Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: Results of a multicenter, randomized double-blind, controlled study

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Background: A fixed-dose combination gel with adapalene 0.1% and benzoyl peroxide (BPO) 2.5% has been developed for the once-daily treatment of acne.

Objective: To evaluate the efficacy and safety of adapalene 0.1% -BPO 2.5% fixed combination gel (adapalene-BPO) for the treatment of acne.

Methods: A total of 517 subjects were randomized in a double-blind controlled trial to receive either adapalene-BPO, adapalene, BPO, or vehicle for 12 weeks (2:2:2:1 randomization). Evaluation included success rate (subjects "clear" or "almost clear"), lesion count, cutaneous tolerability, and adverse events.

Results: The fixed-dose combination gel of adapalene and BPO was significantly more effective than corresponding monotherapies, with significant differences in total lesion counts observed as early as 1 week. Adverse event frequency and cutaneous tolerability profile for adapalene-BPO were similar to adapalene monotherapy.

Limitations: These data were generated in a controlled trial. Results obtained in clinical practice could differ.

Conclusions: The fixed-dose combination of adapalene and BPO provides significantly greater efficacy for the treatment of acne vulgaris as early as week 1 relative to monotherapies, with a comparable safety profile to adapalene. (J Am Acad Dermatol 2007;57:791-9.)

INTRODUCTION

Acne vulgaris is a complex skin disorder involving multiple abnormalities of the pilosebaceous unit, including hyperkeratinization, increased sebum production, bacterial proliferation, and inflammation.[1,2] Existing topical and systemic therapies recommended for the treatment of acne include retinoids, benzoyl peroxide (BPO), antibiotics, and

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Funding source: Galderma R&D, Princeton, NJ.

Disclosure: The investigating authors received payments for this research project. Drs Liu and Graeber are employees of Galderma R&D. Drs Thiboutot, Weiss, and Kang have served as a consultants and speakers for Galderma Laboratories. Drs Bucko, Jones, and Eichenfield have served as consultants for Galderma.

Accepted for publication June 17, 2007.

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Published online July 28, 2007.

0190-9622/$32.00

doi:10.1016/j.jaad.2007.06.006

Abbreviations used:

BPO: benzoyl peroxide
IGA: investigator's global assessment
ITT: intention-to-treat
LOCF: last observation carried forward
PP: per-protocol

hormonal therapy. Combination therapy utilizing agents with complementary mechanisms, such as a topical retinoid and an antimicrobial, is often used in the management of acne, since most anti-acne medications do not act against all 4 of the major pathophysiologic features of acne.[3]

Adapalene is a receptor-selective naphthoic acid derivative with anti-inflammatory, comedolytic, and anticomedogenic properties.[4-8] It is recognized as an effective topical retinoid with a favorable tolerability profile[9] and is therefore a rational selection for combination therapy with an antimicrobial agent. The safety and efficacy of adapalene in the treatment of acne vulgaris have been studied in numerous clinical trials.[10-19] Recent clinical studies investigating the efficacy and safety of adapalene when used in combination with several antibiotics (oral lymecycline, oral doxycycline, and topical clindamycin) for the treatment of inflammatory acne showed that the adapalene-antibiotic combinations were consistently more effective than antibiotic monotherapy.[20-23]

BPO is a safe and effective antimicrobial agent for the treatment of acne.[3] A variety of BPO formulations are available, with concentrations ranging from 1% to 10%. BPO has demonstrated activity against bacterial organisms and yeast.[3,24,25] Compared with topical antibiotics with bacteriostatic properties, BPO exhibits a potent and rapid bactericidal effect against *Propionibacterium acnes*, with no evidence for the development of bacterial resistance.[3] The enhanced efficacy and tolerability of BPO when used in combination with topical antibiotics have led to several BPO-antibiotic fixed-dose products that have met with success in the treatment of acne.[3,26-28] However, there are currently no products that combine the antibacterial efficacy of BPO with the efficacy of a retinoid in reversing the altered follicular keratinization that is key in the pathogenesis of acne.

Recently, a unique, fixed-dose combination gel with adapalene 0.1% and BPO 2.5% has been developed for the once-daily treatment of acne. Adapalene is stable when combined with BPO in the presence or absence of light.[29] A formulation containing 0.1% adapalene and 2.5% BPO was considered optimal to provide the best overall efficacy and tolerability profile.[30] The adapalene-BPO combination has an overall preclinical profile similar to the individual agents.[31] The objective of the present study was to evaluate the efficacy and safety of adapalene 0.1%—benzoyl peroxide 2.5% fixed combination topical gel (adapalene-BPO) versus adapalene 0.1% gel (adapalene), BPO 2.5% gel (BPO), and the gel vehicle (vehicle) in the treatment of acne vulgaris for up to 12 weeks.

METHODS

Study design

The efficacy and safety of a fixed combination topical gel of adapalene-BPO were compared that of adapalene, BPO, as well as the gel vehicle in a randomized, multicenter, double-blind, parallel group study conducted at 36 centers in the United States between February 17, 2004 and December 21, 2004. Subjects were randomized consecutively in a 2:2:2:1 ratio to receive either adapalene-BPO gel, adapalene gel, BPO gel, or gel vehicle for 12 weeks. (Note: the two monotherapies [adapalene and BPO] in this study are monads of the combination formulated in the same vehicle as the combination and therefore have different vehicle formulations than the available commercial products [Differin or Benzac, Galderma Laboratories]). The integrity of the blinding was ensured by packaging the topical medication in identical tubes and requiring a third party other than the investigator/evaluator to dispense the medication. Efficacy and safety evaluations were performed at baseline and at weeks 1, 2, 4, 8, and 12. A urine pregnancy test was required at baseline 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 and in compliance with local regulatory requirements. This study was reviewed and approved by an institutional review board. All patients provided their written informed consent prior to entering the study.

Subjects

Male and female subjects, 12 years of age or older, with 30 to 100 noninflammatory facial lesions, 20 to 50 inflammatory facial lesions, and no nodules or cysts were enrolled in the study. The extent of the subjects' acne for study inclusion was confirmed by a review of standardized photographs taken at the screening visit by an independent, blinded, third-party dermatologist. Specified washout periods were required for subjects taking certain topical and

systemic treatments. Exclusion criteria prohibited enrollment of subjects 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 subjects rated "clear" or "almost clear" on the investigator's global assessment scale [IGA] of acne severity) and percentage of lesion reduction from baseline (total, inflammatory, and noninflammatory). Lesion counts were assessed on the face only, excluding the nose. Secondary efficacy assessments included response rate (percentage of subjects who achieved at least 50% reduction in lesion counts [inflammatory, noninflammatory, and total]); IGA (full-scale); and subject's assessment of acne improvement. The IGA was evaluated on a scale ranging from 0 (clear: residual hyperpigmentation and erythema may be present) to 5 (very severe: highly inflammatory acne covering the face; with nodules and cysts present). The subject's assessment was evaluated on a scale from 0 (complete improvement) to 5 (worse).

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

Statistical analyses

All data analyses were carried out according to a pre-established analysis plan. A 15% difference in success rate and percent reduction in lesion counts between adapalene-BPO and adapalene, and between adapalene-BPO and BPO, was considered clinically relevant and was chosen for the sample size determination. Assuming the alpha level of 0.05 and the standard deviation in percentage lesion count reduction was 40 units, the estimated sample size per arm was 140 patients to detect the 15% difference in percentage lesion reduction at 80% power. Subsequently, the calculation showed that the sample size of 140 per arm was sufficient to detect the 15% difference in success rate (30% vs 15%) at an alpha level of 0.05 and 80% power. Considering the allocation ratio of 2:2:2:1 for adapalene-BPO (140 subjects), adapalene (140 subjects), BPO (140 subjects), and vehicle (70 subjects), the total estimated sample size was 490 subjects for this trial.

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 primary efficacy analyses were to compare adapalene-BPO with adapalene, BPO, and vehicle for (1) success rate and (2) percentage change in inflammatory, noninflammatory, and total lesion counts at end point (week 12, last observation carried forward [LOCF]) based on the ITT population. Success rates and percentage lesion count reduction were analyzed by the Cochran-Mantel-Haenszel test stratified by analysis center, using general association for success rates and row mean differences by relative to identified distribution (RIDIT) transformed scores for percentage lesion changes. These analyses were repeated for the PP population to confirm the efficacy results. IGA (full scale), response rate, and subject's assessment of acne were also analyzed by the Cochran-Mantel-Haenszel test. Rank data on change in lesion counts were analyzed by an analysis of covariance model including ranked baseline lesion count as a covariate, treatment and analysis center as main effects. All tests were two-sided and used the .05 level to declare significance. No adjustment for multiplicity was made.

RESULTS

Subject disposition and baseline characteristics

A total of 517 subjects were randomized and included in the ITT population: 149 receiving adapalene-BPO, 148 receiving adapalene, 149 receiving BPO, and 71 receiving vehicle (Fig 1). Subject disposition was similar among the treatment groups. The PP population consisted of 421 subjects (81%). Overall, 91% of subjects completed the study. There was a lower rate of early discontinuation for subject request in the adapalene-BPO group relative to the other groups. The rates for discontinuation due to adverse events were low for all study groups.

The baseline characteristics of the ITT population are summarized in Table I. The treatment groups were comparable with respect to the demographic characteristics and baseline dermatological scores. Baseline acne severity was moderate for more than 75% of the subjects, for all groups.

Efficacy evaluation

The primary end-point results are shown in Table II. For success rate, defined as the percentage of patients with "clear" or "almost clear" ratings on the IGA, the adapalene-BPO combination (27.5%) was

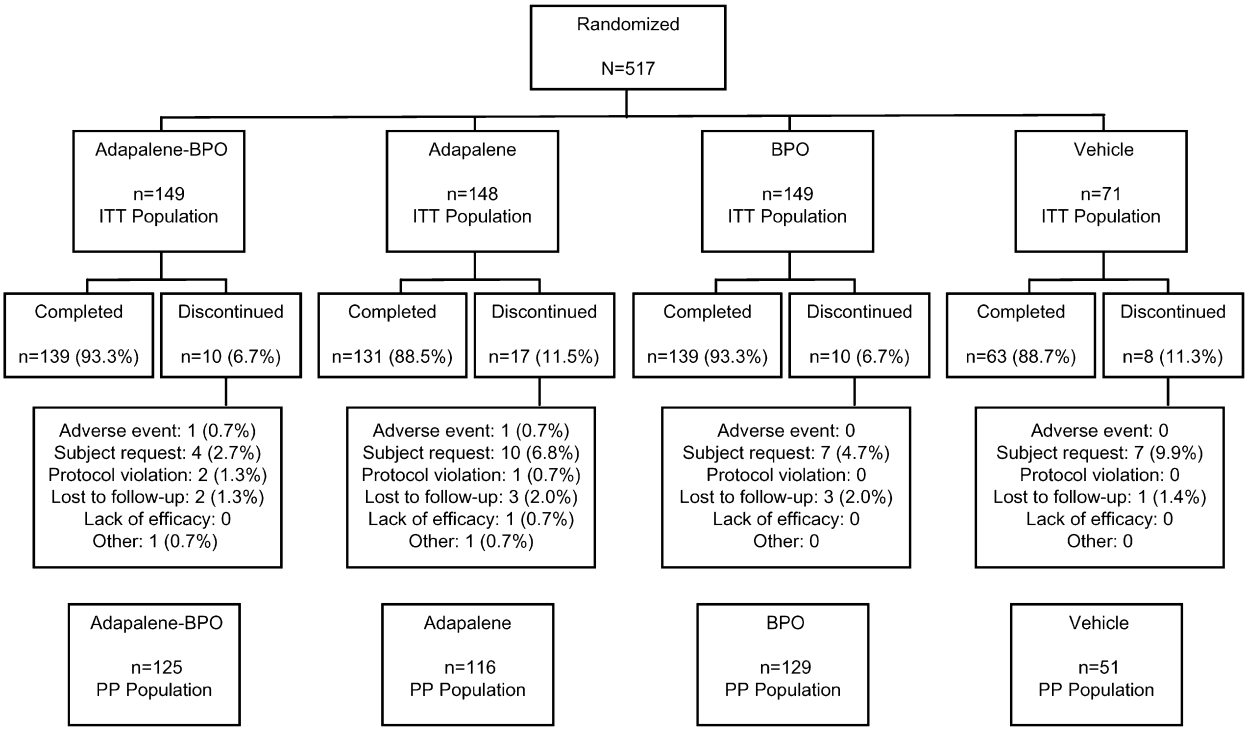

Fig 1. Flow chart of subject disposition.

Table I. Baseline demographic and clinical characteristics of the ITT population

Demographic/clinical parameter	Adapalene-BPO (n = 149)	Adapalene (n = 148)	BPO (n = 149)	Vehicle (n = 71)	Total (n = 517)	*P* value
Age, y						.885
Mean	16.2	16.5	16.5	16.6	16.4	
Minimim, maximum	12, 56	12, 37	12, 37	12, 33	12, 56	
Gender, No. (%)						.534
Male	87 (58.4)	86 (58.1)	96 (64.4)	40 (56.3)	309 (59.8)	
Female	62 (41.6)	62 (41.9)	53 (35.6)	31 (43.7)	208 (40.2)	
Race, No. (%)						.590
Caucasian	101 (67.8)	103 (69.6)	114 (76.5)	52 (73.2)	370 (71.6)	
Black	18 (12.1)	20 (13.5)	10 (6.7)	9 (12.7)	57 (11.0)	
Asian	1 (0.7)	1 (0.7)	2 (1.3)	1 (1.4)	5 (1.0)	
Hispanic	23 (15.4)	18 (12.2)	18 (12.1)	9 (12.7)	68 (13.2)	
Other	6 (4.0)	6 (4.1)	5 (3.4)	0	17 (3.3)	
Lesion counts (median)*						
Total	78	75	74	78		
Inflammatory	27	28	28	29		
Noninflammatory	44	45	43	46		
Baseline IGA, No. (%)						
2 = Mild	25 (16.8)	28 (18.9)	15 (10.1)	13 (18.3)		
3 = Moderate	119 (79.9)	111 (75.0)	127 (85.2)	57 (80.3)		
4 = Severe	5 (3.4)	9 (6.1)	7 (4.7)	1 (1.4)		

BPO, Benzoyl peroxide; *IGA*, investigator's global assessment; *ITT*, intention-to-treat.
*Median total lesion counts may not equal the sum of median inflammatory and median noninflammatory lesion counts.

superior to adapalene (15.5%, $P = .008$), BPO (15.4%, $P = .003$), and the vehicle (9.9%, $P = .002$) at end point (ITT population, week 12, LOCF). Success rate results among the treatment groups began to diverge early in favor of adapalene-BPO and continued to separate throughout the course of the study (Fig 2).

PP analyses confirmed results obtained in the ITT population with a success rate at week 12 of 30.1% for

Table II. Primary efficacy parameters (success rate and median percentage change in total, inflammatory, and noninflammatory lesions) at week 12 (LOCF, ITT population)

	Treatment group				*P* value		
	Adapalene-BPO (n = 149) (1)	Adapalene (n = 148) (2)	BPO (n = 149) (3)	Vehicle (n = 71) (4)	(1) vs (2)	(1) vs (3)	(1) vs (4)
Success rate (%)	27.5	15.5	15.4	9.9	.008	.003	.002
Lesion count*							
Total	−51.0	−35.4	−35.6	−31.0	<.001	<.001	<.001
Inflammatory	−62.9	−45.7	−43.6	−37.8	<.001	<.001	<.001
Noninflammatory	−51.2	−33.3	−36.4	−37.5	<.001	<.001	<.001

BPO, Benzoyl peroxide; *ITT*, intention-to-treat; *LOCF*, last observation carried forward.
*Data of treatment groups are expressed as percentage change.

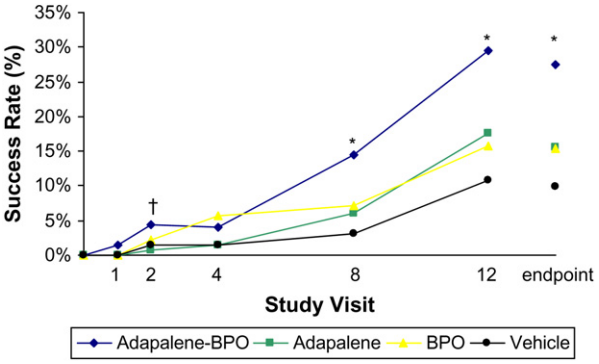

Fig 2. Success rates (percentage of patients "clear" or "almost clear" during the course of the study; ITT population, LOCF). *Asterisk* (*), Differences between adapalene-BPO and all other treatments were statistically significant at week 8, week 12, and end point (at least $P < .05$). *Dagger* (†), Differences between adapalene-BPO and adapalene were significant at week 2 ($P = .042$).

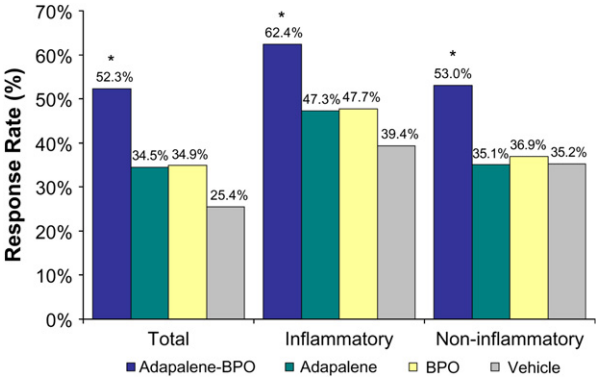

Fig 3. Response rates (percentage of subjects with at least 50% reduction in lesion counts from baseline). *Asterisk* (*), Differences between adapalene-BPO and all other treatments were statistically significant for total (vs adapalene, $P = .001$; vs BPO, $P = .002$; vs vehicle, $P < .001$), inflammatory (vs adapalene, $P = .005$; vs BPO, $P = .005$; vs vehicle, $P = .001$), and noninflammatory lesions (vs adapalene, $P = .001$; vs BPO, $P = .004$; vs vehicle, $P = .012$) at week 12 (ITT population, LOCF).

adapalene-BPO, 18.1% for adapalene ($P = .016$), 16.5% for BPO ($P = .001$), and 13.7% for the vehicle ($P = .009$).

Median percentage changes from baseline for total, inflammatory, and noninflammatory lesion counts at week 12 are presented in Table II. As with the success rate analysis, the lesion count analysis revealed a greater response for combination therapy relative to the other study groups. At week 12, the adapalene-BPO was significantly superior to adapalene, BPO, and vehicle for change from baseline in total, inflammatory, and noninflammatory lesion counts (all, $P < .001$). Significant differences in total lesion count reductions for adapalene-BPO were demonstrated as early as week 1 (adapalene-BPO, 19.7%; adapalene, 13% [$P = .001$]; BPO, 11.3% [$P = .01$]; vehicle, 7.8% [$P = .002$]). Early onset of action was also observed in inflammatory lesion count reductions at week 1 (adapalene-BPO, 25.7%; adapalene, 14.7% [$P < .001$]; BPO, 20% [$P = .001$]; vehicle, 13.6% [$P < .001$]) as well as noninflammatory lesion count reductions by week 4 (adapalene-BPO, 31.3%; adapalene, 19.5% [$P < .001$]; BPO, 21.8% [$P = .009$]; vehicle, 20.6% [$P < .05$]).

Secondary efficacy assessments also revealed consistent differences between adapalene-BPO and the other study groups. The response rates for total, inflammatory, and noninflammatory lesions were significantly superior for adapalene-BPO relative to adapalene, BPO, and the vehicle (all at least $P < 0.05$; Fig 3). For full-scale IGA, differences between adapalene-BPO and all other treatments were statistically significant ($P < .001$) at week 12, LOCF: more adapalene-BPO subjects had an IGA of mild, almost clear, or clear (70.5%) at week 12 (LOCF) relative to adapalene (54.1%), BPO (53.7%), or vehicle (47.9%) (Table III). Differences in subject's assessment of acne were also significant for adapalene-BPO versus BPO ($P = .011$) and vehicle ($P < .001$), and approached significance versus adapalene ($P = .062$). At week 12, the percentages of subjects rating

Table III. Investigator's global assessment full-scale assessment at week 12 (LOCF, ITT population)*

IGA	Adapalene-BPO, n = 149 No. (%)	Adapalene (n = 148) No. (%)	BPO (n = 149) No. (%)	Vehicle (n = 71) No. (%)
0 = Clear	3 (2.0)	1 (0.7)	2 (1.3)	0
1 = Almost clear	38 (25.5)	22 (14.9)	21 (14.1)	7 (9.9)
2 = Mild	64 (43.0)	57 (38.5)	57 (38.3)	27 (38.0)
3 = Moderate	43 (28.9)	62 (41.9)	63 (42.3)	30 (42.3)
4 = Severe	1 (0.7)	6 (4.1)	5 (3.4)	7 (9.9)
5 = Very severe	0	0	1 (0.7)	0

BPO, Benzoyl peroxide; *ITT*, intention-to-treat; *LOCF*, last observation carried forward.
*Differences between adapalene-BPO and all other treatments and were statistically significant ($P < .001$) at week 12.

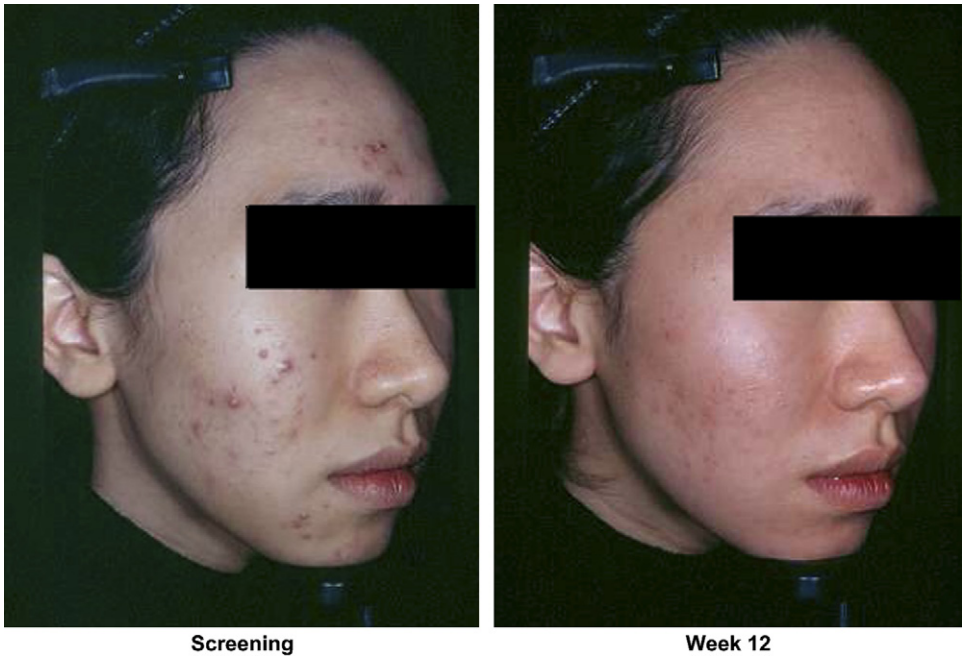

Fig 4. Effect of adapalene-BPO on facial lesions after 12 weeks of treatment.

their skin as "clear" or showing a "marked improvement" were 42.5% for adapalene-BPO, 34.8% for adapalene, 30.6% for BPO, and 14.5% for vehicle. The efficacy results were similar regardless of age, gender, or race. Fig 4 illustrates the effect of adapalene-BPO combination therapy on facial acne during the course of the 12-week study.

Safety evaluation

Overall, the safety and tolerability results of adapalene-BPO were comparable with those of adapalene. The scores for severity of erythema, scaling, dryness, and stinging/burning after study treatment are summarized in Fig 5. Local cutaneous tolerability was good for all treatments, with all mean tolerability scores at each visit and worst postbaseline scores for erythema, dryness, scaling, and burning/stinging less than 1 (mild). A majority of subjects in all of the groups experienced mild or no irritation.

The overall incidence of subjects experiencing at least one adverse event was 38.3% for adapalene-BPO gel, 42.6% for adapalene, 29.5% for BPO, and 26.8% for the vehicle. For adverse events judged to be related to therapy, the incidence was 17.4% for adapalene-BPO, 20.3% for adapalene, 6.7% for BPO, and 5.6% for vehicle The majority of "related" adverse events were of a dermatological nature, mild to moderate in severity; they occurred early in the study and resolved without residual effects. The most frequently reported related adverse event was dry skin: 9.4% for adapalene-BPO, 10.1% for adapalene, 2.0% for BPO, and 1.4% for the vehicle. One subject experienced a serious adverse event that was unrelated to study therapy (drug abuse). Two subjects experienced adverse events leading to discontinuation: one subject in the adapalene-BPO group (drug abuse/social circumstance) and one subject in the adapalene group (impetigo/infection

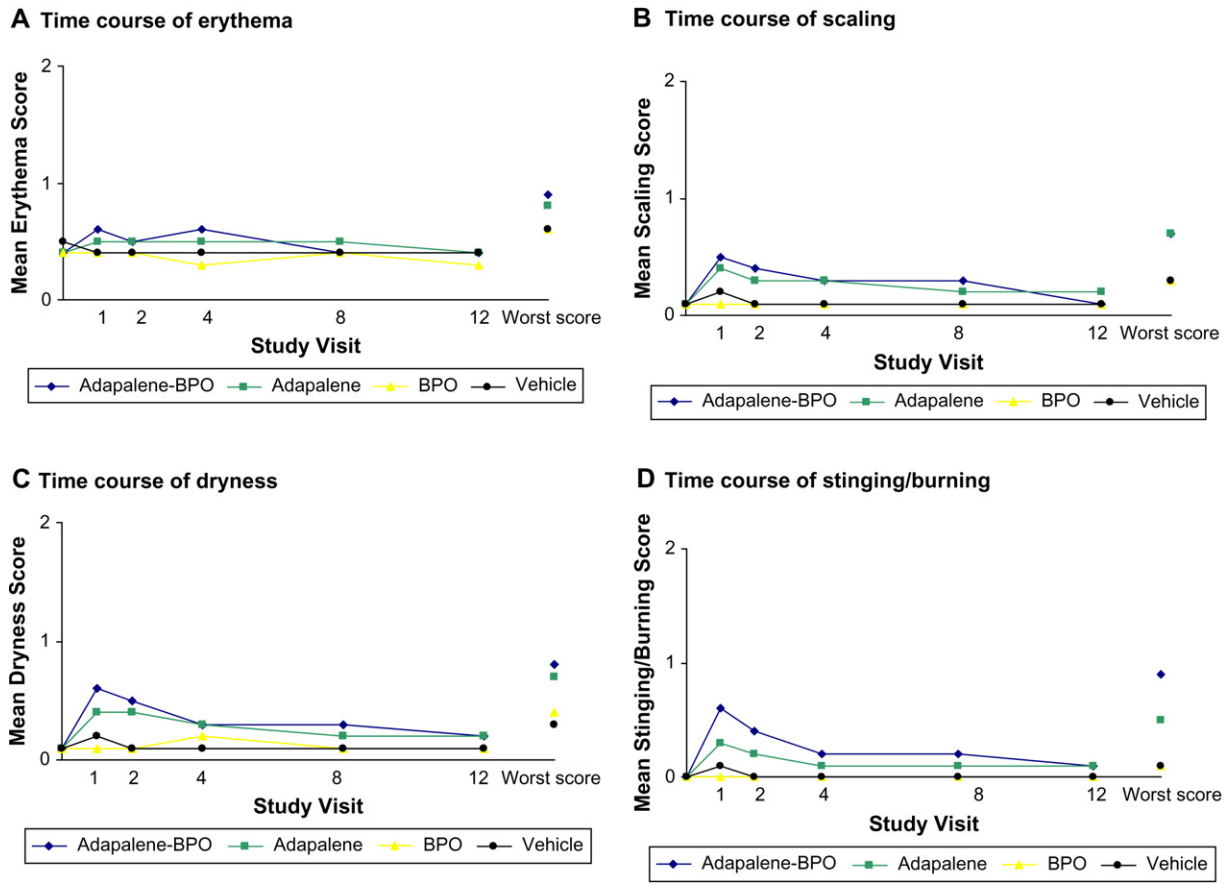

Fig 5. Local tolerability. Effects of adapalene-BPO combination therapy on skin tolerance variables: (**A**) erythema, (**B**) scaling, (**C**) dryness, and (**D**) stinging/burning. Skin tolerability variables were assessed according to the following scoring scale: none = 0, mild = 1, moderate = 2, 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.

and infestation). Both events were assessed "definitely unrelated" to study drug by the investigator.

DISCUSSION

Combination therapy for the treatment of acne is widely prescribed and extensively cited throughout the literature as a highly effective treatment approach for this complex and chronic disease.[3,32] Currently, there are relatively few anti-acne fixed-dose combination products and none containing a topical retinoid with BPO. The fixed-dose combination of adapalene 0.1% and BPO 2.5% for the treatment of acne combines two agents with different modes of action to address multiple pathophysiological factors of acne. The aim of the current study was to evaluate the efficacy and safety of the adapalene-BPO combination relative to the gel vehicle as well as individual monotherapies formulated in the same vehicle (ie, not the same vehicle formulation as the commercially available products).

Overall, results of this study show the fixed-dose combination gel of adapalene and BPO to be significantly more effective and to have a faster onset of action than monotherapy. The combination therapy regimen consistently provided an additional decrease of inflammatory and noninflammatory lesions, with statistically significant differences in total lesion counts observed as early as the first postbaseline assessment. Adapalene-BPO was superior to the other treatment arms for all efficacy assessments, in both ITT and PP populations, including the success rate analysis, which sets a high threshold by limiting "success" to those subjects whose acne had cleared or almost cleared at the end of the study.

Importantly, the tolerability profile of adapalene-BPO was comparable to adapalene monotherapy.[9,12-19] Studies have shown that adapalene can be added to other therapies without significantly increasing skin irritation.[18,19]

Topical retinoids are highly effective anticomedogenic and comedolytic agents that reverse the process

of abnormal follicular keratinization and inhibit microcomedo formation. Subsequently, they decrease the number of inflammatory lesions that result from rupture of microcomedones. In addition, topical retinoids have an effect on inflammation by modulating the immune response, inflammatory mediators, and the migration of inflammatory cells.[3,33] For example, adapalene and tretinoin have been shown to induce a dose-dependent inhibition of toll-like receptor 2 in cultured human monocytes.[7,34] *P acnes* acts through the toll-like receptor 2 to induce the production of proinflammatory cytokines.[35] In this regard, it is reasonable to hypothesize that there is a synergistic anti-inflammatory action of adapalene and BPO wherein BPO kills *P acnes* and adapalene down-regulates the cell surface receptor that *P acnes* uses to induce cytokine production. These two active ingredients could then potentially decrease the impact of *P acnes* in acne.

The penetration of BPO is likely to be enhanced when combined with a retinoid, which alters the follicular microclimate.[3] Results of the present study are consistent with previous studies that have demonstrated significantly greater reductions in both inflammatory lesions and comedones when topical retinoids have been combined with a topical antimicrobial treatment because of their complementary and additive mechanisms of action.[20-23] Based on data reported in the literature, adapalene-BPO appears to induce similar magnitude of effect in reducing lesion counts relative to other available fixed-dose combinations, such as clindamycin-BPO.[26-28,34] The availability of a new fixed-dose combination of a retinoid and BPO gel will provide patients and clinicians greater opportunity for customizing care and improving outcomes for patients with acne, particularly those who are treated with antibiotics.

The use of an adapalene-BPO combination is in accord with the recently published consensus recommendations for the management of acne.[3] Early initiation of combination therapy with topical retinoids and antimicrobials for all but the most severe cases of acne is often recommended. For acne with a predominantly inflammatory component, guidelines recommend benzoyl peroxide and/or topical antibiotics, in combination with a topical retinoid, to help speed the clearing of inflammatory acne lesions. It is preferable to combine BPO with other topical medications that have different modes of action, with the best match being a topical retinoid because of the complementary mechanisms of action. Maintenance therapy with effective, tolerable agents is often recommended to prevent future lesion development. A long-term study of adapalene-BPO demonstrated that the combination was safe and effective when used once daily for up to 12 months.[35] In addition, another potential benefit of a retinoid plus BPO combination for long-term use is the absence of risk of development of bacterial resistance.[3]

Fixed-dose combination products can offer several benefits for physicians and their patients. They eliminate the guesswork involved regarding the timing of application of topical products as well as concerns regarding stability and chemical compatibility of two separate formulations. Beyond the enhanced efficacy of utilizing two agents with synergistic and complementary pharmacological properties, the use of fixed-dose combinations may be more convenient and simplify the treatment regimen, thereby potentially improving treatment adherence and outcomes.

In summary, the fixed-dose combination of adapalene and BPO provides additional efficacy compared with either agent alone for the treatment of acne vulgaris and a faster onset of action relative to monotherapy with a safety profile comparable to that of adapalene.

We thank the members of the Adapalene-BPO Study Group: Elizabeth A. Arthur, MD (Rochester, NY); James Aton, MD (Martinez, Ga); Arthur K. Balin, MD (Media, Pa); Alicia Barba, MD (Miami, Fla); Fernando deCastro, MD (Lexington, Ky); Sunil Dhawan, MD (Fremont, Calif); Jonathan Dosik, MD (Paramus, NJ); Nancy Egan, MD (Rockland, Me); Ellen Frankel, MD (Johnston, RI); Paul S. Gillum, MD (Norman, Okla); Michael Gold, MD (Nashville, Tenn); James H. Herndon, Jr, MD (Carrollton, Tex); Charles P. Hudson, MD (Evansville, Ind); Joseph L. Jorizzo, MD (Winston-Salem, NC); David L. Kaplan, MD (Overland Park, Kan); Steven E. Kempers, MD (Fridley, Minn); Mark Russell Ling, MD, PhD (Newnan, Ga); Robert Loss, MD (Rochester, NY); Keith Loven, MD (Goodlettsville, Tenn); Nicholas Lowe, MD (Santa Monica, Calif); Anne Lucky, MD (Cincinnati, Ohio); Robert Matheson, MD (Portland, Ore); Alan Menter, MD (Dallas, Tex); Amy Morris, MD (Mobile, Ala); Phoebe Rich, MD (Portland, Ore); Ronald Savin, MD (New Haven, Conn); Harry Sharata, MD (Madison, Wis); Leonard J. Swinyer, MD (Salt Lake City, Utah); David A. Whiting, MD (Dallas, Tex). We also thank David Cox, PhD, for editorial assistance.

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