

# Adapalene Gel, 0.1%, as Maintenance Therapy for Acne Vulgaris

## A Randomized, Controlled, Investigator-Blind Follow-up of a Recent Combination Study

Diane M. Thiboutot, MD; Alan R. Shalita, MD; Paul S. Yamauchi, MD, PhD; Catherine Dawson; Nabil Kerrouche; Stéphanie Arsonnaud; Sewon Kang, MD

**Objective:** To assess the maintenance effect of adapalene gel, 0.1%, relative to gel vehicle in subjects successfully treated in a previous 12-week study of adapalene-doxycycline, 100 mg, combination therapy.

**Design:** Multicenter, investigator-blind, randomized, controlled study.

**Setting:** Thirty-four US centers.

**Subjects:** A total of 253 subjects with severe acne vulgaris who showed at least moderate improvement from baseline (50% improvement from baseline) when treated with either adapalene plus doxycycline or doxycycline plus gel vehicle in a previous 12-week study.

**Interventions:** Subjects were randomized to receive adapalene gel, 0.1%, or gel vehicle once daily for 16 weeks.

**Main Outcome Measures:** Efficacy and safety criteria included maintenance rate (subjects maintaining at least 50% improvement in lesion counts from previous therapy), lesion counts (total, inflammatory, and noninflammatory), global severity assessment, cutaneous tolerability, and adverse events.

**Results:** Adapalene maintenance therapy resulted in significantly larger maintenance rates (75% vs 54%;  $P < .001$ ) and significantly lower lesion counts (total [ $P = .005$ ], inflammatory [ $P = .01$ ], and noninflammatory [ $P = .02$ ]) compared with gel vehicle. Adapalene was safe and well tolerated in this study.

**Conclusion:** This study demonstrates a clinical benefit of continued treatment with adapalene gel, 0.1%, as a maintenance therapy for acne.

*Arch Dermatol.* 2006;142:597-602

**A**CNE VULGARIS IS AN EXCEPTIONALLY common, recurring disease involving multiple etiological factors including follicular hyperkeratinization, increased sebum production, *Propionibacterium acnes* proliferation, and inflammation.<sup>1-3</sup> The management of acne can be complex, often requiring aggressive combination therapy and a long-term therapeutic strategy.<sup>4,5</sup> Maintenance therapy is necessary for many patients with acne because acne lesions have been shown to return after discontinuing a successful treatment regimen.<sup>5,6</sup> Despite the variety of medications available for the treatment of acute acne, to our knowledge, there are no published well-controlled studies providing evidence for long-term or maintenance efficacy.

An effective maintenance therapy should prevent acne recurrence by targeting the early stages of comedogenesis and the precursor of mature acne lesions, the micro-comedo.<sup>5,7</sup> At present, the most effective comedolytic agents are oral isotretinoin and topical retinoids.<sup>8</sup> Oral isotretinoin is an impractical choice for long-term therapy owing to the potential for toxic and terato-

genic effects. Topical antiacne medications, such as retinoids, could be associated with elevated skin irritation. Therefore, careful consideration must be given to the tolerability of a potential maintenance therapy because cutaneous adverse effects may decrease treatment adherence.<sup>9</sup>

### See also pages 605 and 638

Recently published guidelines recommend topical retinoids with or without benzoyl peroxide for maintenance following initial combination treatment with an antimicrobial agent.<sup>5</sup> The present well-controlled study intended to mirror this practice recommendation: in an initial study, the efficacy and safety of adapalene, a naphthoic acid derivative with anti-inflammatory and receptor-selective retinoid properties,<sup>10-12</sup> was evaluated when used concomitantly with oral doxycycline by subjects with severe acne for 12 weeks.<sup>13</sup> Eligible subjects were randomized to receive doxycycline, 100 mg once daily, in the morning and either adapalene gel, 0.1%, or gel vehicle once daily in the evening. At week

**Author Affiliations:** The Pennsylvania State University College of Medicine, Milton S. Hershey Medical Center, Hershey (Dr Thiboutot); SUNY Downstate Medical Center, Brooklyn, NY (Dr Shalita); University of California, Los Angeles, School of Medicine, Santa Monica (Dr Yamauchi); Galderma Research & Development, Princeton, NJ (Mss Dawson and Arsonnaud); Galderma Medical Affairs, Sophia-Antipolis, France (Mr Kerrouche); and University of Michigan, Ann Arbor (Dr Kang).

12, the combination of adapalene and doxycycline produced significantly larger reductions in total ( $P < .001$ ), inflammatory ( $P = .02$ ), and noninflammatory lesions ( $P < .001$ ) relative to treatment with doxycycline alone, confirming results from previous adapalene-antimicrobial combination studies.<sup>14,15</sup>

In the present study, the maintenance effect of adapalene gel, 0.1%, was evaluated relative to its gel vehicle in those subjects who showed at least moderate improvement (50% improvement from baseline) from the previous adapalene-doxycycline combination therapy study.

## METHODS

### STUDY DESIGN AND SUBJECTS

The efficacy and safety of adapalene gel, 0.1% (Differin Gel, 0.1%; Galderma Laboratories, LP, Ft Worth, Tex), as a maintenance therapy were compared with gel vehicle in a randomized, multicenter, vehicle-controlled, investigator-blind, parallel group study conducted at 34 centers in the United States between November 13, 2003, and May 25, 2004. Male and female subjects with acne, aged 12 to 30 years, who showed at least moderate improvement from baseline (on a 6-point scale ranging from clear to worse) to after treatment with either adapalene plus doxycycline, 100 mg once daily, or doxycycline, 100 mg once daily, plus gel vehicle in a previous 12-week study<sup>13</sup> were enrolled. In that study, a total of 467 subjects were randomized to receive doxycycline once daily in the morning and either adapalene or gel vehicle once daily in the evening for 12 weeks. Eligible subjects completing the combination study were rerandomized consecutively in a 1:1 ratio to receive either adapalene gel, 0.1%, or its gel vehicle once daily in the evening for an additional 16 weeks as part of the present study. Randomization was achieved using a central telephone system to assure that the numbers of subjects who received adapalene in the first part of the study would be evenly distributed between the 2 groups in the maintenance phase. The randomization schedule remained blinded from those involved in the clinical conduct of the study. The integrity of the blinding was ensured by packaging the topical medication in identical tubes and requiring a third party other than the investigator to dispense the medication.

Exclusion criteria prohibited enrollment of subjects with 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. Subjects were provided with a daily facial moisturizer with sun protection factor 15 to use as needed for the symptomatic relief of skin dryness or irritation.

Evaluations for this study occurred at baseline and at weeks 4, 8, 12, and 16. The final visit from the previous 12-week combination study served as the baseline visit for this 16-week maintenance study. A urine pregnancy test was required at screening and at the final study visit for all female subjects of childbearing potential. Subjects were free to withdraw from the study at any time and for any reason. Subjects 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 guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and in compliance with local regulatory requirements. This study was reviewed and approved by institutional review boards. All patients provided their written informed consent prior to entering the study.

## EFFICACY AND SAFETY VARIABLES

The primary efficacy variable was the failure rate at week 16, defined as the percentage of subjects unable to maintain 50% improvement in the total lesion count from the previous 12-week combination therapy study (eg, treatment in a subject entering the maintenance phase after having lost 40 lesions in the combination study was considered a failure if the lesion count at the end of the maintenance study was increased by more than 20 lesions). Data from this assessment are presented graphically herein as a maintenance rate, which is simply 100% minus the failure rate. Secondary efficacy variables included lesion counts (total, inflammatory, and noninflammatory), failure rates for inflammatory and noninflammatory lesions, and global severity of the disease. At the last visit, subject satisfaction was assessed via a 5-question survey.

Safety and tolerability were assessed through evaluations of local facial tolerability and adverse events. At each visit, the investigator rated erythema, scaling, dryness, and stinging and/or burning on a scale ranging from 0 (none) to 3 (severe). Mean scores at each postbaseline visit and worst score (worst observation recorded for a subject during the postbaseline period) were recorded. Adverse events were also evaluated at each visit.

### STATISTICAL ANALYSES

All data analyses were carried out according to a preestablished analysis plan unless specifically noted. A sample size of 113 subjects per group was deemed necessary to detect a statistically significant difference in failure rate between treatment groups based on the use of a 2-tailed test with  $\alpha = .05$  and a power of 90%, an assumption of a 15% difference in efficacy between the 2 treatment groups, and a dropout rate of 10%.

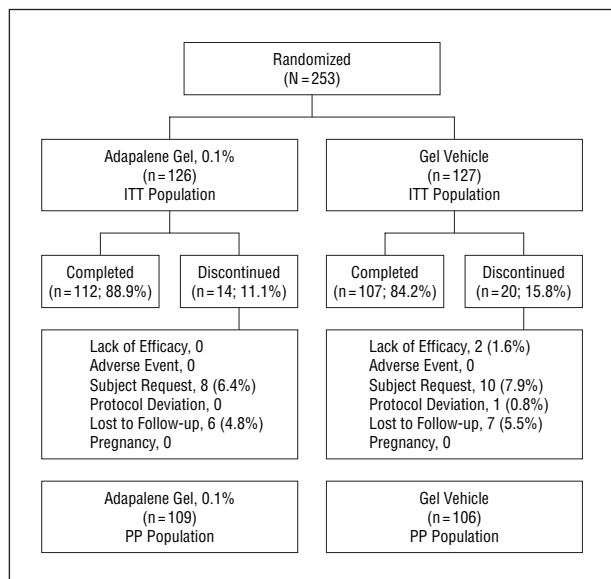
Three study populations were analyzed. The safety population was defined as all patients randomized and treated at least once. The intent-to-treat (ITT) population included all randomized subjects who were dispensed study medication. The per-protocol (PP) population included all randomized subjects without any major protocol deviations.

The aim of this study was to show superior efficacy of maintenance therapy with adapalene gel relative to gel vehicle. Analyses for efficacy were performed on week 16 data for the ITT population and the PP population. Last observation carried forward (LOCF) methodology was used for the ITT population analysis (lesion counts) to account for missing data or for data from patients who withdrew from the study. In addition, treatment was considered a failure for the failure rate analysis (worst case) in all subjects with missing data at week 16. Age was tested at baseline with the analysis of variance model with treatment, center, and their interaction as factors. All other variables were analyzed by using the Cochran-Mantel-Haenszel test controlling for "analysis center" and previous treatment for both the ITT and PP populations. All tests were 2 sided, and  $P < .05$  was considered significant. No adjustment for multiplicity was made.

## RESULTS

### SUBJECT DISPOSITION AND BASELINE CHARACTERISTICS

Of the 309 eligible subjects, 253 (82%) were enrolled in this study. The subjects were rerandomized to receive either adapalene gel, 0.1% (126 subjects), or its gel vehicle (127 subjects; **Figure 1**). Subject disposition was similar between the 2 treatment groups. The PP population comprised 215 subjects (85%). Discontinuation rates were higher in the vehicle group (15.8%) relative to the ada-



**Figure 1.** Flowchart of subject disposition. ITT indicates intent-to-treat; PP, per-protocol.

palene group (11.1%). The most common reason for discontinuation in both groups was subject request (6.4% and 7.9% for the adapalene and vehicle groups, respectively). A total of 219 subjects (87%) completed the study.

Baseline subject characteristics of the ITT population are summarized in the **Table**. Demographic characteristics and baseline dermatological scores were comparable between the 2 treatment groups.

### EFFICACY EVALUATION

The maintenance rates for total, inflammatory, and non-inflammatory lesion counts at the study end point (week 16, ITT population, worst case) are shown in **Figure 2**. These rates reflect the percentage of subjects maintaining at least 50% improvement from the previous combination study; missing data were treated as treatment failures. Continued treatment with adapalene gel, 0.1%, resulted in significantly higher maintenance rates in total lesion counts (75% vs 54%;  $P < .001$ ), inflammatory lesion counts (74% vs 57%;  $P = .003$ ), and noninflammatory lesion counts (71% vs 55%;  $P = .007$ ) compared with treatment with vehicle (Figure 2).

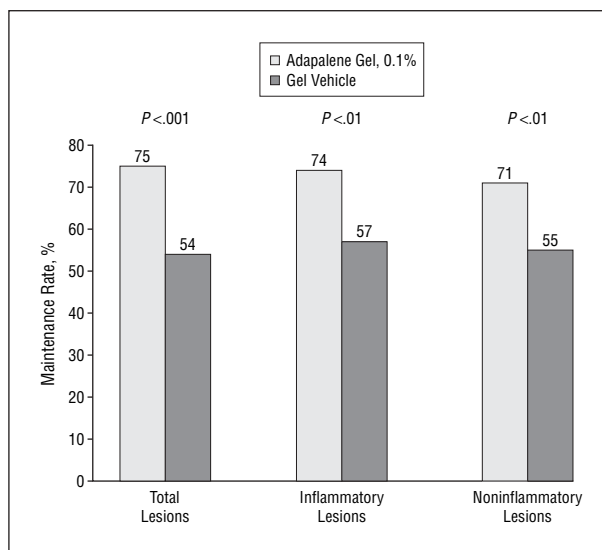
To our knowledge, no formal definition of acne maintenance currently exists, and therefore this was the first study for which this definition of maintenance was used (maintaining at least 50% improvement). To support the validity of this assessment, a post hoc analysis was performed in which maintenance was defined in stricter terms (maintaining the same number of lesions relative to baseline). A significant benefit was also observed for adapalene relative to vehicle (46.4% vs 31.8%;  $P = .03$ ) for this analysis.

Significantly lower total ( $P = .005$ ), inflammatory ( $P = .01$ ), and noninflammatory ( $P = .02$ ) lesion counts were observed for subjects receiving maintenance therapy with adapalene gel, 0.1%, relative to vehicle at the study end point (week 16, ITT, LOCF; **Figure 3**). During the course of the study, lesion counts for the vehicle group gradually increased from baseline values, while the le-

**Table. Subject Demographics and Baseline Characteristics (Intention-to-Treat Population)\***

Demographic Parameter	Adapalene Gel, 0.1% (n = 126)	Gel Vehicle (n = 127)	P Value
Age (range), y	18.1 ± 4.2 (12-30)	17.8 ± 3.9 (12-32)	.61
Sex			
Male	65 (51.6)	73 (57.5)	.34
Female	61 (48.4)	54 (42.5)	
Race			
White	74 (58.7)	76 (59.8)	.56
Black	17 (13.5)	14 (11.0)	
Asian	6 (4.8)	3 (2.6)	
Hispanic	29 (23.0)	32 (25.2)	
Other	0	2 (1.6)	
Lesion counts, No.			
Total	32.7 ± 23.1	33.2 ± 22.9	.98
Inflammatory	9.7 ± 7.2	10.2 ± 8.3	.73
Noninflammatory	22.9 ± 19.7	22.9 ± 19.0	.88
Global severity assessment			
Clear	5 (4.0)	2 (1.6)	.69
Minimal	24 (19.1)	26 (20.5)	
Mild	64 (50.8)	61 (48.0)	
Moderate	33 (26.2)	38 (29.9)	
Severe	0	0	
Very severe	0	0	

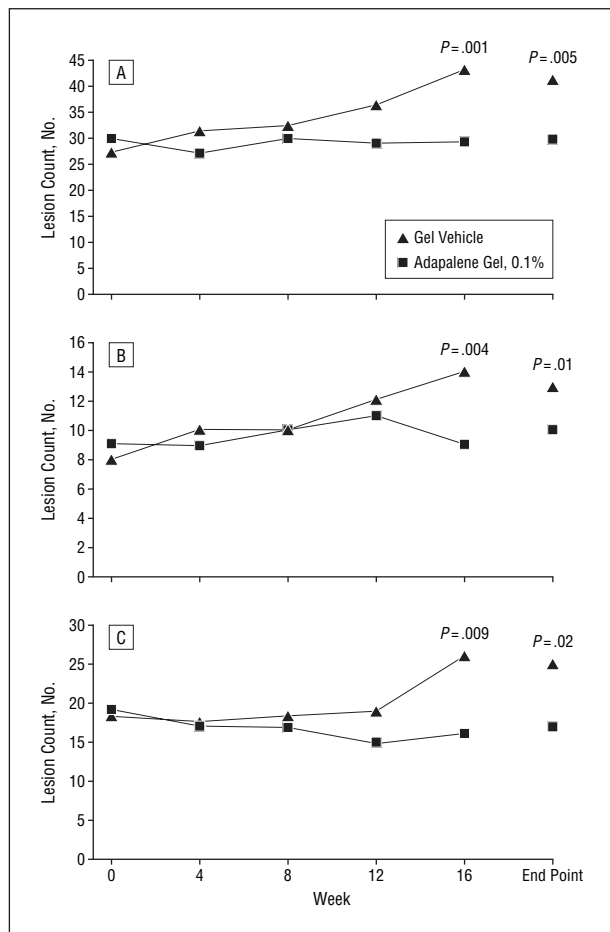
\*Data are given as mean ± SD value or number (percentage) of subjects unless otherwise indicated.



**Figure 2.** Maintenance rates (percentage of subjects maintaining at least 50% improvement in lesion counts; intent-to-treat population, worst case).

sion counts for the adapalene group remained stable or decreased. Statistically significant differences in favor of adapalene could be observed at week 16 (Figure 3) for total lesions ( $P = .001$ ) and inflammatory lesion ( $P = .004$ ) and noninflammatory lesion ( $P = .009$ ) counts.

Analyzing the full-scale global severity assessment, a significant difference in the distribution of severity scores favoring the adapalene group was observed between the 2 treatment groups ( $P = .005$ ), with more subjects "clear" or "almost clear" in the adapalene group relative to the vehicle group (27% vs 16%). Similar efficacy results were ob-



**Figure 3.** Total (A), inflammatory (B), and noninflammatory (C) lesion counts (intent-to-treat population).



**Figure 4.** Effect of 16 weeks of maintenance therapy with adapalene gel, 0.1%, following 12 weeks of combination therapy with adapalene gel, 0.1%, plus doxycycline on severe facial acne lesions. Photographs show subject treated with doxycycline and adapalene gel, 0.1%, at baseline of the combination study (A); after 12 weeks of combination treatment with adapalene gel, 0.1%, plus doxycycline (this time point is also the baseline for the maintenance study) (B); and following 16 weeks of maintenance treatment with adapalene gel, 0.1% (C).

tained in the PP population analysis. **Figure 4** illustrates the effect of 16 weeks of maintenance therapy with adapalene gel, 0.1%, following 12 weeks of combination therapy with adapalene gel, 0.1%, plus doxycycline on severe facial acne lesions.

### SAFETY EVALUATION

Severity scores for erythema, scaling, dryness, and stinging and/or burning are summarized graphically in **Figure 5**. As expected, local cutaneous tolerability of study treatments was excellent for both groups. Mean tolerability scores for erythema, scaling, dryness, and stinging and/or burning were less than 1 (mild) for all study visits. Worst scores at any time during the study for these tolerability

parameters were all less than 1 (mild) as well. Most subjects in both groups experienced mild or no irritation.

The number of subjects experiencing adverse events was similar in both treatment groups, with 25% and 23% reported for the adapalene and vehicle groups, respectively. During the course of the study, treatment-related adverse events occurred in 3 (2.4%) of adapalene-treated subjects and 1 (0.8%) of vehicle-treated subjects. The most common treatment-related adverse event was pruritus (2 subjects, possibly related). One subject experienced a serious adverse event deemed unrelated to study treatment (suicide attempt by subject with a history of depression). There were no adverse events that led to a study discontinuation, and all treatment-related adverse events were mild in severity.

### SUBJECT SURVEY

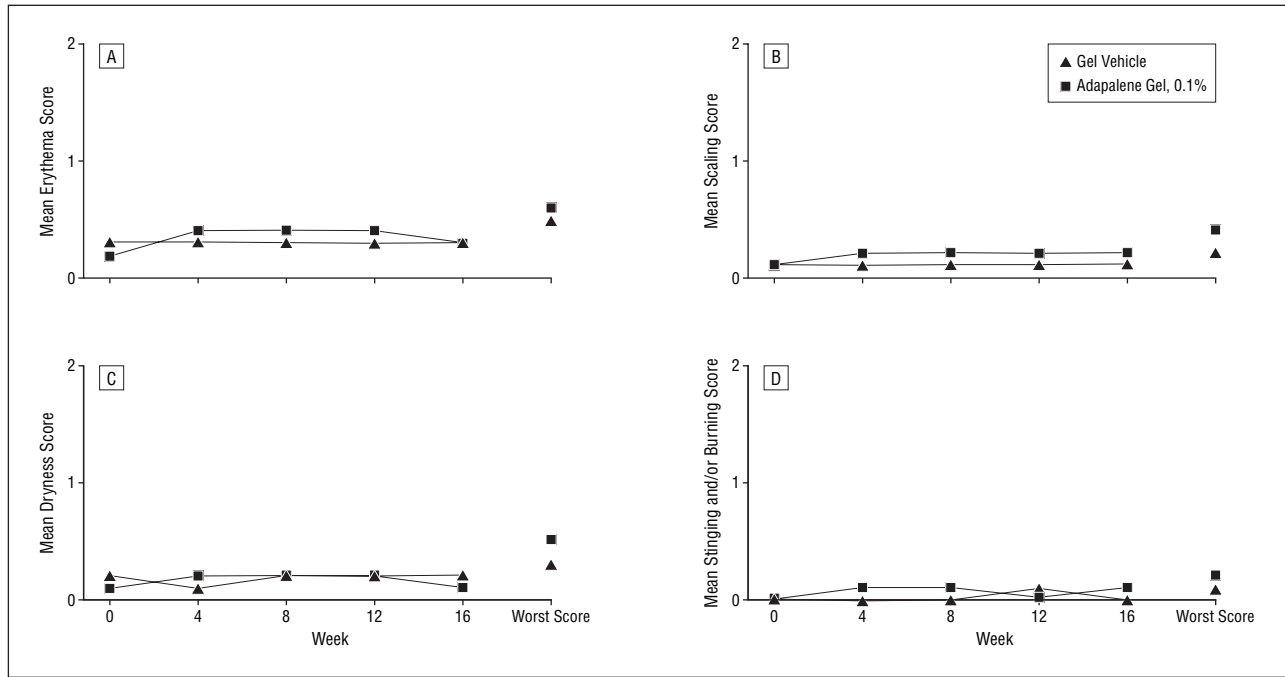
The results from the 5-question survey are illustrated in **Figure 6**. Most subjects in both treatment groups were not bothered by adverse effects (90% in both the adapalene and vehicle groups;  $P = .94$ ). Significantly more subjects in the adapalene group than in the vehicle group were “very satisfied” or “satisfied” with the treatment effectiveness (75% vs 58%;  $P = .003$ ) and the overall maintenance treatment (76% vs 65%;  $P = .01$ ). Similarly, when subjects were asked how they regarded the overall treatment scheme beginning with the combination therapy, a significantly larger percentage of subjects receiving adapalene maintenance therapy were “very satisfied” or “satisfied” compared with subjects receiving vehicle (84% vs 73%;  $P = .02$ ).

### COMMENT

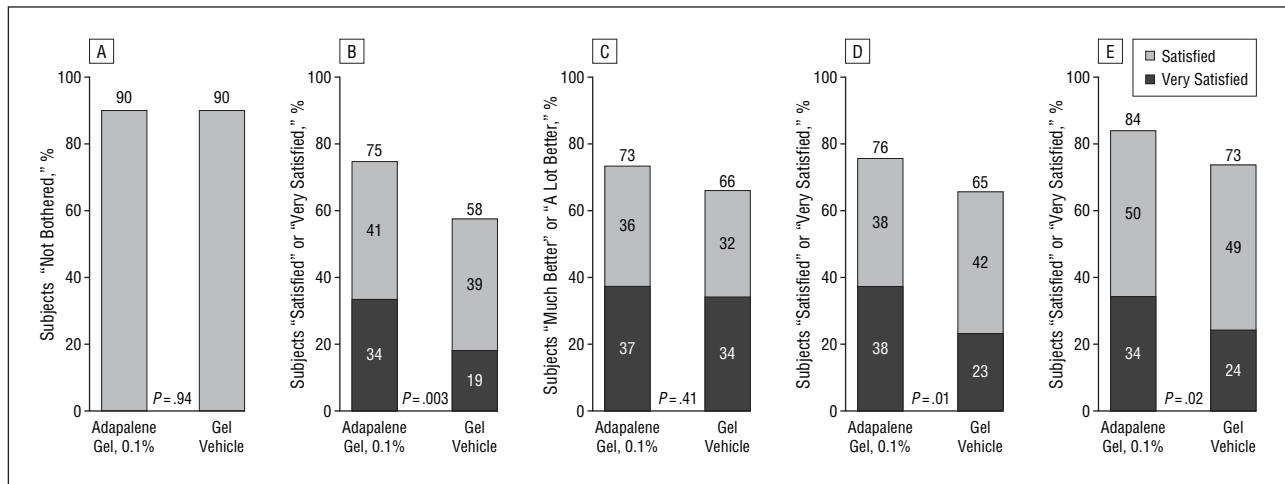
In light of the chronic nature of acne, maintenance therapy is considered important for suppressing the development of subclinical microcomedones and thereby preventing the recurrence of the disease.<sup>5,7</sup> At present, to our knowledge, there are no published well-controlled studies evaluating the clinical benefits of maintenance therapies available to guide evidence-based decisions for the long-term management of this disease. In an effort to add to our current understanding of the potential of maintenance therapies, this 16-week study evaluated adapalene gel, 0.1%, as a maintenance therapy in subjects who showed at least moderate improvement in their severe acne in a previous 12-week adapalene-doxycycline combination therapy study.

This is the first rigorously controlled study evaluating a topical retinoid as a maintenance treatment for acne. The design of this study set a high threshold for achieving success by using a parallel control group, LOCF and worst-case statistical methodology, and rerandomizing subjects after the previous 12-week study. No formal definition of acne maintenance exists. Maintaining at least 50% improvement was considered an acceptable level in this study. To support the validity of this assessment, a post hoc analysis was performed in which maintenance was defined in stricter terms (maintaining the same number of lesions relative to baseline). Results confirmed this statistically significant benefit with adapalene relative to the vehicle ( $P < .03$ ).

Overall, the results of this study demonstrate clinical benefit of continued adapalene use as a maintenance therapy



**Figure 5.** Local tolerability. Effects of adapalene gel, 0.1%, vs gel vehicle on mean scores for skin tolerance variables of erythema (A), scaling (B), dryness (C), and stinging and/or burning (D). Skin tolerability variables were assessed according to the 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 a subject during the postbaseline period) are included in the figure.



**Figure 6.** Five-question subject survey. A, Adverse effects? B, Treatment effectiveness? C, How do you feel about yourself? D, Overall maintenance treatment? E, Overall treatment scheme?

for acne and underscore the importance of treatment adherence for the success of long-term maintenance therapy. After 16 weeks of treatment, adapalene provided statistically significantly superior results relative to gel vehicle for all efficacy assessments including total, inflammatory, and noninflammatory lesion counts as well as the maintenance rate and global severity. A statistically significant difference between adapalene and vehicle was first observed at 4 months. These results confirm those seen in a recent open-label adapalene maintenance study.<sup>16</sup> A possible explanation for this unexpected late increase of acne lesions in the vehicle-treated subjects may be that 3 months of previous treatment with doxycycline administered in all subjects produced a prolonged antiacne effect; therefore, a delay of 3 months from baseline was necessary for the disease process to recur and

induce visible inflammatory lesions. This observation may reflect the natural life cycle of a comedone, gradually regenerating back to visible acne and then to an inflammatory lesion over several months in the absence of therapy.

The trend of diverging lesion count differences between the adapalene and vehicle groups in the present study suggests that a continued benefit may be obtained beyond 4 months; however, additional studies of longer duration to support these results will be necessary to confirm this observation. In addition, studies comparing the clinical benefit of adapalene as maintenance with that of other retinoids or benzoyl peroxide may also be of interest.

There was a potential risk that randomization of patients previously treated with the gel vehicle–doxycycline combination to adapalene therapy may have caused local irri-

tation, which could influence the investigator to be blinded. However, as expected from previous studies,<sup>10,11</sup> adapalene was well tolerated from the beginning. Only 3 subjects (2.4%) receiving adapalene experienced treatment-related adverse events (compared with 1 in the vehicle group) and the mean worst score for each of the local cutaneous tolerability variables was none or mild for most adapalene-treated subjects.

In addition, results from the subject satisfaction questionnaire support the physician assessments because subjects indicated that the adverse effects did not bother them and overall they had significantly greater satisfaction with adapalene maintenance therapy ( $P = .01$ ).

In acne, as with many dermatological diseases, individual variations exist in the progression, remission, and responses to therapeutic interventions. The present study demonstrates the efficacy of adapalene therapy at maintaining improvement in acne for 16 weeks following treatment with an oral antibiotic–topical retinoid combination. In many patients, this improvement may persist. In others, such as a young teenager, a woman with a strong hormonal component to their acne, or those with a strong personal or family history of acne, it is reasonable to expect that relapses may occur despite maintenance therapy. Appropriate therapy should then be reinitiated to control the acne and prevent scarring. The present 16-week and previous 12-week studies provide data to support regimens, such as those recommended in the recent acne treatment guidelines,<sup>5</sup> wherein oral antibiotics can be used initially in combination with topical retinoids to gain control over the acne, and maintenance with adapalene can delay the recurrence of acne. This approach is especially attractive in an environment with rising concerns on the part of physicians and patients regarding long-term antibiotic use.

In summary, this study demonstrates the clinical benefit of continued treatment with adapalene gel, 0.1%, as a maintenance therapy following therapy with an oral antibiotic.

**Accepted for Publication:** July 25, 2005.

**Correspondence:** Diane M. Thiboutot, MD, Department of Dermatology, HU14, Milton S. Hershey Medical Center, The Pennsylvania State University, PO Box 850, Hershey, PA 17033-0850 (dthiboutot@psu.edu).

**Author Contributions:** Dr Thiboutot had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Thiboutot, Shalita, Yamauchi, Dawson, Kerrouche, Arsonnaud, and Kang. **Acquisition of data:** Thiboutot, Shalita, Yamauchi, and Kang. **Analysis and interpretation of data:** Thiboutot, Shalita, Yamauchi, Dawson, Kerrouche, Arsonnaud, and Kang. **Critical revision of the manuscript for important intellectual content:** Thiboutot, Shalita, Yamauchi, Dawson, Kerrouche, Arsonnaud, and Kang.

**Financial Disclosure:** At the time this study was conducted, 3 of the authors were employees of Galderma (Mss Dawson and Arsonnaud and Mr Kerrouche). Drs Thiboutot, Shalita, and Kang have served as consultants and conducted clinical trials for Galderma Laboratories and Allergan, Inc. Dr Yamauchi has conducted clinical trials for Galderma Laboratories and Allergan, Inc. Drs Thiboutot and Shalita have served as consultants for Connetics, Inc, and Dermik Laboratories. Dr Shalita has served as a consultant for Medicis

and Steifel and owns stock in Allergan, Medicis, and Johnson & Johnson.

**Funding/Support:** This study was funded by Galderma Research & Development, Princeton, NJ.

**Previous Presentation:** An abstract of this study was presented at the American Academy of Dermatology Meeting; February 18, 2005; New Orleans, La.

**Acknowledgment:** We thank the following investigators for their involvement in data acquisition: Elizabeth Arthur, Rochester, NY; Debra Breneman, Cincinnati, Ohio; Suzanne Bruce, Houston, Tex; Alicia Bucko, Albuquerque, NM; Valerie Callender, Mitchellville, Md; Jeffrey Carmel, Fremont, Calif; James Del Rosso, Las Vegas, Nev; Zoe Diana Draelos, Highpoint, NC; Nancy Egan, Rockland, Me; Javier Flores, Miami, Fla; Joseph Fowler, Louisville, Ky; Jon Hanifin, Portland, Ore; Michael Jarratt, Austin, Tex; Se-won Kang, Ann Arbor, Mich; Norman Kanof, Port Chester, NY; David Kaplan, Overland Park, Kan; Steven Kempers, Fridley, Minn; Bruce Miller, Portland, Ore; Eugene Monroe, Milwaukee, Wis; Amit Pandya, Dallas, Tex; Marina Peredo, Smithtown, NY; Tooraj J. Raoof, Encino, Calif; Phoebe Rich, Portland, Ore; Ronald Savin, New Haven, Conn; Joel Schlessinger, Omaha, Neb; Alan Shalita, Brooklyn, NY; Dow B. Stough, Hot Springs, Ark; Leonard Swinyer, Salt Lake City, Utah; Diane Thiboutot, Hershey, Pa; Helen Mary Torok, Medina, Ohio; James Turner, Memphis, Tenn; David Whiting, Dallas, Tex; Hector Wiltz, Miami, Fla; John Wolf, Houston, Tex; and Paul Yamauchi, Santa Monica, Calif. We also thank David Cox, Galderma Research & Development, Princeton, NJ, for editorial assistance.

## REFERENCES

1. Thiboutot D. Regulation of human sebaceous glands. *J Invest Dermatol.* 2004; 123:1-12.
2. Pawin H, Beylot C, Chivot M, et al. Physiopathology of acne vulgaris: recent data, new understanding of the treatments. *Eur J Dermatol.* 2004;14:4-12.
3. Leyden JJ. A review of the use of combination therapies for the treatment of acne vulgaris. *J Am Acad Dermatol.* 2003;49(3) (suppl):S200-S210.
4. Thiboutot D. New treatments and therapeutic strategies for acne. *Arch Fam Med.* 2000;9:179-187.
5. Gollnick H, Cunliffe W, Berson D, et al; Global Alliance to Improve Outcomes in Acne. Management of acne. *J Am Acad Dermatol.* 2003;49(1) (suppl):S1-S37.
6. Thielitz A, Helmdach M, Ropke E-M, Gollnick H. Lipid analysis of follicular casts from cyanoacrylate strips as a new method for studying therapeutic effects of antiacne agents. *Br J Dermatol.* 2001;145:19-27.
7. Wolf JE. Maintenance therapy for acne vulgaris: the fine balance between efficacy, cutaneous tolerability, and adherence. *Skinmed.* 2004;3:23-26.
8. Cunliffe WJ, Holland DB, Clark SM, Stables GI. Comedogenesis: some new aetiological, clinical and therapeutic strategies. *Br J Dermatol.* 2000;142:1084-1091.
9. Koo J. How do you foster medication adherence for better acne vulgaris management? *Skinmed.* 2003;2:229-233.
10. Haider A, Shaw JC. Treatment of acne vulgaris. *JAMA.* 2004;292:726-735.
11. Waugh J, Noble S, Scott LJ. Adapalene: a review of its use in the treatment of acne vulgaris. *Drugs.* 2004;64:1465-1478.
12. Cunliffe WJ, Poncet M, Loesche C, Verschoore M. A comparison of the efficacy and tolerability of adapalene 0.1% gel versus tretinoin 0.025% gel in patients with acne vulgaris. *Br J Dermatol.* 1998;139:48-56.
13. Thiboutot DB, Shalita AR, Yamauchi PS, Dawson C, Arsonnaud S, Kang S; Differin Study Group. Combination therapy with adapalene gel 0.1% and doxycycline for severe acne vulgaris. *Skinmed.* 2005;4:138-146.
14. Wolf JE Jr, Kaplan D, Kraus SJ, et al. Efficacy and tolerability of combined topical treatment of acne vulgaris with adapalene and clindamycin: a multicenter, randomized, investigator-blinded study. *J Am Acad Dermatol.* 2003;49(3) (suppl):S211-S217.
15. Cunliffe WJ, Meynadier J, Alirezai M, et al. Is combined oral and topical therapy better than oral therapy alone in patients with moderate to moderately severe acne vulgaris? a comparison of the efficacy and safety of lymecycline plus adapalene gel 0.1%, versus lymecycline plus gel vehicle. *J Am Acad Dermatol.* 2003; 49(3) (suppl):S218-S226.
16. Zhang JZ, Li LF, Tu YT, Zheng J. A successful maintenance approach in inflammatory acne with adapalene gel, 0.1% after an initial treatment in combination with clindamycin topical solution, 1% or after monotherapy with clindamycin topical solution, 1%. *J Dermatolog Treat.* 2004;15:372-378.