A North American Study of Adapalene–Benzoyl Peroxide Combination Gel in the Treatment of Acne

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A fixed-dose combination gel with adapalene 0.1% and benzoyl peroxide (BPO) 2.5% recently has been developed for the treatment of acne vulgaris. In this multicenter, randomized, double-blind, parallel-group, active- and vehicle-controlled study conducted at 60 centers in the United States, Puerto Rico, and Canada, we assessed the efficacy and safety of adapalene-BPO combination gel in comparison with adapalene and BPO monotherapies as well as the gel vehicle.

Participants with moderate facial acne vulgaris (rated 3 on the 5-point investigator global assessment of acne severity scale) were recruited and randomized to receive once-daily treatment with adapalene-BPO combination gel, adapalene monotherapy, BPO monotherapy, or gel vehicle for 12 weeks. They were assessed for success rate (the percentage of participants with investigator global assessment of acne severity rated clear or almost clear) and percentage change in inflammatory lesion (IL), noninflammatory lesion (NIL), and total lesion counts.

Of the 1668 participants enrolled, 1429 (85.7%) completed the study. At study end point, adapalene-BPO combination gel showed a significantly higher success rate ($P \leq .006$*) and a greater percentage reduction in all acne lesion counts (*$P \leq .017$*) compared with the other treatment groups. A significant early treatment effect of adapalene-BPO combination gel at week 1 compared with adapalene monotherapy and vehicle also was observed for all lesion count reductions (*$P < .001$*). The safety of adapalene-BPO combination gel was comparable with adapalene and BPO monotherapies and vehicle.*

In a large clinical trial, the adapalene-BPO fixed-dose combination gel has shown superiority in efficacy compared with adapalene and BPO monotherapies and vehicle, with an early onset of efficacy and a good safety profile.

Cutis. 2009;84:110-116.

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This study was supported by Galderma R&D Inc. Dr. Stein Gold is an advisor, investigator, and speaker for Galderma Laboratories, LP. Dr. Tan is an advisory board member and speaker and has received research grants from Galderma Laboratories, LP. Drs. Cruz-Santana and Papp report no conflict of interest. Dr. Poulin has received research grants from Galderma Laboratories, LP. Dr. Schlessinger is an advisory board member for Galderma Laboratories, LP. Mrs. Gidner and Drs. Liu and Graeber are employees of Galderma Laboratories, LP. ClinicalTrials.gov identifier: NCT00422240.

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Acne vulgaris is a chronic disease of the pilosebaceous unit with a multifaceted pathophysiology including sebaceous gland hyperplasia with seborrhea, altered follicular growth and differentiation, *Propionibacterium acnes* proliferation, and inflammation and immune response.[1] Fixed-dose combinations are the mainstay of acne treatment.

The Global Alliance to Improve Outcomes in Acne guidelines recommend combination therapy with a topical retinoid and antimicrobial agents for the treatment of mild to moderately severe inflammatory acne.[2] This type of combination targets 3 of 4 major pathophysiologic features of acne. Furthermore, because topical retinoids target microcomedones,[3] the precursor of all acne lesions, it is stressed that they should be used from the onset of treatment and therefore should be part of all combination therapies. In the context of increasing bacterial resistance attributable to the widespread use of antibiotics including those used to treat acne,[4,5] it has been recommended to reduce the use of antibiotics.

A new antibiotic-free fixed-dose combination of adapalene 0.1% and benzoyl peroxide (BPO) 2.5% recently has been approved and marketed in the United States. Adapalene possesses anticomedogenic, comedolytic, and anti-inflammatory properties,[6-9] whereas BPO, the most potent topical bactericidal agent, is more effective than topical antibiotics against *P acnes*[10] with no evidence for the development of bacterial resistance.[2] Unlike tretinoin, adapalene is stable when combined with BPO in the presence or absence of light.[11]

This is the largest published[12-15] study of adapalene-BPO combination gel, and it assessed efficacy and safety of the combination compared with adapalene and BPO monotherapy as well as the gel vehicle in the treatment of acne vulgaris.

Methods

Study Design—This multicenter, randomized, double-blind, parallel-group, active- and vehicle-controlled study was conducted at 60 centers in the United States, Puerto Rico, and Canada. The efficacy and safety of the adapalene 0.1%–BPO 2.5% combination gel was compared with adapalene and BPO monotherapies as well as the gel vehicle.

Participants were randomized in a 1:1:1:1 ratio to adapalene-BPO combination gel, adapalene gel monotherapy, BPO gel monotherapy, or gel vehicle. Participants were instructed to apply the allocated study treatment to the face or face and trunk (as applicable) once daily in the evening for 12 weeks. In case of dry skin, they were requested to use a moisturizer (Cetaphil® Moisturizing Lotion or their usual moisturizer) daily throughout the study. Efficacy and safety evaluations were performed at baseline and weeks 1, 2, 4, 8, and 12.

This study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and its amendments; the Good Clinical Practice guidelines; local regulatory requirements; and, in the United States, the Health Insurance Portability and Accountability Act.

Participants—Male and female participants of any race that were 12 years and older with facial acne vulgaris rated 3 (moderate) on the investigator global assessment of acne severity scale (0 [clear]; 4 [severe]), 20 to 50 inflammatory lesions (ILs), 30 to 100 noninflammatory lesions (NILs), no cysts, and no more than 1 nodule were recruited for this study. Specified washout periods were required for participants taking certain topical and systemic treatments. Patients with acne conglobata, acne fulminans, secondary acne, or severe acne requiring systemic treatment were excluded from the study.

Outcome Assessments—The efficacy variables of the study included success rate (the percentage of participants rated clear or almost clear on the investigator global assessment scale); median percentage change in facial IL, NIL, and total lesion counts; and each participant's assessment of acne improvement (0=complete improvement; 5=worse).

Safety and tolerability were assessed through evaluations of facial local tolerability signs and symptoms and adverse events (AEs). At each visit, the investigator rated erythema, scaling, dryness, and stinging/burning on a scale ranging from 0 (none) to 3 (severe). Adverse events were evaluated at each visit.

At the end of the treatment, participants were invited to complete a questionnaire scoring their appreciation of the effectiveness, tolerability, and cosmetic properties of the treatment they received.

Statistical Analyses—The primary end point efficacy analyses were evaluated at week 12 using the intention-to-treat (ITT) population and the last observation carried forward (LOCF) imputation for missing data points. Success rates and percentage lesion count reductions were analyzed by the Cochran-Mantel-Haenszel test stratified by center, using general association for success rates and row mean difference statistics after ridit transformation for percentage lesion count reductions. Each participant's assessment of acne also was analyzed using the Cochran-Mantel-Haenszel test. All tests were 2-tailed with a level of .05 to declare significance.

Results

Participant Disposition and Baseline Characteristics—A total of 1668 participants were randomized and included in the ITT population: 415 received adapalene-BPO combination gel, 420 received adapalene monotherapy, 415 received BPO monotherapy, and 418 received vehicle. Among the

Baseline Demographic and Clinical Characteristics (ITT Population)

	Adapalene-BPO Combination Gel (n=415)	Adapalene Monotherapy (n=420)	BPO Monotherapy (n=415)	Vehicle (n=418)	Total (N=1668)	*P* Value
Sex, n (%)						.784
Male	205 (49.4)	203 (48.3)	208 (50.1)	196 (46.9)	812 (48.7)	
Female	210 (50.6)	217 (51.7)	207 (49.9)	222 (53.1)	856 (51.3)	
Age, y						.163
Mean	18.7	17.9	18.4	18.0	18.2	
Minimum, maximum	12, 58	12, 41	12, 56	12, 50	12, 58	
Race, n (%)						.879
White	273 (65.8)	281 (66.9)	258 (62.2)	270 (64.6)	1082 (64.9)	
Black	66 (15.9)	64 (15.2)	81 (19.5)	66 (15.8)	277 (16.6)	
Asian	4 (1.0)	4 (1.0)	4 (1.0)	5 (1.2)	17 (1.0)	
Hispanic	67 (16.1)	66 (15.7)	65 (15.7)	72 (17.2)	270 (16.2)	
Other	5 (1.2)	5 (1.2)	7 (1.7)	5 (1.2)	22 (1.3)	
Baseline lesion count, median						
IL	27	27	27	27	27	.956
NIL	44	47	46	46	46	.911
Total	76	79	76	76	76	.881

Abbreviations: ITT, intention to treat; BPO, benzoyl peroxide; IL, inflammatory lesion; NIL, noninflammatory lesion.

1668 enrolled participants, 1429 (85.7%) completed the study and 239 (14.3%) discontinued early, with only 22 (1.3%) discontinuing because of AEs. Although the rates for discontinuation due to AEs were higher in the adapalene-BPO combination gel group (2.7%) compared with the other groups (adapalene, BPO, and vehicle), they were low for all of the treatment groups (1.0%, 1.2%, and 0.5% of participants, respectively). The per-protocol population consisted of 1335 participants (80%; 319 participants in the adapalene-BPO combination gel group, 347 in the adapalene monotherapy group, 346 in the BPO monotherapy group, 323 in the vehicle group).

The baseline characteristics of the ITT population are summarized in the Table. Participant disposition was similar between groups.

Efficacy Evaluation—At end point, the success rate reached 30.1% with adapalene-BPO combination gel compared with 19.8%, 22.2%, and 11.3% with adapalene monotherapy, BPO monotherapy, and vehicle, respectively (Figure 1). All evaluations of adapalene-BPO combination gel compared with the monotherapies and vehicle were significant ($P \leq .006$). Furthermore, a significant early treatment effect of adapalene-BPO combination gel compared with adapalene monotherapy and vehicle was observed starting at week 4 for success rate and

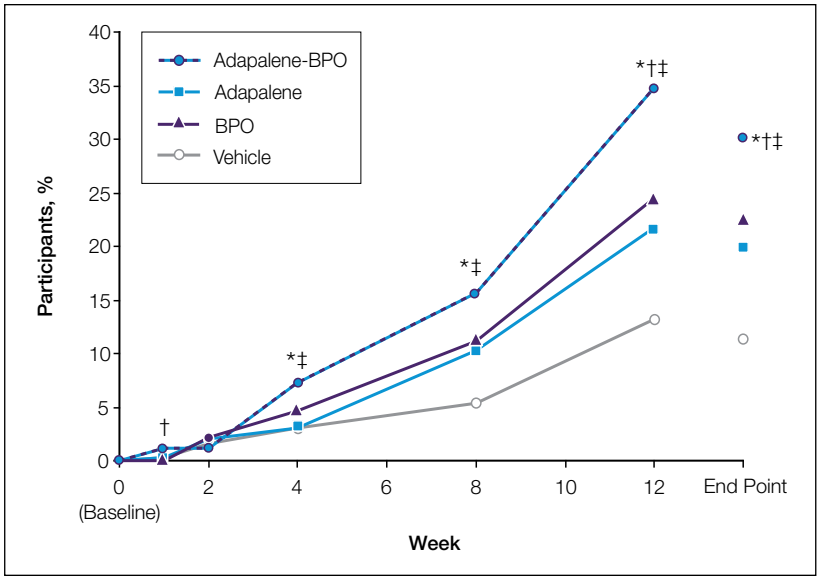


Figure 1. Success rates over time (percentage of participants rated clear or almost clear during the course of the study; intention-to-treat population; last observation carried forward)(N=1668). Differences between adapalene–benzoyl peroxide (BPO) combination gel and all other treatments were statistically significant at week 12 and end point ($P \leq .006$). Asterisk indicates statistically significant difference between adapalene-BPO combination gel and adapalene monotherapy (at least $P < .05$); dagger, statistically significant difference between adapalene-BPO combination gel and BPO monotherapy (at least $P < .05$); double dagger, statistically significant difference between adapalene-BPO combination gel and vehicle (at least $P < .05$).

was sustained until the end of the study ($P = .008$ and $P = .004$, respectively)(Figure 1).

For percentage change in IL, NIL, and total lesion counts at week 12 (ITT population; LOCF), adapalene-BPO combination gel was significantly more effective than adapalene and BPO monotherapy and vehicle ($P \leq .017$)(Figure 2). From baseline to week 12 (LOCF), participants treated with adapalene-BPO combination gel showed a median reduction of 62.1% in IL counts compared with 50.0%, 55.6%, and 34.3% with adapalene monotherapy, BPO monotherapy, and vehicle, respectively. From baseline to week 12 (LOCF), participants treated with adapalene-BPO combination gel showed a median reduction of 53.8% in NIL counts compared with 49.1%, 44.1%, and 29.5% with adapalene monotherapy, BPO monotherapy, and vehicle, respectively. Furthermore, a significant early treatment effect of adapalene-BPO combination gel compared with adapalene monotherapy and vehicle was observed starting at week 1 ($P < .001$) for percentage reduction of IL, NIL, and total lesion counts, and was sustained to the end of the study. These results were confirmed by the per-protocol analyses (data not shown).

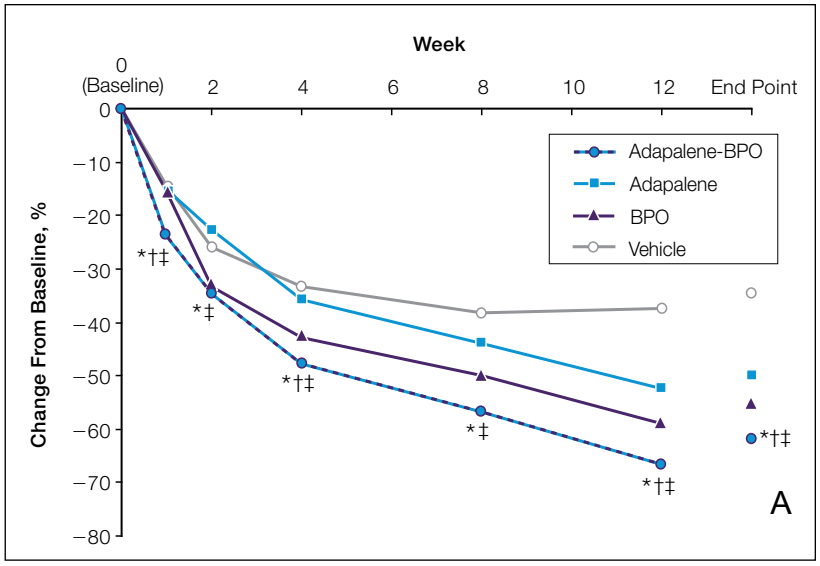
Participant assessment of acne improvement showed that adapalene-BPO combination gel was significantly superior to adapalene and BPO monotherapy and vehicle ($P \leq .008$). At week 12 (LOCF), complete, marked, and moderate improvement was reported for 73.5%, 65.6%, 66.7%, and 55.0% of participants in the adapalene-BPO combination gel, adapalene monotherapy, BPO monotherapy, and vehicle groups, respectively.

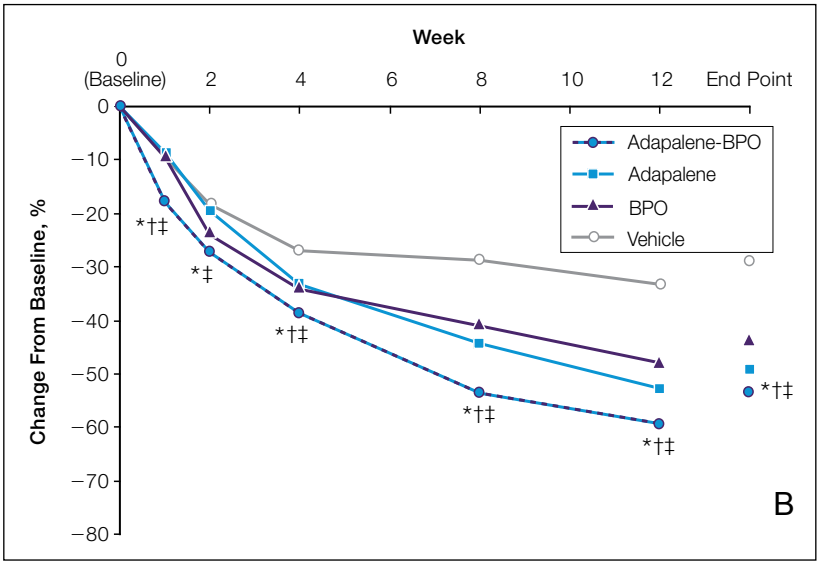
Safety Evaluation—Signs and symptoms of local tolerability in the adapalene-BPO combination gel group were compared with the other treatment groups (Figure 3). They were transient, occurred mainly within the first 2 weeks of treatment, and were mostly of mild to moderate severity with few being recorded as severe. Moreover, the mean worst scores for all tolerability signs and symptoms were all below grade 1 (mild). The overall safety of adapalene-BPO combination gel was comparable with adapalene monotherapy and BPO monotherapy. The number of participants with at least 1 AE was similar across the study treatments. A low incidence (22 of 1668 participants; 1.3%) of AEs leading to discontinuation was observed: 11 (2.7%), 4 (1.0%), 5 (1.2%), and 2 (0.5%) participants in the adapalene-BPO combination gel, adapalene monotherapy, BPO monotherapy, and vehicle groups, respectively. Most treatment-related AEs were cutaneous, mild to moderate in severity, and resolved without residual effects. Dry skin was reported as the most common AE in the adapalene-BPO combination gel group.

Appreciation Questionnaire—The treatment effect—measured by the question "How satisfied were you with the effectiveness?"—showed that the adapalene-BPO combination gel was rated as more effective than adapalene and BPO monotherapy and vehicle: 70.2%, 60.1%, 61.1%, and 49.6% of participants, respectively. Cosmetic properties were equally appreciated among all treatment groups with an average of 81% of participants being satisfied or very satisfied.

Comment

In this multicenter, randomized, double-blind, parallel-group, active- and vehicle-controlled study, adapalene-BPO fixed-dose combination gel





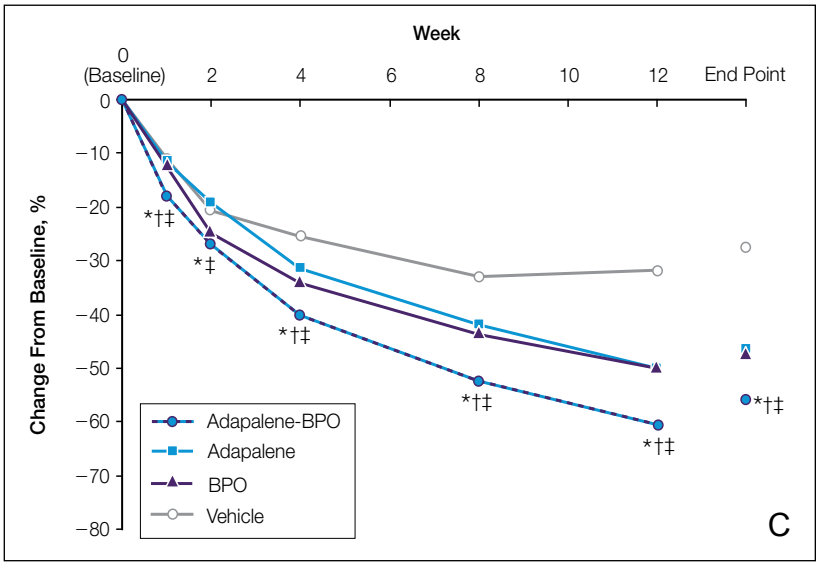


Figure 2. Median percentage change in inflammatory (A), noninflammatory (B), and total lesion counts (C) from baseline (intention-to-treat population; last observation carried forward). Differences between adapalene–benzoyl peroxide (BPO) combination gel and adapalene monotherapy, BPO monotherapy, and vehicle were statistically significant at week 12 and end point ($P \leq .017$). Asterisk indicates statistically significant difference between adapalene-BPO combination gel and adapalene monotherapy (at least $P < .05$); dagger, statistically significant difference between adapalene-BPO combination gel and BPO monotherapy (at least $P < .05$); double dagger, statistically significant difference between adapalene-BPO combination gel and vehicle (at least $P < .05$).

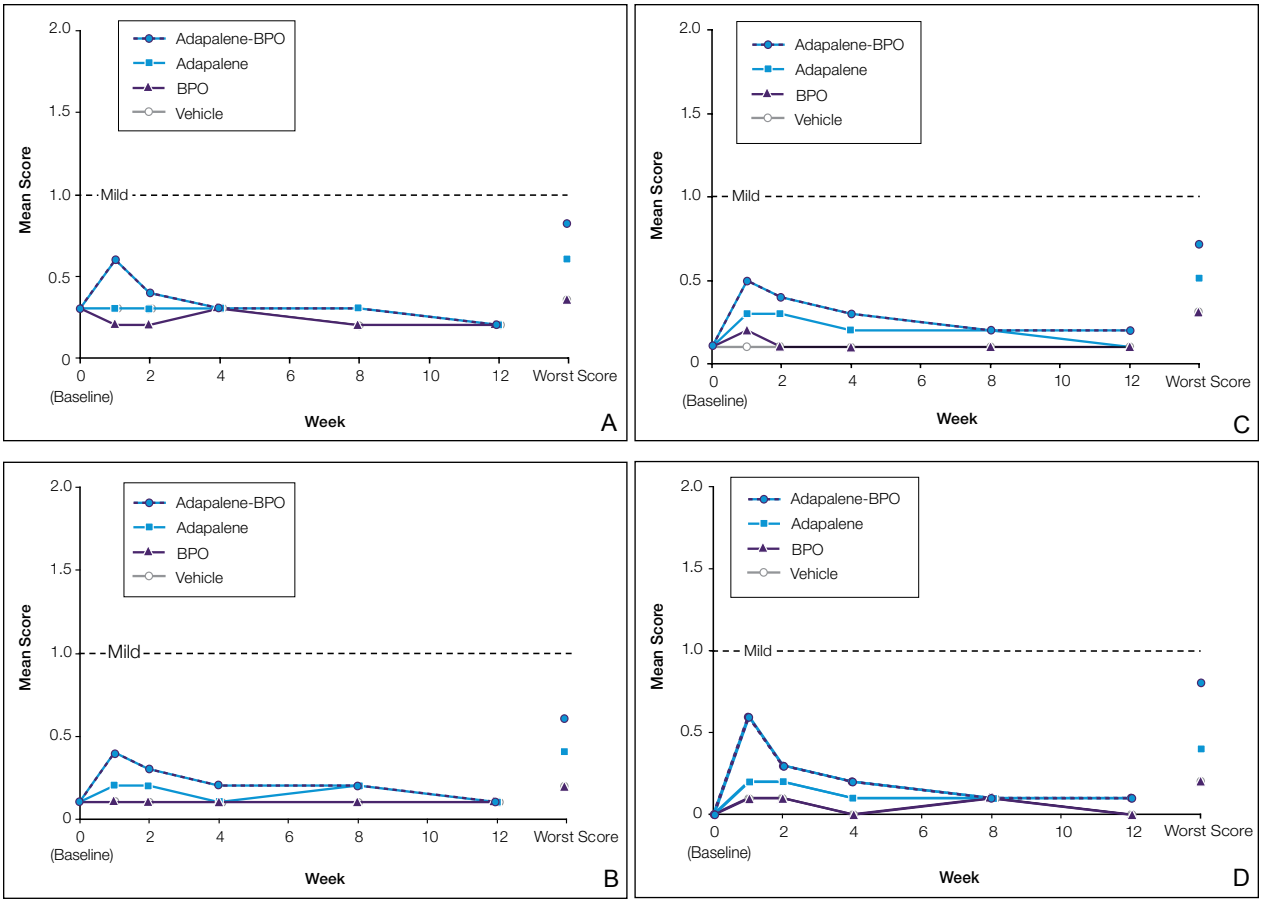


Figure 3. Local tolerability signs and symptoms including erythema (A), scaling (B), dryness (C), and stinging/burning (D) were assessed in all treatment groups (adapalene–benzoyl peroxide [BPO] combination gel, adapalene monotherapy, BPO monotherapy, vehicle)(safety population) using a scale ranging from 0 (none) to 3 (severe).

demonstrated superior efficacy compared with its active components and vehicle in the treatment of participants with moderate facial acne vulgaris. A significant early treatment effect of adapalene-BPO combination gel compared with adapalene monotherapy and vehicle was observed in the percentage reduction of IL, NIL, and total lesion counts starting at week 1 ($P<.001$), and was sustained to the end of the study. Furthermore, it is noteworthy that the trend line of combination product efficacy continued to increase to end of study (week 12), suggesting that superior efficacy outcomes may be achievable with a longer treatment period.

Signs and symptoms of local tolerability were observed, mainly within the first 2 weeks of treatment, with greater incidence in the adapalene-BPO combination gel group compared with the adapalene monotherapy, BPO monotherapy, or vehicle groups. However, most of the signs and symptoms were transient, occurred early in the treatment course, and were mild to moderate in severity. The most common side effect was skin dryness, which is expected with a retinoid-containing combination therapy and can be easily minimized by use of noncomedogenic moisturizers at the beginning of treatment, proper cleansing, or temporary adjustment of the therapeutic regimen (one application every other day instead of once daily).

Our study results are comparable with those observed in initial clinical studies that demonstrated a favorable benefit-risk profile for adapalene-BPO combination therapy.[12-15] Other combination regimens have been previously studied and are part of the current treatment strategy for acne, including combinations of topical retinoids with oral or topical antimicrobial agents,[16,17] or a clindamycin-BPO fixed combination.[18] Adapalene-BPO fixed-dose combination gel is a unique treatment strategy because of the complementary modes of action of adapalene and BPO that address 3 of 4 pathophysiologic features of acne. In addition, adapalene-BPO combination gel is to be used once daily, does not require refrigeration, and is stable for up to 6 months after opening the tube. These convenience factors may provide greater potential for increased patient

adherence to treatment. Indeed, it has been reported that treatment regimens that are effective and well-tolerated as well as simple and easy to incorporate into the patient's lifestyle are the most likely to enhance patient adherence.[19]

The development of antibiotic-resistant bacteria with the overuse of antibiotics for the treatment of acne, other dermatologic conditions, and nondermatologic infectious diseases is of increasing medical concern.[5,20] Adapalene-BPO combination gel offers the advantage of being antibiotic free and therefore may be expected to decrease the incidence of bacterial resistance relative to antibiotics.[21] Furthermore, it can be used for long-term management of acne.

In conclusion, the adapalene-BPO fixed-dose combination gel has a superior benefit-risk ratio to the corresponding monotherapies in the treatment of acne vulgaris.

Acknowledgment—We are indebted to Zeina Saab, PharmD, medical writer, for editorial assistance.

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