |
| **Severity*** | | |
| Mild | 29 (55) | 39 (62) |
| Moderate | 21 (40) | 17 (27) |
| Severe | 3 (6) | 7 (11) |
| Not reported† | 2 | 1 |
| **Relationship to study medication*** | | |
| Definitely unrelated | 22 (40) | 20 (31) |
| Unlikely | 13 (24) | 7 (11) |
| Possible | 6 (11) | 3 (5) |
| Probably | 3 (5) | 5 (8) |
| Definitely related | 11 (20) | 29 (45) |

*Proportion based on number of events; †Pregnancies reported on the serious adverse event case report form did not report severity.

locystic lesions. Exclusion criteria included subjects with severe nodulocystic acne, female subjects who were or planning to become pregnant during the study or nursing, subjects with facial hair that would impair study assessments, subjects with washout periods less than 4 weeks for topical acne treatments or less than 6 months for systemic therapy, or subjects with other dermatologic conditions with which treatment may interfere. Treatment was assigned according to a computer-generated randomization scheme and evaluations were performed at baseline, weeks 2, 6, 8, and 12.

### *Efficacy*

The primary efficacy outcome was measured by the percent of change in total lesion counts from baseline to week 12. Inflammatory and noninflammatory lesions were counted and added together to form the total lesion count. Secondary outcomes included the percent of change from baseline in total lesion counts at week 6, percent of change from baseline in inflammatory lesion counts at weeks 6 and 12, the percent change from baseline in noninflammatory lesion counts at weeks 6 and 12, global severity assessment at weeks 6 and 12, global severity assessment on a dichotomous scale (success or failure) at weeks 6 and 12, and global assessment of improvement from baseline at week 12.

The global severity assessment of acne at each visit was a static assessment based on a scale of 0 (clear) to 5 (very severe); the evaluator was instructed not to reference previous visits when evaluating the subject's facial acne. Success on the dichotomous scale was defined as a score of either 0

**Table 3.** Treatment-related* adverse events (adapalene arm: n=98; tazarotene arm: n=99).

| | Adapalene 0.1% gel: n (%) | Tazarotene 0.1% cream: n (%) |
|---|---|---|
| **Number of events reported** | 20 | 37 |
| **Application site** | | |
| Exfoliation | 4 (4) | 11 (11) |
| Dryness | 4 (4) | 6 (6) |
| Irritation | 6 (6) | 9 (9) |
| Erythema | 1 (1) | 3 (3) |
| Pruritis | 1 (1) | 1 (1) |
| Burn | 1 (1) | 1 (1) |
| **Sunburn** | 1 (1) | 1 (1) |
| **Skin irritation** | 1 (1) | 0 |
| **Burning sensation** | 1 (1) | 0 |

*Related=possibly, probably, or definitely related; †Subjects with at least 1 event; subjects may have reported more than 1 event.

(clear) or 1 (almost clear). Global assessment of improvement was performed by comparing facial skin condition at week 12 (or early termination) to baseline based on a scale of 0 (clear) to 6 (worse).

### *Tolerability and Safety*

Tolerability, as measured by the degree of erythema, scaling, dryness, and stinging/burning, was evaluated at each visit based on a scale of 0 (none) to 3 (severe). All adverse events were monitored and reported on an adverse event case report form without omitting any requested and known information. Descriptions of adverse events included the date of onset, the date the adverse event ended, the severity of the adverse event, and the outcome, including any intervening treatment required. All reported adverse events were summarized by the number of subjects reporting adverse events, system organ class, preferred term, severity, seriousness, and relationship to study medication.

### *Statistical Analyses*

Ninety-five percent confidence intervals (CIs) were computed for the primary and secondary analyses to test for noninferiority and superiority in a pair-wise fashion. Noninferiority was established if the lower confidence limit (LCL) of the 95% CI was between 0% and -15% and superiority was established if the LCL of the 95% CI was greater than 0. Analyses were conducted for both the intent-to-treat and per-protocol populations. Due to the non-normal distribution of the primary efficacy results, the Cochran-Mantel-Haenszel (CMH) statistic (stratified on analysis center after ridit transformation) was used. For the global assessment of acne severity, noninferiority was established if the LCL of the 1-sided 97.5% CI for the difference in success rates was between 0% and 15% using Wald's confidence interval with Yates' continuity correction. Superiority was established if the LCL was greater than 0.

**Figure 1.** Efficacy of adapalene gel compared to tazarotene cream in reducing total lesion counts of the intent-to-treat population.

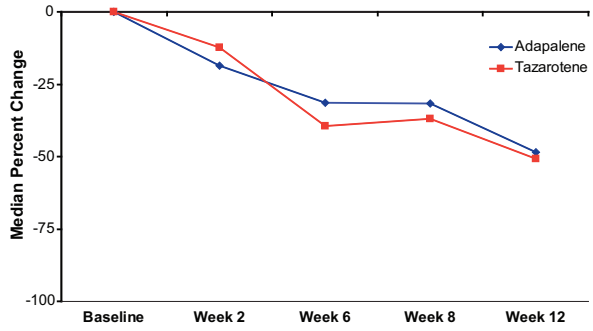
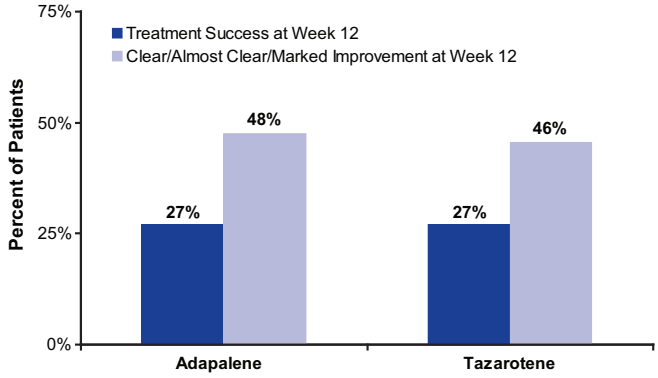


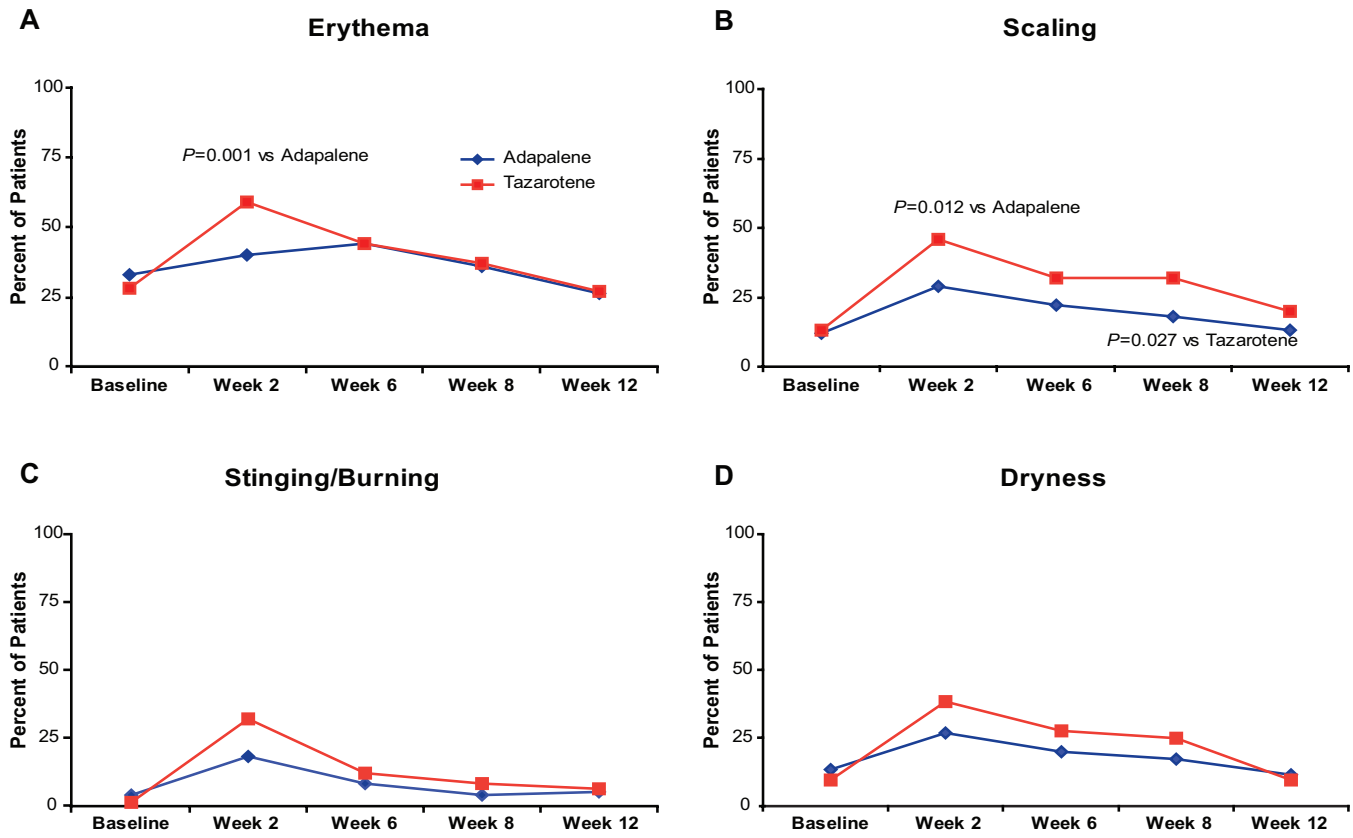

**Figure 2.** Treatment success and global improvement at week 12 of the intent-to-treat population.




The clinical study was conducted under a common protocol for each investigational site with the intention of pooling the data for analysis. The consistency of treatment response was investigated across the analysis centers to identify possible treatment by center interactions at an alpha level of .10. A sensitivity analysis excluding analysis center(s) with extreme efficacy results was performed to determine the robustness of the treatment effect.

Other efficacy endpoints were summarized using descriptive statistics. For adverse events, the Fisher's exact test was used to compare the proportion of subjects in each treatment arm who reported any adverse event at a significance level of .05. The last observation carried forward (LOCF) method was used to extrapolate missing lesion counts and global severity data for subjects who prematurely discontinued from the study. SAS®

**Figure 3.** Tolerability assessments of **a)** erythema, **b)** scaling, **c)** stinging/burning, and **d)** dryness of the safety population.




software (SAS Institute, Cary, NC, version 8.2) was used for all data analyses and tabulations, unless otherwise stated.

The study was conducted in accordance with the World Medical Association's Declaration of Helsinki and its amendments, and good clinical practice guidelines. Protocols were approved by institutional review boards and subjects provided written informed consent prior to the start of the study.

## Results

A total of 202 subjects was enrolled during the period from February 7, 2006 to September 5, 2006 and randomized to receive treatment with adapalene 0.1% gel or tazarotene 0.1% cream. The safety population (all subjects who took at least 1 dose of study medication) had 197 subjects and the per-protocol population (all subjects who completed the entire treatment course as described in the protocol) had 168 subjects. On a self-reported basis, more than 90% of subjects in all treatment arms adhered to the assigned treatment regimens. The average age of subjects was 19 years in each arm and the majority of subjects were male. A detailed description of subject demographics is given in Table 1. There were no significant differences among the treatment arms for baseline acne severity, total lesion counts, or inflammatory or noninflammatory lesion counts.

### *Efficacy*

The primary efficacy outcome was measured as the percent change in total lesion counts from baseline to posttreatment. Adapalene 0.1% gel and tazarotene 0.1% cream both showed improvements in lesion counts from baseline to 12 weeks (Figure 1). When comparing the adapalene 0.1% gel arm to the tazarotene 0.1% cream arm, the adapalene gel arm was shown to be noninferior to the tazarotene cream arm in percent change in total lesion counts at week 12 (median difference: -1.18%; LCL: -9.26). Results from the per-protocol population were similar to the intent-to-treat population. The adapalene 0.1% gel arm was also shown to be noninferior to the tazarotene cream 0.1% arm for percent reduction in total lesion counts at week 6 (median difference: -7.24%; LCL: -14.26) and percent reduction in inflammatory lesion counts at week 6 (median difference: 3.62%; LCL: -4.44) and week 12 (median difference: 4.23%; LCL: -4.43). For percent reduction in noninflammatory lesion counts at week 6 and week 12, adapalene 0.1% gel was noninferior to tazarotene 0.1% cream (median difference: -13.02%; LCL: -23.58 at week 6 and median difference: -6.15; LCL: -15.86 at week 12). However, superiority testing did not reveal that tazarotene was superior to adapalene.

A preplanned analysis of the primary endpoint designed to detect significant treatment by investigational site interac-

tion revealed a single center contributed outlying data to the percent change from baseline in total lesion counts (*P*=.037). Exclusion of subjects treated at this site (n=10 in both treatment arms) did not affect the outcome of the primary efficacy results in that the adapalene gel arm was still shown to be noninferior to the tazarotene cream arm (median difference: -2.80%; LCL: -11.53) demonstrated in the percent reduction in total lesion counts at week 12. Superiority testing under these conditions did not reveal either treatment arm to be superior to the other.

Assessments of acne severity and improvement were also used to evaluate efficacy. On the static global assessment of acne severity at week 12, 27% of subjects in each treatment arm had treatment success (clear or almost clear) (Figure 2). Adapalene 0.1% gel was shown to be noninferior by assessment (median difference: 0.0; LCL: -13.20), as well as on the week 6 assessment (median difference: -4.0; LCL: -12.79). Superiority testing did not reveal either treatment as superior to the other. On the global assessment of acne improvement at week 12, 48 of 101 subjects treated with adapalene 0.1% gel were rated as clear, almost clear, or markedly improved relative to baseline, when compared to 46 of 101 subjects treated with tazarotene 0.1% cream (Figure 2).

### *Tolerability*

The percentage of subjects reporting cutaneous irritation (erythema, scaling, stinging/burning, or dryness) of any severity generally peaked at week 2 (except for erythema, which peaked at week 6 in the adapalene 0.1% gel arm) and then resolved over the remainder of the study. At week 2, the number of patients who experienced erythema and scaling with tazarotene 0.1% cream compared with adapalene 0.1% gel was statistically significant. By week 12, the percentage of subjects reporting cutaneous irritation had returned to or near baseline levels and was similar between treatment arms for all parameters assessed.

The incidence of erythema was similar between the adapalene 0.1% gel and tazarotene 0.1% cream arms except at week 2, where a significantly greater proportion of subjects treated with tazarotene (59%) reported erythema compared to those treated with adapalene gel (40%; *P*=.001) (Figure 3). Of the 40% reporting erythema in the adapalene gel arm, only 8% of subjects reported moderate erythema (compared to 14% in the tazarotene group) and no subjects in either group reported severe erythema. The incidence of moderate scaling was higher for tazarotene-treated subjects (28%) than for adapalene-treated subjects (10%). Furthermore, the proportion of subjects in the tazarotene arm who had scaling was statistically significantly greater at week 2 (47% of subjects treated with tazarotene cream versus 29% of subjects treated with adapalene gel, *P*=.012) and at week 8 (32% of subjects treated with tazarotene cream versus 18% of subjects treated with adapalene gel, *P*=.027) (Figure 3). The majority of subjects did not experience stinging and burning (Figure 3). Subjects in both arms of the study experienced dryness, but the differences for dryness reported between the 2 arms were not statistically significant (Figure 3).

### *Adverse Events*

The total percentage of subjects reporting adverse events was 36% and 33% in the adapalene gel 0.1% and tazarotene cream 0.1% arms, respectively (Table 2). Ninety-five percent or greater of adverse events were considered to be not serious and >85% of adverse events were mild or moderate in severity. Tazarotene cream was associated with more related (possible/probably/definitely related) adverse events (58% of events) compared to adapalene gel (36% of events). The tazarotene 0.1% cream arm also had more than twice as many events that were definitely related to the study medication when compared to the adapalene 0.1% gel arm (45% and 20%, respectively). The treatment-related adverse events reported by the most subjects in the adapalene 0.1% gel arm were exfoliation (4%), dryness (4%), and irritation (6%), while the treatment-related adverse events reported by the most subjects in the tazarotene 0.1% cream arm were exfoliation (11%), dryness (6%), irritation (9%), and erythema (3%) (Table 3).

## Discussion

Acne vulgaris involves multiple etiological factors, an understanding of which has led to more effective treatments for the disease. Topical retinoids, such as adapalene gel and tazarotene cream, are an integral part of acne management due to their ability to target abnormal epithelial turnover and inflammation as well as to facilitate penetration of other topical therapies.[12] Results from the comparison of the adapalene and tazarotene arms demonstrate that 12 weeks of treatment with adapalene 0.1% gel or tazarotene 0.1% cream both led to comparable reductions in total lesion counts but that adapalene 0.1% gel was associated with better cutaneous tolerability during early stages of treatment with respect to erythema and scaling, and fewer treatment-related adverse events over the course of the study.

Adapalene 0.1% gel produced reductions (~50%) in total lesion counts at week 12, a result that was statistically noninferior to tazarotene 0.1% cream. Results from other measures of efficacy, such as reductions in total lesion counts at week 6, reductions in inflammatory lesion counts at weeks 6 and 12, and global assessment of acne severity also demonstrated that adapalene gel 0.1% was noninferior to tazarotene 0.1% cream. For reductions in noninflammatory lesions, adapalene gel 0.1% was not statistically noninferior to tazarotene cream; however superiority testing failed to show that tazarotene cream was superior to adapalene gel. These findings suggest that a larger sample size may be required to fully elucidate the comparative efficacy of adapalene 0.1% gel and tazarotene 0.1% cream for the treatment of noninflammatory lesions.

These results differ somewhat from a previous comparison of the tazarotene 0.1% gel and adapalene 0.1% gel, in which subjects treated with tazarotene 0.1% gel had significantly greater reductions in inflammatory and noninflammatory lesions and a greater proportion of subjects achieving ≥50% improvement in their acne.[10] In that prior comparison, tazarotene 0.1% gel demonstrated better efficacy in that

study, while adapalene 0.1% gel was better tolerated, especially during the first 4 weeks of treatment, when tolerability scores for erythema, pruritus, burning, and peeling showed significant differences favoring adapalene 0.1% gel.[10]

In summary, results of the current study support the hypothesis that adapalene 0.1% gel has efficacy that is not inferior compared to tazarotene 0.1% cream in the treatment of acne vulgaris. The availability of medications with similar efficacy but different formulations allows physicians greater flexibility in tailoring appropriate therapies for individual subjects, particularly when tolerability may affect treatment compliance.

**Disclosures**: Luz E. Colón MS, Lori A. Johnson PhD, and Ronald W. Gottschalk MD FRCPC are employees of Galderma Laboratories LP. None of the authors has a financial interest in the company.

An overview of some of the results (Figures 1, 2, and 3) were included in a scientific poster presented at the 2007 meeting of the American Academy of Dermatology.

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# LONG-TERM SAFETY AND EFFICACY STUDY OF ADAPALENE 0.3% GEL

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## Abstract

The efficacy and safety of adapalene 0.1% gel in the treatment of acne vulgaris has been demonstrated in multiple controlled clinical trials. A higher concentration formulation, adapalene 0.3% gel, has been developed to provide a broader range of treatment options for acne management. Phase 3 clinical studies have demonstrated the superior efficacy of adapalene 0.3% gel compared to adapalene 0.1% gel and its vehicle at the end of a 12-week treatment period. The goal of this study was to evaluate the long-term safety of adapalene 0.3% gel in subjects treated once daily for 52 weeks, with a secondary objective to evaluate long-term efficacy. Subjects 12 years of age or older (N=551) with acne vulgaris participated in a multicenter, open-label study of the long-term (up to 52 weeks) efficacy and safety of once-daily applications of adapalene 0.3% gel. Of those enrolled, 167 subjects completed 12 months of treatment. Expected signs and symptoms of local cutaneous irritation (erythema, dryness, scaling, and stinging/burning) were mostly mild or moderate, with mean tolerability scores below 1 (mild) at all time points for the parameters assessed. Treatment-related, dermatologic adverse events were experienced by 21% of subjects and dry skin, skin discomfort, and scaling were reported by 10.5%, 8.3% and 3.3% of subjects, respectively. Most of the adverse events reported occurred in the first quarter of treatment. Adverse events were mostly mild to moderate in severity. Subjects treated with adapalene 0.3% gel for 52 weeks achieved a >75% median reduction in total, inflammatory, and noninflammatory lesions in this open-label study by the end of the treatment period. Adapalene 0.3% gel was safe and effective in the long-term (up to 1 year) treatment of subjects with acne vulgaris.

## Introduction

Acne vulgaris is the most common of all skin disorders, affecting 30% to 85% of adolescents and persisting into adulthood in many subjects.[1,2] Although acne is not life-threatening, acne can negatively impact a patient's quality of life. Persistent acne may cause permanent scarring, and lead to depression and other emotional and social problems that can extend into adulthood.[3]

The pathophysiology of acne vulgaris involves several factors: abnormal follicular keratinocyte desquamation leading to the formation of a follicle plug, increased sebum production within the pilosebaceous follicle, proliferation of *Propionibacterium acnes* in the sebum, and inflammation.[4,5]

Topical retinoids (ie, adapalene, tretinoin, and tazarotene) have been mainstays in the treatment of acne and are currently recommended as first-line therapy in all but the most severe forms of acne.[6] The efficacy and safety of retinoids in 12-week treatment regimens have been well studied in several controlled clinical trials.[7-9] Retinoids are known to be potent comedolytic agents and adapalene has been shown to have anti-inflammatory activity comparable to other anti-inflammatory standards in multiple *in vitro* and *in vivo* models at a variety of concentrations.[1,10,11] A more recent study shows that adapalene effected the inhibition of specific inflammatory mediators that play a role in cutaneous inflammation (toll-like receptor-2 [TLR-2] and CD1d) in a variety of *in vitro* assays employing skin samples taken from acne patients.[12] The clinical benefit of retinoids is realized in reducing microcomedone formation, the primary lesion in acne.[1,10] More specifically, retinoids help normalize desquamation of the follicular epithelium, promote turnover of comedones, and prevent the formation of new acne lesions.[1,13]

The therapeutic effect of topical retinoids is usually accompanied by some degree of local cutaneous irritation (erythema, dryness, scaling, or stinging and burning). Signs and symptoms of local cutaneous irritation are mostly mild to moderate in severity and transient in time. However, subject compliance to long-term treatment can be reduced by poor tolerability, making acne management a challenge.[14,15] Adapalene has a more favorable local tolerability profile compared to tretinoin and tazarotene and is generally considered to be the most tolerable topical retinoid available.[7,9,16-20]

Adapalene 0.3% gel has been developed to expand therapeutic flexibility in the management of acne vulgaris with a higher dose of a well-tolerated retinoid. In a previous phase 2 dose-assessment study, adapalene 0.3% gel was found to be superior to the vehicle and provided an increase in clinical benefit relative to the lower concentration of adapalene gel (0.1%).[21] The objective of this study was to determine the safety and efficacy of adapalene 0.3% gel in the long-term treatment (up to 52 weeks) of subjects with acne vulgaris. This study was run concurrently with a phase 3 pivotal trial.[22]

## Methods

### *Study Design*

The study was a phase 3, open-label, multicenter study designed to assess the long-term safety and efficacy of adapalene 0.3% gel applied once daily for 52 weeks to acne-affected

**Table 1.** Subject demographic and baseline characteristics.

| Parameter | Adapalene 0.3% gel (N=551) |
|---|---|
| **Gender: n (%)** | |
| Male | 276 (50.1) |
| Female | 275 (49.9) |
| **Race: n (%)** | |
| Caucasian | 399 (72.4) |
| Black | 69 (12.5) |
| Asian | 3 (0.5) |
| Hispanic | 69 (12.5) |
| Other | 11 (2.0) |
| **Skin type: n (%)** | |
| Dry | 10 (1.8) |
| Normal | 175 (31.8) |
| Oily | 352 (63.9) |
| Oily + Normal | 5 (0.9) |
| Oily + Dry | 9 (1.6) |
| **Age (years):** | |
| Mean | 18.9 |
| SD | 6.99 |
| Median | 16.0 |
| Min, Max | 11, 52 |
| **Fitzpatrick skin phototype: n (%)** | |
| I | 29 (5.3) |
| II | 93 (16.9) |
| III | 194 (35.2) |
| IV | 139 (25.2) |
| V | 55 (10.0) |
| VI | 41 (7.4) |

areas on the face and trunk. Evaluations were performed at baseline, week 1, and months 1, 2, 4, 6, 8, 10, and 12 (or early termination visit). Laboratory tests including pregnancy testing, as applicable, were performed at screening and months 6 and 12 (or early termination).

**Table 2.** Adverse events reported after daily treatment with adapalene 0.3% gel over 52-week period (N=551).*

| | n (%) |
|---|---|
| **Subjects with at least 1 adverse event** | 244 (44) |
| Dermatological adverse events | 142 (26) |
| Nondermatological adverse events | 155 (28) |
| **Subjects with at least 1 adverse event related to study medication** | 119 (21.6) |
| Dermatological adverse events | 117 (21.2) |
| Nondermatological adverse events | 4 (0.7) |
| **Discontinuations due to adverse events** | 15 (2.7) |

*Subjects could have reported more than 1 adverse event.

### *Subjects*

The target enrollment was approximately 450 male and female subjects from 20 independent sites in the US. Sample size of 450 subjects was determined based on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E1a Guideline: Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Nonlife-threatening Conditions. Subjects 12 years of age or older with 20 to 100 noninflammatory lesions, 20 to 50 inflammatory lesions, and no active nodules or cysts on the face were eligible for the study. Excluded from enrollment were those who were pregnant or planned to become pregnant; subjects with acne conglobata, acne fulminans, secondary acne (chloracne, drug-induced acne, etc.) or severe acne in need of systemic treatment; and subjects with underlying diseases or dermatological conditions necessitating the use of interfering topical or systemic therapy such as, but not limited to, atopic dermatitis, perioral dermatitis, or rosacea.

### *Safety and Efficacy*

The primary objective of the study was to evaluate the safety of adapalene 0.3% gel in the long-term treatment of subjects with acne vulgaris. Signs and symptoms of local cutaneous irritation (erythema, scaling, dryness, and stinging/burning), were evaluated at each visit using a scale ranging from 0 (none) to 3 (severe). Adverse events and routine laboratory parameters (hematology, chemistry, and urinalysis) were monitored throughout the duration of the study.

The secondary objective of the study was to evaluate the efficacy of adapalene 0.3% gel in the long-term treatment of subjects with acne vulgaris. Efficacy outcomes included percent of change from baseline in noninflammatory, inflammatory, and total lesion counts (sum of non-inflammatory, inflammatory, and nodules/cysts) on the face at baseline, week 1, and months 1, 2, 4, 6, 8, 10, and 12. Investigators also assessed subjects' facial oiliness on a scale of 0 (none) to 3 (se-

**Figure 1.** Mean tolerability scores (0=none, 1=mild, 2=moderate, and 3=severe) for erythema, scaling, dryness, and stinging/burning during 52 weeks of treatment with adapalene 0.3% gel.

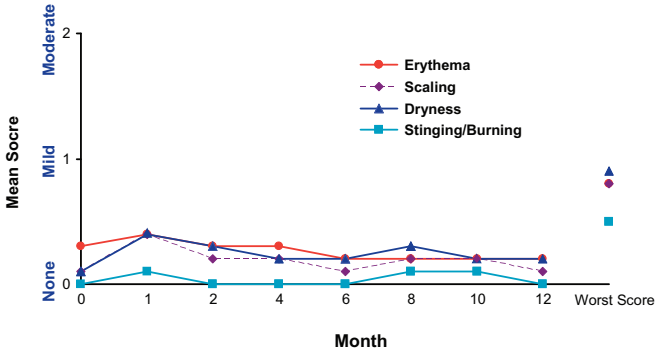
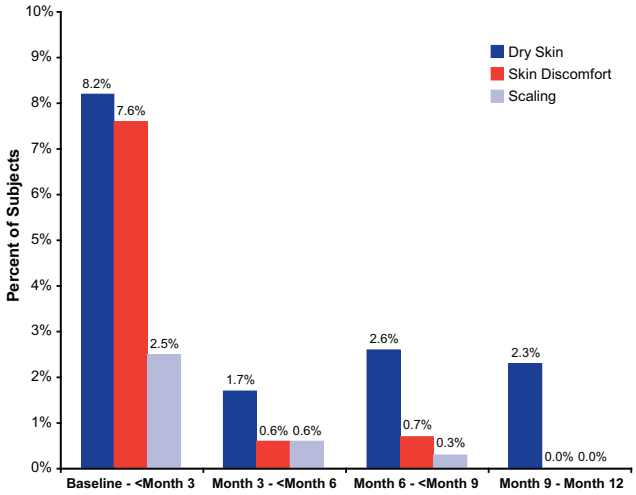



**Figure 2.** Percent of subjects with treatment-related adverse events in 3-month intervals during the study (n=551, 362, 303, and 174 in the intervals ending at 3, 6, 9 and 12 months respectively).




vere) at baseline, month 6, and month 12. In addition, subjects evaluated changes in their facial acne compared to baseline on a scale of 1 (marked improvement) to 5 (worse) at months 6 and 12.

### *Statistical Analyses*

As the study was open-label design, all data were summarized using descriptive statistics and no formal statistical hypotheses were tested. The intent-to-treat (ITT) and safety populations (all subjects who applied the study drug at least once) both contained all treated subjects; no subject was excluded from either analysis. Percent of change from baseline in noninflammatory, inflammatory, and total lesion counts and subject's assessment of acne were summarized at each visit. Scores for erythema, dryness, scaling, and stinging/burning were summarized by severity at each visit. Adverse events that were considered serious, related to the study drug, and leading to discontinuation were also summarized along with facial oiliness. For data analysis at study endpoint, the last observation carried forward (LOCF) method was used to impute missing values. SAS® software (SAS Institute, Cary, NC, Version 6.12) was used for all data analyses and tabulations, unless otherwise stated.

The study was conducted in accordance with the World Medical Association's Declaration of Helsinki and its amendments, and Good Clinical Practice Guidelines. Protocols were approved by institutional review boards and subjects provided written informed consent prior to the start of the study.

## Results

A total of 551 subjects were enrolled between March 2002 and June 2003 at 20 study centers in the US. The average age of subjects at enrollment was 19 years (range: 11-52 years). Males and females were equally represented. The majority (72%) of subjects was Caucasian and most (64%) subjects had oily skin at baseline. A detailed description of subject demographics is provided in Table 1. Of the 551 subjects enrolled, 362 (66%) were treated for 3 months or more, 303 (55%) were treated for 6 months or more, and 167 (30%) were treated for 1 year (≥353 days). Discontinuations due to adverse events were low (2.7%) and only 3 subjects (0.5%) discontinued due to lack of efficacy.

### *Safety Evaluation*

Assessments of signs and symptoms of local cutaneous irritation (erythema, dryness, scaling, and stinging/burning) demonstrated that adapalene 0.3% gel was well-tolerated over the course of treatment (Figure 1). Most signs and symptoms of local cutaneous irritation were mild to moderate in severity with less than 2% of subjects experiencing severe signs and symptoms; mean scores were between none and mild.

Forty-four percent of subjects reported 1 or more adverse events during the course of the study and 26% of subjects reported at least 1 dermatologic adverse event (Table 2). Treatment-related adverse events were reported by 119 (22%) subjects, of which 117 subjects reported dermatologic, treatment-related adverse events. The incidence of treatment-related adverse events was highest during the first 3 months (18% of subjects) compared to the remainder of the study (3.3%, 4.3%, and 3.4% during the second, third, and fourth quarters of the study, respectively) (Figure 2). The most common treatment-related adverse events (those occurring in ≥1% of subjects) included dry skin, skin discomfort, and scaling. Four subjects reported treatment-related adverse events that were nondermatologic (1 subject was found to have an abnormal lab test, 1 subject reported of headaches, and 2 subjects reported of eye pain). A total of 6 subjects reported serious adverse events, but none were related to study treatment. Routine laboratory assessments (hematology, blood chemistry, and urinalysis) revealed no evidence of systemic toxicity.

**Figure 3.** Time course of median percent changes from baseline in inflammatory, noninflammatory and total lesion counts. Values are based on the number of subjects evaluated at each time point except for study endpoint, which is based on the last observation carried forward for each subject in the ITT population (N=551).

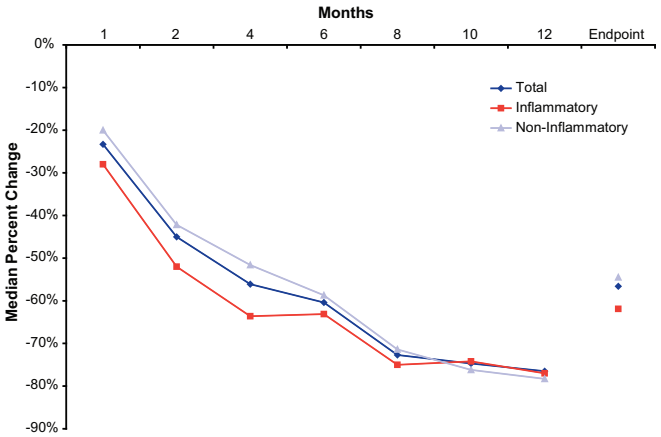
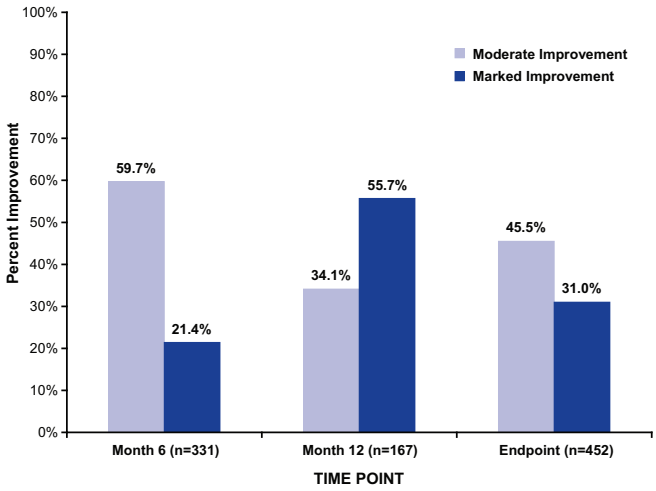



**Figure 4.** Subject assessment of percent improvement in acne, relative to baseline, at month 6, 12, and study endpoint. N=313, 167, and 462 at month 6, month 12, and study endpoint, respectively. The last observation carried forward was included in the analysis of improvement at study endpoint.




### *Efficacy Evaluation*

Treatment with adapalene 0.3% gel once daily for 52 weeks resulted in continuous reductions in total, inflammatory, and noninflammatory lesions. For subjects who received 52-week of treatment, a median reduction from baseline of >75% was achieved for inflammatory, noninflammatory, and total lesion counts (Figure 3).

Physician ratings of facial oiliness improved from some degree of oiliness to no oiliness from baseline to month 6 and 12. At baseline, 69 (13%) subjects had no oiliness compared to 130 (42%) with no oiliness at months 6 and 111 (66%) with no oiliness at month 12.

A summary of subject self-assessments of their overall improvement in acne severity showed that subjects assessed themselves as having moderate improvement or better in 81.1% of subjects at month 6 (n=313) and in 89.8% of subjects at month 12 (n=167) (Figure 4).

## Discussion

This open-label study was designed to evaluate the safety and efficacy of once-daily application of a higher concentration (0.3%) of a adapalene gel in the long-term (52 weeks) treatment of subjects with acne vulgaris. This study shows that adapalene 0.3% gel is well tolerated, safe, and effective in the treatment of acne for up to 1 year. The safety and efficacy of adapalene 0.3% gel observed in this study confirm the results from a previous study demonstrating good tolerability and superior efficacy of adapalene 0.3% gel compared to adapalene 0.1% gel in shorter-term treatment (12 weeks) of acne vulgaris.[22]

Although all topical retinoids are associated with some degree of local cutaneous irritation, adapalene is considered to have a favorable tolerability profile among the topical retinoids currently available. As in previous studies of adapalene 0.1% gel, signs and symptoms of local cutaneous irritation (erythema, scaling, dryness, stinging/burning) observed with adapalene 0.3% gel were transient and mostly mild to mod(mild) for all signs and symptoms. Over the 12-month course of the study, less than 2% of subjects reported tolerability scores that were severe. Based on the favorable tolerability findings in this study, it is doubtful that patient compliance with long-term treatment using adapalene 0.3% gel would be negatively affected by poor tolerability. Treatment-related adverse events were experienced by a relatively low (22%) proportion of subjects in the study and the highest incidence (18%) was observed during the first 3 months of treatment, with low incidences observed thereafter (≤4.3%). Only 15 subjects discontinued the study due to an adverse event and the most common treatment-related adverse events observed in this study (dry skin, skin discomfort, and scaling) were similar to those observed in previous studies of topical retinoids.[15,24-26] No unexpected systemic or dermatologic adverse events or evidence of cumulative toxicity were observed over the course of the 52-week study.

A higher concentration of adapalene gel was well tolerated and safe in this 1-year study. One-year safety data are relevant in light of the recommendation to use retinoids for long-term maintenance strategies to prevent formation of new or recurring acne lesions.[7,23,24] This study provides those relevant long-term tolerability and safety data for adapalene 0.3% gel.[6] It is interesting to note that with long-term treatment, the benefit (efficacy) increases while the risks (signs and symptoms of local cutaneous irritation and incidence of adverse events) remain relatively constant over time.

Continuous reductions in inflammatory, noninflammatory, and total lesions were observed over the course of the study, with a >75% median reduction observed after 52 weeks of treatment. Furthermore, long-term treatment with adapalene

0.3% gel in this open-label safety study resulted in reductions in acne lesions greater than those observed after 12 weeks of treatment (~55% at endpoint).[22] There is little available data that examines the efficacy of topical retinoids beyond a 12-week period. This study is among the first to look at the efficacy and safety of a topical retinoid over the long term. Although this was an open-label study, the results suggest that acne can continue to improve with the use of topical retinoids over time. Placebo-controlled studies however would be required to fully test this hypothesis. Other relevant parameters for long-term treatment, including subjects' assessment of acne improvement, also had favorable outcomes in this study. The higher, more efficacious concentration of adapalene gel (0.3%) provides physicians with an additional treatment option for improving short-term and long-term therapeutic outcomes in subjects with acne.

## Conclusion

This open-label study demonstrated adapalene 0.3% gel to be well tolerated, safe, and effective in the long-term (up to 1 year) treatment of subjects with acne vulgaris, and hence supports long-term use of this new retinoid for treatment and maintenance strategies in clinical practice.

**Disclosure**: Joyce Hwa, Yin Liu PhD, and Michael Graeber MD are employees of Galderma Research & Development. None of the authors has a financial interest in the company.

An overview of some of the results (Figures 1-4) was included in a scientific poster presented at the 2007 meeting of Fall Clinical and World Congress Meetings.

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