# Adapalene gel 0.3% for the treatment of acne vulgaris: A multicenter, randomized, double-blind, controlled, phase III trial

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***Background:*** A new 0.3% gel formulation of adapalene has been developed.

***Objective:*** We sought to provide evidence of the superiority of adapalene gel 0.3% over adapalene gel 0.1% and gel vehicle in the treatment of acne.

***Methods:*** A total of 653 patients were randomized to receive adapalene gel 0.3%, adapalene gel 0.1%, or vehicle once daily for 12 weeks (2:2:1 randomization). Analysis for efficacy was conducted on correlated repeated measurements at weeks 8 and 12 using Generalized Estimating Equation methodology.

***Results:*** Adapalene gel 0.3% was significantly superior to adapalene gel 0.1% and vehicle in success rate, total lesion count, and inflammatory lesion count. A consistent, dose-dependent effect was demonstrated for all efficacy measures. Signs and symptoms were mostly mild to moderate and transient in nature.

***Limitations:*** Adjunctive topical or oral agents and their impact on acne were not studied in this trial.

***Conclusions:*** Adapalene gel 0.3% was effective and well tolerated in the treatment of acne. (J Am Acad Dermatol 2006;54:242-50.)

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*Abbreviations used:*

GEE: Generalized Estimating Equation
IGA: Investigator's Global Assessment
ITT: intent-to-treat

Acne vulgaris is a chronic skin disease of the pilosebaceous unit, affecting approximately 80% of young adults and adolescents.[1-4] The management of acne can be challenging because of the variability in response to treatment and the need for long-term therapy. 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.[5,6] Currently, there is a variety of topical and systemic therapies that are recommended for the treatment of acne, including retinoids, antibiotics, benzoyl peroxide, and hormone therapy. Topical retinoids, such as adapalene,

are an integral part of acne therapy and are considered appropriate first-line therapy, either alone or in combination with antimicrobials, for all cases of acne with the exception of the most severe.[6]

Adapalene is a synthetic naphthoic acid derivative with retinoid activity, which has been shown to reverse the abnormal follicular desquamation and inflammatory responses involved in the pathogenesis of acne.[7-11] The efficacy of adapalene has been established in numerous clinical trials as monotherapy[11-15] and in combination with other topical and oral antibiotics.[16,17] In addition, adapalene has demonstrated a more favorable tolerability profile than other topical retinoids, including all tazarotene[18,19] and tretinoin[19-23] formulations.

Adapalene is marketed in several formulations, including gel, cream, pledgets, and solution, but is currently only available in a single 0.1% concentration. Considering the broad range of severity in acne presentations and the variability in response to current therapies, there is a need for an increase in the number of well-tolerated treatment options available to manage this disorder. In this regard, a new, higher concentration (0.3%) gel formulation of adapalene has been developed to provide the dermatology community with increased flexibility in the management of acne. In a recent phase II dose-assessment study, adapalene gel 0.3% was found to be superior to the corresponding gel vehicle and to provide a concentration-dependent increase in clinical benefit relative to adapalene gel 0.1%.[24] The primary objective of the present phase III study was to provide additional evidence of the superiority of adapalene gel 0.3% over adapalene gel 0.1% and the corresponding vehicle in a larger cohort of patients with acne vulgaris.

## METHODS

### Study design

The efficacy, safety, and tolerability of adapalene gel 0.3%, adapalene gel 0.1%, and gel vehicle were compared in a multicenter, randomized, active- and vehicle-controlled, double-blind, parallel group phase III study conducted at 33 centers in the United States and Canada. Eligible patients were randomized consecutively in 2:2:1 ratio to receive adapalene gel 0.3%, adapalene gel 0.1%, or vehicle gel, respectively. The randomization schedule remained blinded from those involved in the clinical conduct of the study. To ensure the integrity of the blinding, medication was packaged in identical tubes and a third party other than the investigator/evaluator dispensed the medication. Patients were instructed to apply treatment once daily in the evening for 12 weeks. Evaluations occurred at baseline and at weeks 1, 2, 4, 8, and 12. Approximately half of the centers obtained blood and urine samples for evaluating blood chemistry, hematology, and urinalysis. A urine pregnancy test was required at screening and at the final study visit for all female patients of childbearing potential. Patients were free to withdraw from the study at any time for any reason. Patients not completing the entire study were to be fully evaluated when possible.

This study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and Good Clinical Practices and in compliance with local regulatory requirements. This study and all appropriate amendments were reviewed and approved by an institutional review board. All patients provided written informed consent before entering the study.

### Patients

Male and female patients, 12 years or older, with 20 to 100 noninflammatory facial lesions, 20 to 50 inflammatory facial lesions, and no nodules or cysts were enrolled in the study. Specified washout periods were required for patients taking certain topical and systemic treatments. Exclusion criteria prohibited enrollment of patients with severe acne requiring isotretinoin therapy or other dermatologic conditions requiring interfering treatment. Women were excluded if they were pregnant, nursing, or planning a pregnancy as were men with facial hair that would interfere with the assessments.

### Efficacy and safety assessments

The primary efficacy variables were success rate (the percentage of patients rated "clear" or "almost clear" on the Investigator's Global Assessment [IGA]) (Table I) and percent lesion reduction from baseline (total, inflammatory, and noninflammatory). Lesion counts were assessed on the face only. Secondary efficacy assessments included response rate, the percentage of patients who achieved at least 50% reduction in lesion counts (inflammatory, noninflammatory, and total); IGA (full scale); and patient's assessment of acne.

Safety and tolerability were assessed through evaluations of local facial tolerability, adverse events, and clinical laboratory evaluations. At each visit, the investigator rated erythema, scaling, dryness, and stinging/burning on a scale ranging from 0 (absence) to 3 (severe). Adverse events were evaluated at each visit. At specified centers, blood and urine samples were collected at screening and last visit for hematology, blood chemistry, and urinalysis.

**Table I.** Investigator's Global Assessment

| | | | |
|---|---|---|---|
| SUCCESS | 0 | Clear | Residual hyperpigmentation and erythema may be present |
| | 1 | Almost clear | A few scattered comedones and a few (<5) small papules |
| FAILURE | 2 | Mild | Easily recognizable; less than half the face involved; many comedones and many papules and pustules |
| | 3 | Moderate | More than half of the face is involved; numerous comedones, papules, and pustules |
| | 4 | Severe | Entire face is involved; covered with comedones, numerous papules, and pustules, and few nodules and cysts |
| | 5 | Very severe | Highly inflammatory acne covering the face with nodules and cysts present |

### Statistical analyses

All data analysis was carried out according to a pre-established analysis plan. The primary hypotheses were to show superiority of adapalene gel 0.3% over 0.1% and corresponding vehicle on success rate and two of the three (total, inflammatory, and noninflammatory) percent lesion reductions using intent-to-treat (ITT) data. A sample size of 630 patients (252 in each active treatment arm and 126 in the vehicle arm) was required to detect a 10% difference to variability in percent lesion reduction and success rate between adapalene gel 0.3% and adapalene gel 0.1% with $\alpha = 0.05$ and a power of at least 80%. This is based on a ratio of treatment difference to variability in percent lesion reduction of 0.29 to 0.32 as observed in a recent phase 2, dose-assessment study.[24]

Based on a recommendation from the Food and Drug Administration, the primary efficacy assessments (success rate and the percent lesion reductions from baseline for total, inflammatory, and noninflammatory lesions) were performed on data from weeks 8 and 12 for the ITT population using Generalized Estimating Equation (GEE) methodology to account for the correlation of repeated measurements from individual patients in the study.[25] For success rates, the logit link function was used to model the marginal expectation. For percent changes in lesion counts, the identity link function was used. The Cochran-Mantel-Haenszel test at single time points was performed as a secondary analysis to validate the results. All tests were 2-sided and used the .05 level to declare significance.

Demographic variables were tested for comparability among the 3 treatment groups. Three study populations were analyzed. The safety population was defined as all patients randomized, and treated at least once. The ITT population included all randomized patients who were dispensed study medication. The per-protocol population included all randomized patients without any major protocol violations.

## RESULTS

### Patient disposition and baseline characteristics

A total of 653 patients were randomized and included in the ITT population (258 receiving adapalene gel 0.3%, 261 receiving adapalene gel 0.1%, and 134 receiving adapalene gel vehicle) (Fig 1). The safety population included all patients with ITT. The per-protocol population consisted of 543 patients (83%). Overall, 90% of patients completed the study. Discontinuation rates were 12% in the adapalene gel 0.3% treatment group, 8% in the adapalene gel 0.1% group, and 10% in the gel vehicle group. Patient request (4.6%) was the most frequent reason for discontinuation.

Baseline characteristics of the ITT population are summarized in Table II. There were no significant differences among the treatment groups in demographic and baseline characteristics.

### Efficacy evaluation

The success rates, defined as the percentage of patients with "clear" or "almost clear" ratings on the IGA, at week 12 are shown in Table III. GEE analysis demonstrated the success rates for the adapalene gel 0.3% group to be significantly superior to those for the adapalene gel 0.1% group ($P = .020$) and the gel vehicle group ($P = .005$). A consistent dose-dependent response was observed at each time point. Success rates (patients rated "clear" or "almost clear" on IGA) were 23.3%, 16.9%, and 10.0% in the adapalene gel 0.3%, adapalene gel 0.1%, and vehicle gel groups, respectively, for patients completing 12 weeks of the study. A post hoc analysis of subgroups stratified by baseline IGA severity confirms the dose-dependent trend for patients with moderate to severe IGA at baseline. Success rates at week 12 were 21.8%, 15.4%, and 4.2% for moderate to severe cases ($n = 404$) in the adapalene gel 0.3%, adapalene gel 0.1%, and vehicle gel groups, respectively.

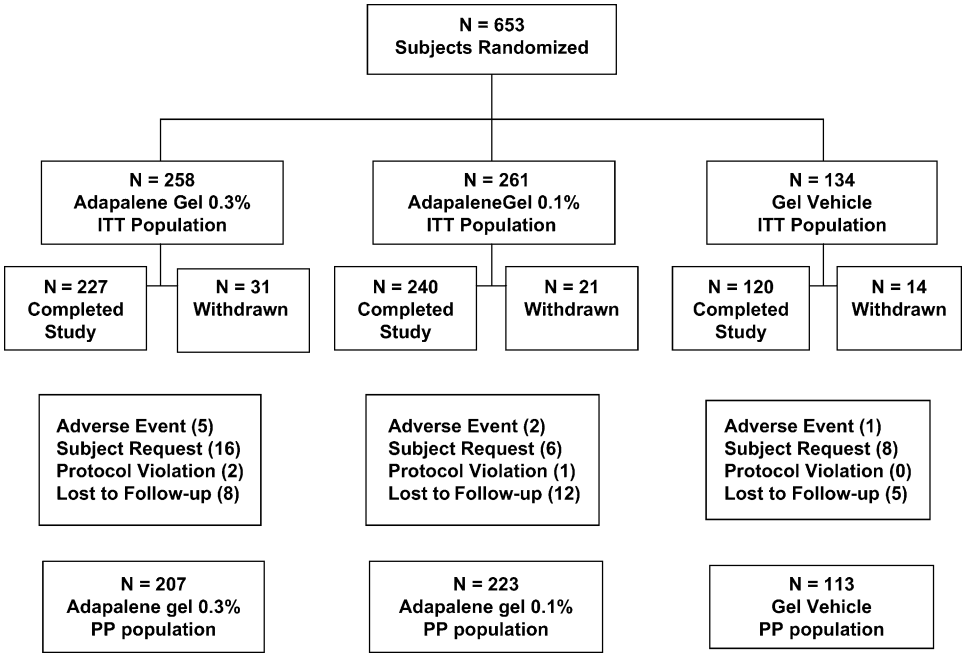


**Fig 1.** Patient disposition. *ITT*, Intent to treat; *PP*, per protocol.

Median percentage changes from baseline for total, inflammatory, and noninflammatory lesion counts at week 12 are presented in Table III. As with the success rate analysis, lesion count analysis revealed a dose-dependent response in the adapalene gel 0.3% and adapalene gel 0.1% groups. GEE analysis showed a statistically significant difference between the adapalene gel 0.3% and adapalene gel 0.1% groups in the percent reduction in total lesion counts ($P = .020$) and inflammatory lesion counts ($P = .015$). The difference in the percent reduction in noninflammatory lesion counts between the active treatment groups was marginally significant ($P = .061$). As expected, the GEE analyses also showed the superiority of adapalene gel 0.3% over gel vehicle in success rate ($P = .005$) and in the percent lesion reduction in total, inflammatory, and noninflammatory lesion counts (all $P < .001$).

The Cochran-Mantel-Haenszel test at single time points was performed as a secondary efficacy analysis on week 12 total lesion count data (ITT, last observation carried forward) to validate the results. This analysis also showed adapalene gel 0.3% statistically superior to adapalene gel 0.1% in the percent reduction in total lesion counts ($P = .02$) at end point. In addition, adapalene gel 0.3% was statistically superior to vehicle gel in percent lesion reduction in total lesion counts ($P < .001$ at end point) with significant differences observed as early as the first postbaseline visit ($P = .010$ at week 1) (Fig 2). The results were confirmed in the per-protocol population. Fig 3 depicts the effects of 12 weeks of treatment with adapalene gel 0.3%.

Secondary efficacy assessments also revealed a consistent dose-dependent difference between active treatment groups in response rates for total lesions (59.5% vs 48.7%; $P = .016$), inflammatory lesions (66.1% vs 59.7%; $P = .107$), and noninflammatory lesions (53.7% vs 43.7%; $P = .027$) for patients completing 12 weeks of the study. The percentages of patients rating their skin as "clear" or showing a "marked improvement" were 29.8% and 24.2% for adapalene gel 0.3% and adapalene gel 0.1% groups, respectively. As expected, adapalene gel 0.3% was statistically superior to gel vehicle at the end of the study for all secondary efficacy assessments (all $P < .02$). Results were similar regardless of age, sex, or race.

## Safety evaluation

The results of local tolerability assessments are reported in Fig 4. As expected with a topical retinoid, concentration-dependent increases in the incidence of scaling, dryness, and stinging/burning were noted early in the study (Fig 4). The incidence of erythema was similar between the two adapalene gel treatment groups. Erythema, scaling, dryness, and stinging/burning were transient in duration, peaking during the first weeks of treatment and decreasing over time. Signs and symptoms of skin irritation were mostly mild or moderate in severity. Few patients experienced severe erythema (0.4% vs 0.8% for

**Table II.** Baseline characteristics of the intent-to-treat population

| Demographic parameter | Adapalene gel 0.3% (N = 258) | Adapalene gel 0.1% (N = 261) | Vehicle gel (N = 134) | Total (N = 653) | *P* value* |
|---|---|---|---|---|---|
| Sex, n (%) | | | | | |
| Male | 129 (50.0) | 132 (50.6) | 62 (46.3) | 323 (49.5) | .703 |
| Female | 129 (50.0) | 129 (49.4) | 72 (53.7) | 330 (50.5) | |
| Race, n (%) | | | | | |
| White | 194 (75.2) | 186 (71.3) | 91 (67.9) | 471 (72.1) | .422 |
| Black | 26 (10.1) | 23 (8.8) | 18 (13.4) | 67 (10.3) | |
| Asian | 6 (2.3) | 12 (4.6) | 4 (3.0) | 22 (3.4) | |
| Hispanic | 27 (10.5) | 35 (13.4) | 18 (13.4) | 80 (12.3) | |
| Other | 5 (1.9) | 5 (1.9) | 3 (2.2) | 13 (2.0) | |
| Age, y | | | | | |
| Mean | 18.4 | 17.8 | 18.6 | 18.2 | .409 |
| SD | 6.19 | 5.97 | 6.39 | 6.14 | |
| Median | 16.0 | 16.0 | 16.0 | 16.0 | |
| Minimum, maximum | 12, 41 | 12, 52 | 12, 39 | 12, 52 | |
| 12-17, n (%) | 162 (62.8) | 178 (68.2) | 79 (59.0) | 419 (64.2) | .134 |
| 18-64, n (%) | 96 (37.2) | 83 (31.8) | 55 (41.0) | 234 (35.8) | |
| Lesion counts, mean† | | | | | |
| Total | 61.0 | 64.0 | 62.5 | | .227 |
| Inflammatory | 25.0 | 25.0 | 24.0 | | .581 |
| Noninflammatory | 33.0 | 34.0 | 34.0 | | .222 |
| IGA, n (%)† | | | | | |
| 0 = Clear | — | — | — | | |
| 1 = Almost clear | — | — | — | | |
| 2 = Mild | 97 (37.6) | 101 (38.7) | 51 (38.1) | | |
| 3 = Moderate | 159 (61.6) | 158 (60.5) | 80 (59.7) | | |
| 4 = Severe | 2 (0.8) | 2 (0.8) | 3 (2.2) | | |
| 5 = Very severe | — | — | — | | |
| Total | 258 (100.0) | 261 (100.0) | 134 (100.0) | | .817 |

*IGA*, Investigator's Global Assessment.
**P* values for categorical variables were based on the Cochran-Mantel-Haenszel general association statistic, adjusted for center; *P* values for continuous variables were based on 2-way analysis of variance model with terms for treatment and center.
†*P* values for lesion counts and IGA were pair-wise comparisons between the active treatment groups.

adapalene gel 0.3% and adapalene gel 0.1%, respectively), scaling (1.2% vs 1.6%), dryness (0.8% vs 2.7%), or stinging/burning (3.6% vs 3.9%), with comparable incidence in the adapalene gel 0.3% and adapalene gel 0.1% treatment groups.

Treatment-related adverse events were experienced by 22%, 12%, and 4.5% of patients in the adapalene gel 0.3%, adapalene gel 0.1%, and vehicle gel groups, respectively. As expected with a topical medication, most of these events were observed on the treated areas of skin. Dry skin (14% and 6.9% for adapalene gel 0.3% and adapalene gel 0.1%, respectively) and skin discomfort (5.8% and 4.6% for adapalene gel 0.3% and adapalene gel 0.1%, respectively) were the most frequently reported adverse events in the active treatment groups. Most treatment-related adverse events were either mild or moderate. No treatment-related serious adverse events were reported. A total of 8 patients discontinued from the study because of adverse events, 6 of whom were deemed to have done so related to treatment (3 for adapalene gel 0.3%; 2 for 0.1%; 1 for gel vehicle).

There were no trends in hematology, blood chemistry, or urinalysis parameters indicative of any systemic toxic effect of study medications.

## DISCUSSION

This phase III study was designed to confirm the superiority of a new 0.3% formulation of adapalene gel over the currently marketed adapalene gel 0.1% and the corresponding vehicle for patients with acne vulgaris demonstrated in a recent phase II study.[24] Present results showed that adapalene gel 0.3% was statistically superior to adapalene gel 0.1% in the treatment of acne vulgaris. A clear, dose-dependent response was observed for all efficacy assessments, with adapalene gel 0.3% providing an incremental increase in clinical efficacy relative to adapalene gel 0.1%. GEE analyses demonstrated the 0.3% concentration to be significantly superior to the 0.1%

**Table III.** Total, inflammatory, and noninflammatory lesion counts (median percent change) at week 12

| | Treatment group | | | | |
|---|---|---|---|---|---|
| | Adapalene gel 0.3% (1) | Adapalene gel 0.1% (2) | Vehicle gel (3) | *P* value* (1) vs (2) | *P* value* (2) vs (3) |
| Success rate, % | 23.3 | 16.9 | 10.0 | .020 | .005 |
| Lesion count | | | | | |
| Total, % change | −55.6 | −48.2 | −36.4 | .020 | <.001 |
| Inflammatory, % change | −62.5 | −57.8 | −47.2 | .015 | <.001 |
| Noninflammatory, % change | −52.1 | −43.4 | −29.3 | .061 | <.001 |

Intent-to-treat (ITT) population.
**P* values based on correlated repeat measurements at weeks 8 and 12 using generalized estimating equation methodology.

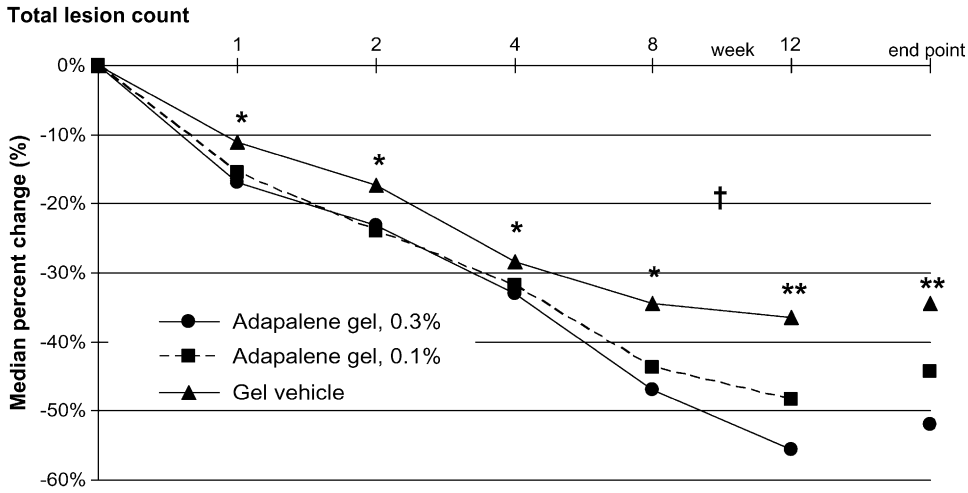


**Fig 2.** Total lesion count. *CMH*, Cochran-Mantel-Haenszel; *GEE*, generalized estimating equation. *CMH test: at least $P < .05$ for adapalene gel 0.3% versus gel vehicle. **CMH test: at least $P < .05$ for adapalene gel 0.3% versus adapalene gel 0.1% and adapalene gel 0.3% versus gel vehicle. †GEE analysis $P = .02$ for adapalene gel 0.3% versus adapalene gel 0.1% and $P = .005$ for adapalene gel 0.3% versus gel vehicle based on week 8 and week 12 data.

concentration in success rate ($P = .020$), percent lesion reduction in total lesion counts ($P = .020$), and inflammatory lesion counts ($P = .015$), and marginally significant in noninflammatory lesion counts ($P = .061$). Interestingly, the increase in adapalene concentration seemed to have a more significant effect on inflammatory lesions than on noninflammatory lesions. A possible explanation for this observation could be that the optimal doses for adapalene's comedolytic and anti-inflammatory properties are different and, therefore, the higher concentration of adapalene may provide a comparatively larger benefit against inflammatory relative to noninflammatory lesions. Additional studies would be necessary to investigate this theory. Also, these results may reflect the GEE statistical methodology used for the primary efficacy assessment, which uses data at weeks 8 and 12. If a full 12 weeks was necessary to observe a statistically significant difference in noninflammatory lesions, then the week-8 data would have diluted the significance of the noninflammatory lesion effect at week 12.

As expected, adapalene gel 0.3% was also statistically superior to the corresponding gel vehicle in all primary and secondary efficacy assessments. Adapalene gel 0.3% demonstrated a fast onset of action as statistically significant differences in total lesions were observed as early as week 1 for the 0.3% concentration relative to vehicle. The results of this study support a previous phase II study in 214


**Fig 3.** Effect of adapalene gel 0.3% on facial lesions at baseline and after 4, 8, and 12 weeks of treatment.

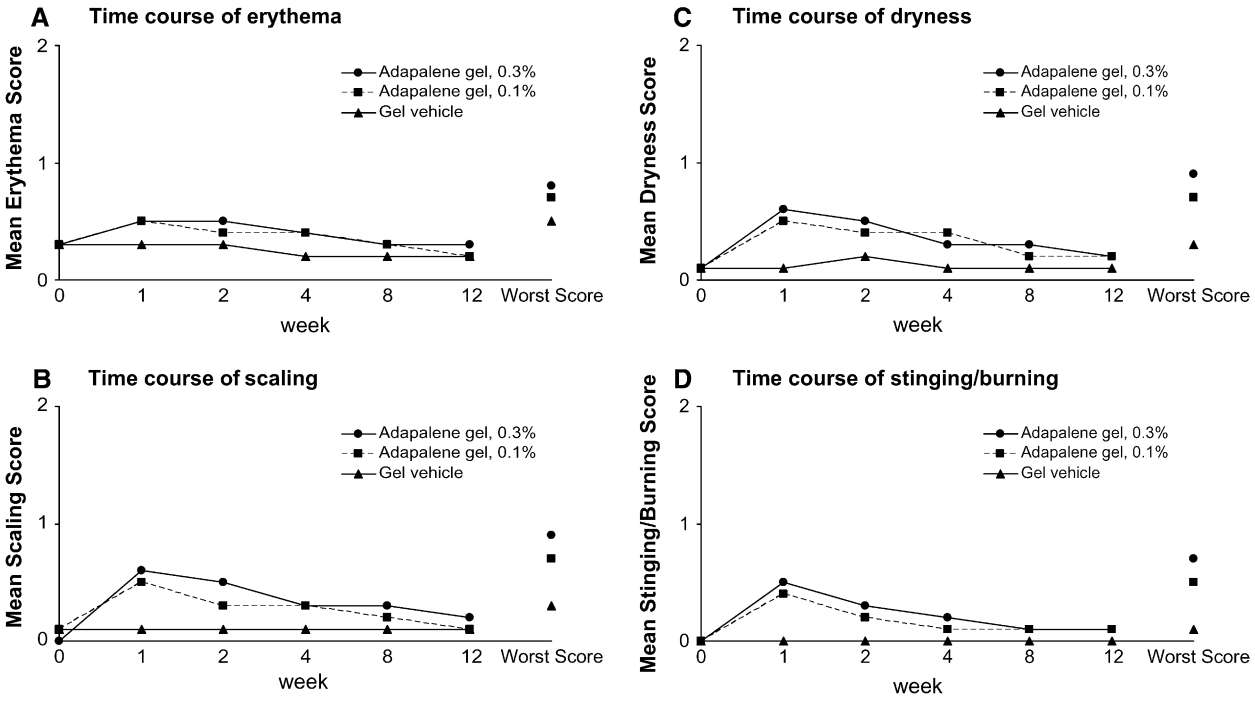


**Fig 4.** Local tolerability. Effects of adapalene gel 0.3% versus adapalane gel 0.1% and gel vehicle on mean scores for skin tolerance variables: erythema (**A**), scaling (**B**), dryness (**C**), and stinging/burning (**D**). Skin tolerability variables were assessed according to following scoring scale: none = 0, mild = 1, moderate = 2, and severe = 3. Mean scores at each postbaseline visit and worst score (worst observation recorded for patient during postbaseline period) are included.

patients in which adapalene gel 0.3% started to work quickly and provided an enhanced benefit in clinical efficacy relative to 0.1%.[24]

Both concentrations of adapalene gel were safe and well tolerated in this study. The signs and symptoms of skin irritation were mostly mild to moderate in severity and transient in nature. Importantly, despite the increase in adapalene concentration, the incidence of severe skin irritation was low and comparable between the two treatment groups. As is common with topical retinoids,[10] side effects subsided within the first 4 weeks of the study. Dose-dependent increases in mild/moderate adverse events were observed, but the incidence of severe adverse events was comparable between the active formulations. Of clinical importance, no treatment-related serious adverse events were reported and the systemic safety of the two adapalene concentrations was comparable with the corresponding gel vehicle. The results of this study confirm that adapalene gel 0.3% retains the safety profile of the 0.1% formulation.[11,12,18-24]

The results of this study have implications for the management of acne vulgaris. The superior clinical efficacy of adapalene gel 0.3% relative to the 0.1% formulation demonstrated in this study in combination with the fast onset of action relative to vehicle establishes adapalene gel 0.3% as an effective new treatment option for the management of acne. The availability of two concentrations of adapalene gel will provide greater flexibility for customizing care and improving outcomes for patients with acne. For example, for patients who are more sensitive to topical retinoids, it may be preferable to start therapy with the 0.1% formulation and increase to the 0.3% formulation as needed. Alternatively, other patients may prefer to begin therapy with the 0.3% formulation alone or in combination with antimicrobials depending on the severity of the disease.[6]

In summary, this phase III study demonstrated that once-daily adapalene gel 0.3% is effective in the treatment of acne vulgaris. A consistent and significant dose-dependent effect was observed, with adapalene gel 0.3% providing a superior clinical response relative to the 0.1% formulation and vehicle. As expected with a topical retinoid, signs and symptoms of skin irritation were observed with both adapalene concentrations, but were mostly mild or moderate and transient.

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