Adapalene–benzoyl peroxide, a unique fixed-dose combination topical gel for the treatment of acne vulgaris: a transatlantic, randomized, double-blind, controlled study in 1670 patients

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Summary

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Background Combination therapy utilizing agents with complementary mechanisms of action is recommended by acne guidelines to help simultaneously target multiple pathogenic factors. A unique, topical, fixed-dose combination gel with adapalene 0·1% and benzoyl peroxide (BPO) 2·5% has recently been developed for the once-daily treatment of acne.

Objectives To evaluate the efficacy and safety of adapalene 0·1%–BPO 2·5% fixed-dose combination gel (adapalene–BPO) relative to adapalene 0·1% monotherapy (adapalene), BPO 2·5% monotherapy (BPO), and the gel vehicle (vehicle) in a large population for the treatment of acne vulgaris.

Methods In total, 1670 subjects were randomized in a double-blind controlled trial to receive adapalene–BPO, adapalene, BPO or vehicle for 12 weeks (1 : 1 : 1 : 1 randomization). Evaluations included success rate (subjects 'clear' or 'almost clear'), percentage change in lesion count from baseline, cutaneous tolerability and adverse events.

Results Adapalene–BPO was significantly more effective than corresponding monotherapies, with significant differences in percentage lesion count change observed as early as 1 week. Cutaneous tolerability profile was similar to adapalene. Adverse events were more frequent with the combination therapy (mainly due to an increase in mild-to-moderate dry skin), occurred early in the study, and were transient.

Conclusions Adapalene–BPO provides significantly greater and synergistic efficacy and a faster onset of action with an acceptable safety profile in the treatment of acne vulgaris when compared with the corresponding vehicle and the adapalene and BPO monotherapies.

Due to the multifactorial pathogenesis of acne vulgaris and the limitations of the current therapeutic armamentarium, combination therapy utilizing agents with complementary mechanisms, such as a topical retinoid and an antimicrobial, is frequently used in the management of the disorder.[1–3] Acne often involves multiple abnormalities of the pilosebaceous unit, including ductal hyperkeratinization and increased cohesiveness of keratinocytes, increased sebum production, *Propionibacterium acnes* hypercolonization, and inflammation.[1,2] Consequently, combination therapy provides the opportunity to target multiple pathogenetic causes of acne.[3]

Recently, an antibiotic-free, fixed-dose combination gel with adapalene 0·1% and benzoyl peroxide (BPO) 2·5% (adapalene–BPO, Epiduo™; Galderma, Princeton, NJ, U.S.A.)

has been developed for the once-daily treatment of acne. The complementary modes of action as well as the efficacy/safety profiles of these two agents make adapalene–BPO a rational choice for treatment for all but the most severe cases of acne. Adapalene possesses anticomedogenic, comedolytic and anti-inflammatory properties,[4–11] whereas BPO, the most potent bactericidal agent, is more effective than topical antibiotics against P. *acnes*.[12] Because neither retinoids nor BPO create selective pressure for resistance, this combination may be expected to decrease the incidence of bacterial resistance relative to antibiotics.[3,13–16] Furthermore, unlike tretinoin, adapalene is stable when combined with BPO even in the presence of light.[17]

Initial clinical studies have demonstrated a favourable efficacy/safety profile for adapalene–BPO. In a recent 12-week study in 517 subjects, an adapalene–BPO combination provided a significant additional reduction in acne lesions and a quicker onset of action relative to respective monotherapies, with a safety and tolerability profile comparable with adapalene.[18] In addition, a 12-month continuous-use study supports the safe and effective use of adapalene–BPO for the long-term management of subjects with acne vulgaris.[19] In that study, most adverse events and symptoms of skin irritation were mild-to-moderate, occurred early in the study, and were transient. Clinically significant inflammatory and noninflammatory lesion count reductions were observed as early as week 1 and were sustained for up to 1 year (70% and 76%, respectively). The objective of the present study was to confirm the efficacy and safety of adapalene 0·1%–BPO 2·5% fixed combination topical gel (adapalene–BPO) vs. adapalene 0·1% gel (adapalene), BPO 2·5% gel (BPO), as well as the gel vehicle (vehicle) in a larger population for the treatment of acne vulgaris for up to 12 weeks.

Materials and methods

Study design

The efficacy and safety of adapalene–BPO were compared with adapalene, BPO, and the gel vehicle in a randomized, multicentre, double-blind, active- and vehicle-controlled parallel group study conducted at 61 centres in the U.S.A., Canada and Europe. Subjects were randomized consecutively in a 1 : 1 : 1 : 1 ratio to receive either adapalene–BPO gel, adapalene gel, BPO gel, or gel vehicle, once daily in the evening for 12 weeks [adapalene gel and BPO gel, used as monotherapies in this study, are formulated in the same vehicle as the combination and not as the available commercial products (Differin® or Benzac®; Galderma)]. Blinding integrity was ensured by packaging the topical medication in identical tubes. A third party other than the investigator/evaluator was required 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 females 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 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 institutional review boards/ethics committees. All patients provided their written informed consent prior to entering the study.

Subjects

Enrolled subjects were male or female of any race, 12 years of age or older with acne vulgaris, having on the face 20–50 inflammatory lesions, 30–100 noninflammatory lesions and an Investigator's Global Assessment (IGA) score of 3, corresponding to moderate acne (Table 1). Patients were to have no more than one active nodule at baseline. Lesion counts were assessed on the face only, excluding the nose. Specified washout periods were required for subjects taking certain topical and systemic treatments. Exclusion criteria prohibited enrolment of subjects with severe acne requiring isotretinoin therapy or other dermatological 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. If the subjects were assessed to have dry skin, they were requested to use a moisturizer throughout the study. Noncomedogenic cosmetics were permitted during the study period, as well as eye and lip cosmetics.

Efficacy and safety assessments

The efficacy variables included success rate (the percentage of subjects rated 'clear' or 'almost clear' on the IGA scale of acne severity), percentage change in lesion counts (total, inflammatory and noninflammatory), change in IGA, and subject's

Table 1 Investigator's Global Assessment of acne severity

0	'Clear'	Residual hyperpigmentation and erythema may be present
1	'Almost clear'	A few scattered comedones and a few small papules
2	'Mild'	Easily recognizable; less than half the face is involved. Some comedones and some papules and pustules
3	'Moderate'	More than half of the face is involved. Many comedones, papules and pustules. One nodule may be present
4	'Severe'	Entire face is involved, covered with comedones, numerous papules and pustules, and few nodules and cysts

'Success' was defined as 'clear' or 'almost clear' (scores 0 and 1).

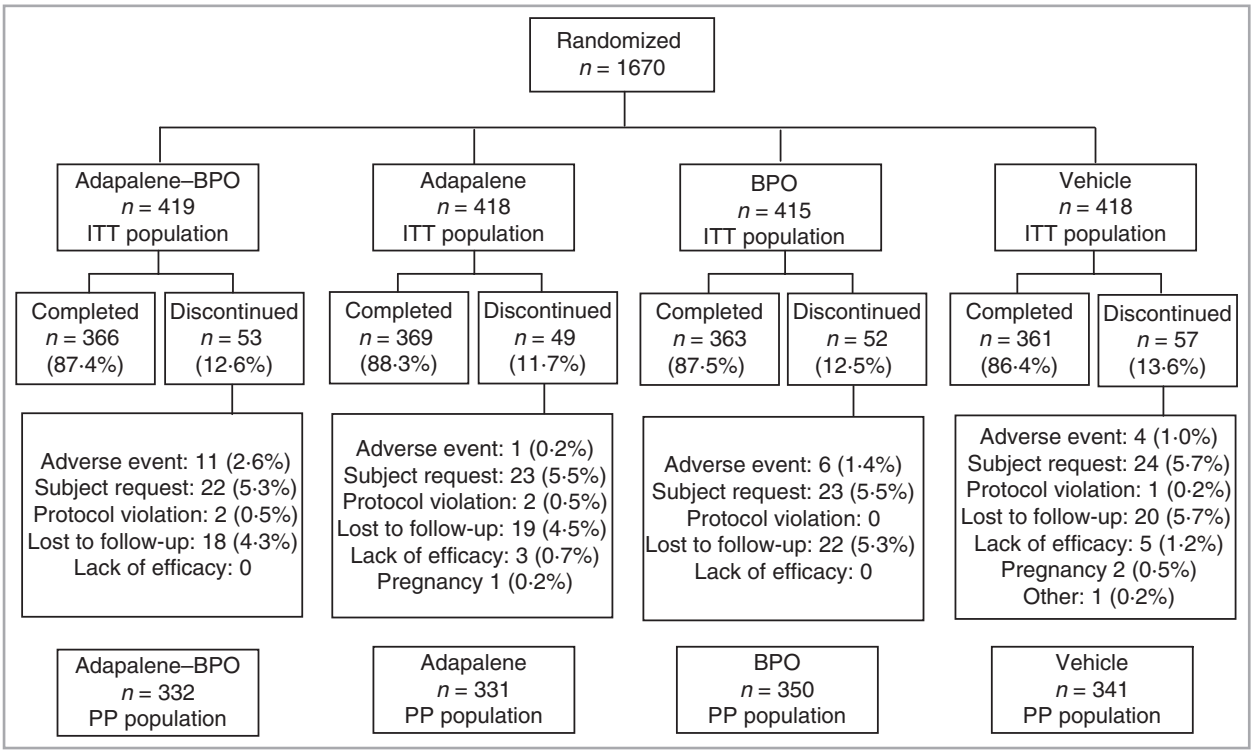

Fig 1. Flow chart of subject disposition. BPO, benzoyl peroxide; ITT, intent-to-treat; PP, per-protocol.

Table 2 Baseline demographic and clinical characteristics of the intent-to-treat population

Demographic/clinical parameter	Adapalene–BPO (n = 419)	Adapalene (n = 418)	BPO (n = 415)	Gel vehicle (n = 418)	Total (n = 1670)	P-value
Age (years), mean (range)	19·5 (12–48)	18·5 (12–50)	18·9 (12–55)	19·2 (12–51)	19·0 (12–55)	0·127
Gender, *n* (%)						
Male	183 (43·7)	189 (45·2)	185 (44·6)	174 (41·6)	731 (43·8)	0·745
Female	236 (56·3)	229 (54·8)	230 (55·4)	244 (58·4)	939 (56·2)	
Race, *n* (%)						
Caucasian	335 (80·0)	328 (78·5)	329 (79·3)	331 (79·2)	1323 (79·2)	0·933
Black	37 (8·8)	37 (8·9)	39 (9·4)	42 (10·0)	155 (9·3)	
Asian	15 (3·6)	14 (3·3)	16 (3·9)	18 (4·3)	63 (3·8)	
Hispanic	22 (5·3)	31 (7·4)	22 (5·3)	22 (5·3)	97 (5·8)	
Other	10 (2·4)	8 (1·9)	9 (2·2)	5 (1·2)	32 (1·9)	
Lesion counts (median)						
Inflammatory	26·0	27·0	26·0	26·0	26·0	0·861
Noninflammatory	45·0	46·0	45·0	46·0	45·0	0·493
Total	76·0	77·5	74·0	76·0	76·0	0·486
Baseline IGA of 3 (moderate), *n* (%)	419 (100)	418 (100)	415 (100)	418 (100)	1670 (100)	–
Phototype, *n* (%)						
I	11 (2·6)	12 (2·9)	12 (2·9)	17 (4·1)	52 (3·1)	0·163
II	126 (30·1)	106 (25·4)	131 (31·6)	122 (29·2)	485 (29·0)	
III	132 (31·5)	145 (34·7)	127 (30·6)	147 (35·2)	551 (33·0)	
IV	96 (22·9)	99 (23·7)	94 (22·7)	76 (18·2)	365 (21·9)	
V	34 (8·1)	32 (7·7)	27 (6·5)	35 (8·4)	128 (7·7)	
VI	20 (4·8)	24 (5·7)	24 (5·8)	21 (5·0)	89 (5·3)	

BPO, benzoyl peroxide; IGA, Investigator's Global Assessment. P-values for nominal categorical variables were based on the Cochran–Mantel–Haenzsel (CMH) general association statistic, controlling for centre. P-values for ordinal categorical variables were based on the CMH row mean difference statistic, RIDIT transformed score, controlling for centre. P-values for continuous variables were based on two-way ANOVA model with terms for treatment and centre.

Table 3 Summary of efficacy analyses at week 12 (last observation carried forward, intent-to-treat population)

	Treatment group				P-value		
	Adapalene–BPO (n = 419) (1)	Adapalene (n = 418) (2)	BPO (n = 415) (3)	Vehicle (n = 418) (4)	(1) vs. (2)	(1) vs. (3)	(1) vs. (4)
Success rate (%)	37·9	21·8	26·7	17·9	< 0·001	< 0·001	< 0·001
Median percentage (%) change in lesion count							
Total	−65·4	−52·3	−48·2	−37·1	< 0·001	< 0·001	< 0·001
Inflammatory	−70·3	−57·1	−61·9	−45·5	< 0·001	< 0·001	< 0·001
Noninflammatory	−62·2	−50·4	−48·8	−36·7	< 0·001	< 0·001	< 0·001
IGA[a] (%): subjects with 'clear', 'almost clear', or 'mild'	75	63	59	53	< 0·001	< 0·001	< 0·001
Subject assessment[a] (%): subjects with 'complete improvement' or 'marked improvement'	50	44	39	29	0·006	< 0·001	< 0·001

BPO, benzoyl peroxide; IGA, Investigator's Global Assessment. [a]P-values for change in IGA and subject assessment were based on the Cochran–Mantel–Haenzsel test with row mean difference statistic using RIDIT score, controlling for analysis centre.

assessment of acne improvement. The IGA was evaluated on a scale ranging from 0 (clear) to 4 (severe). The subject's assessment was evaluated on a scale from 0 (complete improvement) to 5 (worse) as well as through a satisfaction questionnaire.

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/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. The sample size calculation was based on the assumptions that (i) success rates are 25%, 15%, 15% and 10% for adapalene–BPO, adapalene, BPO and gel vehicle, respectively; (ii) median difference is four inflammatory lesions (SD = 15) between adapalene–BPO and each monotherapy; and (iii) median difference is five noninflammatory lesions (SD = 20) between adapalene–BPO and each monotherapy. These assumptions were based on a previous study.[18] Assuming a two-sided test with 0·05 significance level, a 15% drop-out rate and 90% power, a total of 1656 subjects (414 subjects per treatment group) was deemed sufficient.

Three study populations were analysed. 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 ITT subjects without any major protocol deviations.

The primary efficacy criterion was success rate evaluated at endpoint [week 12, last observation carried forward (LOCF)] based on the ITT population. Success rate and percentage lesion count reduction were analysed by the Cochran–Mantel–Haenzsel (CMH) test stratified by analysis centre, using general association for success rates and row mean differences by RIDIT transformed scores for percentage lesion changes. Success rate analysis was repeated for the PP population to confirm the efficacy results. Sensitivity analyses for success rate were conducted with (i) 'failure' assigned to missing data at week 12; and (ii) 'success' assigned to missing data at week 12. Change in IGA (full scale) and subject's assessment of acne were also analysed by the CMH test. All tests were two sided and used the 0·05 level to declare significance. No adjustment for multiplicity was made.

Results

Subject disposition and baseline characteristics

In total, 1670 subjects were randomized and included in the ITT population: 419 receiving adapalene–BPO, 418 receiving

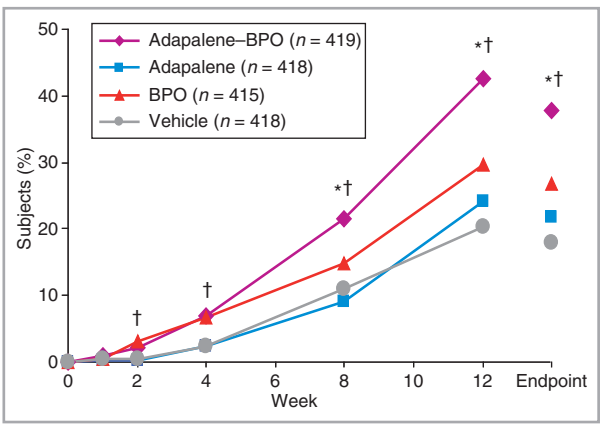

Fig 2. Success rates (percentage of patients 'clear' or 'almost clear' during the course of the study; intent-to-treat population, last observation carried forward). *Differences between adapalene–benzoyl peroxide (BPO) and all other treatments were statistically significant at week 8, week 12 and endpoint ($P < 0·001$). †Differences between adapalene–BPO and adapalene and vehicle were also significant at week 2 and week 4 (at least $P < 0·05$).

adapalene, 415 receiving BPO, and 418 receiving vehicle (Fig. 1). Subject disposition was similar between the treatment groups. Overall, 87·4% of subjects completed the study. There was a similar drop-out rate among the different groups. In the adapalene–BPO group, no subjects discontinued due to lack of efficacy and slightly more subjects discontinued early due to adverse events. The PP population included 1354 patients (332 receiving adapalene–BPO, 331 receiving adapalene, 350 receiving BPO, 341 receiving vehicle).

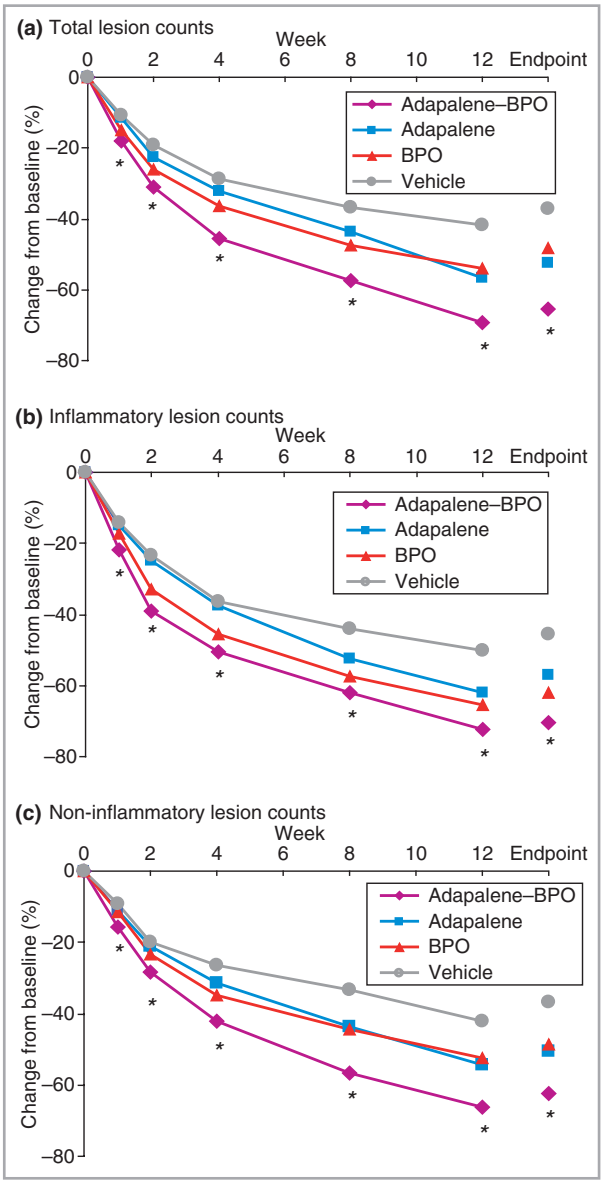

Fig 3. Median percentage change from baseline in total, inflammatory and noninflammatory lesions (intent-to-treat population). (a) Total. *Differences between adapalene–benzoyl peroxide (BPO) and other treatment groups were all statistically significant (at least $P < 0·05$). (b) Inflammatory. *Differences between adapalene–BPO and other treatment groups were all statistically significant (at least $P < 0·05$) (c) Noninflammatory. *Differences between adapalene–BPO and other treatment groups were all statistically significant (at least $P < 0·05$), with the exception of week 1 vs. BPO ($P = 0·08$).

The baseline characteristics of the ITT population are summarized in Table 2. The treatment groups were comparable with respect to the demographic characteristics and baseline dermatological scores. Baseline acne severity was moderate for all of the subjects in all treatment groups.

Efficacy evaluation

An overview of the efficacy results is shown in Table 3. For success rate, the adapalene–BPO combination (37·9%) was superior to adapalene (21·8%, $P < 0·001$), BPO (26·7%, $P < 0·001$) and the vehicle (17·9%, $P < 0·001$) at endpoint (ITT population, week 12, LOCF). Success rates increased throughout the course of the study, with significant differences in the percentage of patients 'clear' or 'almost clear' by week 8 for adapalene–BPO vs. all other comparators (Fig. 2). A significant early treatment effect was observed starting at week 2 for success rate and was sustained until the end of the study. The net beneficial effect (active minus vehicle) obtained from adapalene–BPO (20%) was greater than the sum of the net benefits obtained from the individual components (3·9% for adapalene plus 8·8% for BPO), thus indicating a synergistic effect of the therapeutic activities of these substances when used in a fixed-dose combination.

At week 12 (LOCF, ITT population), adapalene–BPO was significantly superior to adapalene, BPO and vehicle for median percentage change from baseline in inflammatory, noninflammatory and total lesions (all $P < 0·001$; LOCF, ITT population; Fig. 3). Results from the ITT population were confirmed by PP analysis (data not shown). An early onset of action was observed, with adapalene–BPO demonstrating significantly larger reductions in total, inflammatory and noninflammatory lesions relative to the other treatment arms as early as week 1 ($P < 0·05$). The lone exception was adapalene–BPO vs. BPO, which showed early onset starting at week 2.

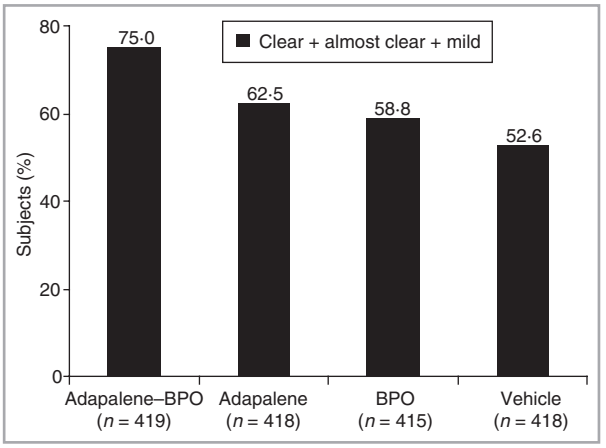

Fig 4. Investigator's Global Assessment full scale assessment: percentage of subjects with clear, almost clear, or mild acne at week 12 (last observation carried forward, intent-to-treat population). Differences between adapalene–benzoyl peroxide (BPO) and all other treatments were statistically significant ($P < 0·001$) at week 12.

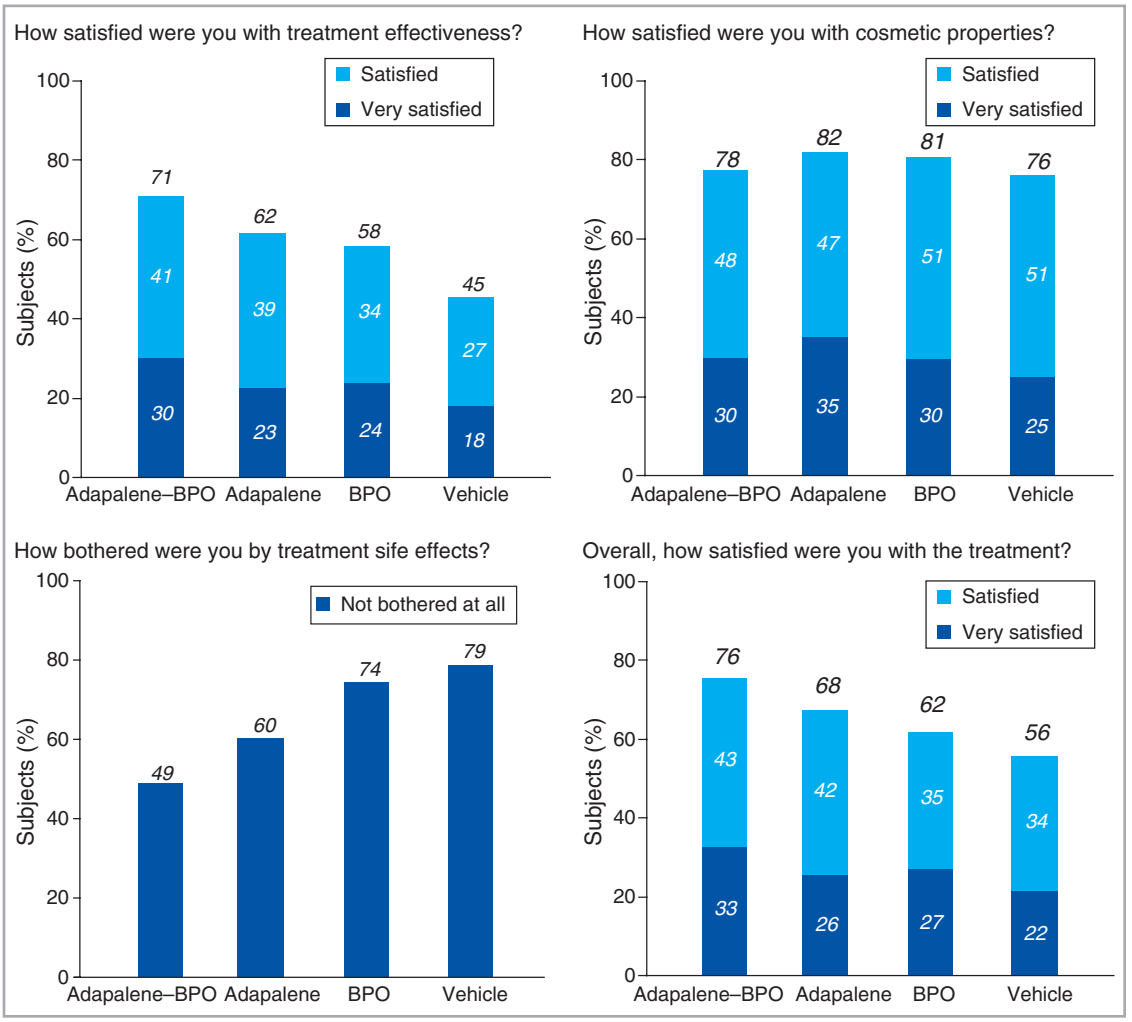

Fig 5. Summary of subject appreciation questionnaire. BPO, benzoyl peroxide.

For IGA, differences between adapalene–BPO and all other treatments were statistically significant ($P < 0{\cdot}001$) at week 12 (ITT population; LOCF). More adapalene–BPO subjects had an IGA of 'mild', 'almost clear' or 'clear' (75·0%) at week 12 relative to adapalene (62·5%), BPO (58·8%) or vehicle (52·6%) (Fig. 4). Conversely, the number of patients with moderate acne vulgaris decreased from 100% at baseline to 22·9% with adapalene–BPO, 37·3% with adapalene, 40·5% with BPO and 45·7% with vehicle.

The subject assessment results mirrored the efficacy evaluations by the investigators. The percentages of subjects rating their skin showing a 'complete improvement' or 'marked improvement' were 50·2% for adapalene–BPO, 43·8% for adapalene, 39·4% for BPO and 28·6% for vehicle. Differences in subject assessment of acne were significant for adapalene–BPO vs. adapalene ($P = 0{\cdot}006$), BPO ($P < 0{\cdot}001$) and vehicle ($P < 0{\cdot}001$). The results of the subject appreciation questionnaire are summarized in Figure 5. Subjects were more satisfied with adapalene–BPO for treatment effectiveness whereas subject satisfaction with cosmetic properties was similar among the treatment groups. More adapalene–BPO subjects were bothered by side-effects; however, for the overall treatment experience, more subjects were satisfied with adapalene–BPO than with other treatments. The effect of adapalene–BPO on facial lesions after 12 weeks of treatment is shown in Figure 6.

Safety evaluation

Overall, the local tolerability of adapalene–BPO was comparable with adapalene. The scores for the severity of erythema, scaling, dryness and stinging/burning after study treatment are summarized in Figure 7. 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 consistent with mild scores (score of ≤ 1). Peak scores at week 1 were generally higher for adapalene–BPO, but tolerability profiles were then comparable at subsequent visits. A majority of subjects in all of the groups experienced mild or no irritation.

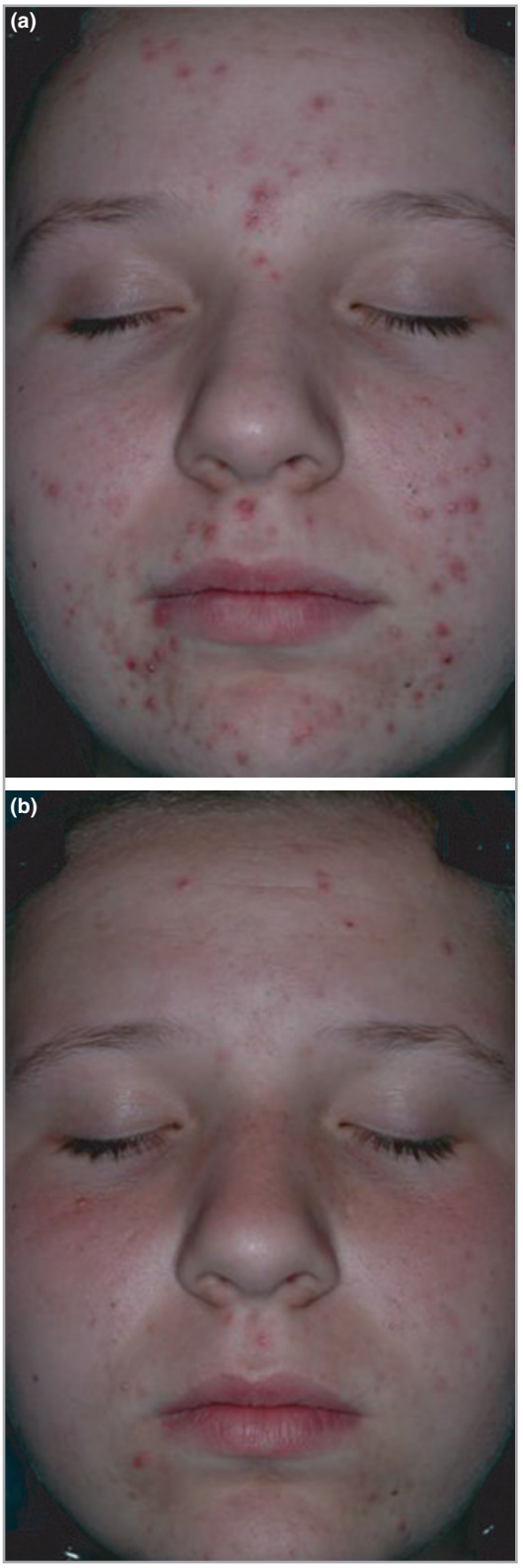

Fig 6. Facial lesions before (a) and after (b) 12 weeks of treatment with adapalene–benzoyl peroxide (reproduced with patient's consent).

The overall incidence of subjects experiencing at least one adverse event was 48% for adapalene–BPO, 39% for adapalene, 33% for BPO and 28% for vehicle. Eleven (2·6%) subjects in the adapalene–BPO group, one (0·2%) subject in the adapalene group, six (1·4%) subjects in the BPO group and four (1·0%) subjects in the vehicle group discontinued due to an adverse event. For adverse events judged to be related to therapy, the incidence was 31% for adapalene–BPO, 19% for adapalene, 13% for BPO and 8% for vehicle. The majority of 'related' adverse events were of dermatological nature, mild to moderate in severity, occurred early in the study, and resolved without residual effects. The difference in related adverse events among the groups was mainly driven by an increase in dry skin: 21·2% for adapalene–BPO, 14·1% for adapalene, 8·4% for BPO and 5·3% for the vehicle. There were no cases of severe dry skin and two subjects (0·5%) in the adapalene–BPO group discontinued due to dry skin.

Serious adverse events during the study occurred in three (0·7%) adapalene–BPO subjects (furuncle, appendicitis, scoliosis), one (0·2%) adapalene subject (schizoaffective disorder), one (0·2%) BPO subject (spontaneous abortion) and two (0·5%) vehicle subjects (cervical vertebral fracture, abcess limb). No serious adverse events were deemed related to the study treatments.

Discussion

The aim of this study was to evaluate the efficacy and safety of the unique adapalene–BPO fixed-dose topical combination gel relative to adapalene monotherapy, BPO monotherapy, as well as the gel vehicle in a large population of subjects with acne from North America and Europe. Overall, this study confirms that adapalene–BPO is more effective than monotherapy, as the combination therapy regimen consistently provided significant additional decreases of inflammatory and noninflammatory lesions. In both the ITT and PP study populations, adapalene–BPO was superior to the other treatment arms for all efficacy assessments, including success rate, percentage change in lesion counts and subject assessment. Significant early effect of adapalene–BPO was observed as early as week 1 in percentage change in lesion counts and was sustained until the end of study.

A potential synergistic effect of adapalene–BPO relative to the individual monotherapies was observed in this study. For success rate, the vehicle-subtracted results for adapalene–BPO (20%) were larger than the vehicle-subtracted results for the adapalene group (4%) and the BPO group (9%) combined. Theoretically, a synergistic anti-inflammatory effect may result from BPO eliminating *P. acnes* and adapalene downregulating the cell surface receptor[7] (toll-like receptor 2) that *P. acnes* uses to induce inflammatory cytokine production. As a result, these two active ingredients could then synergistically decrease the impact of *P. acnes* in acne. In addition, the penetration of BPO is likely to be enhanced when combined with a retinoid, which alters the follicular microclimate.[3]

Previous studies have shown that adapalene can be added to other therapies without significantly increasing skin irritation.[18,20,21] In this study, adapalene–BPO had local cutaneous tolerability comparable with adapalene monotherapy, the best

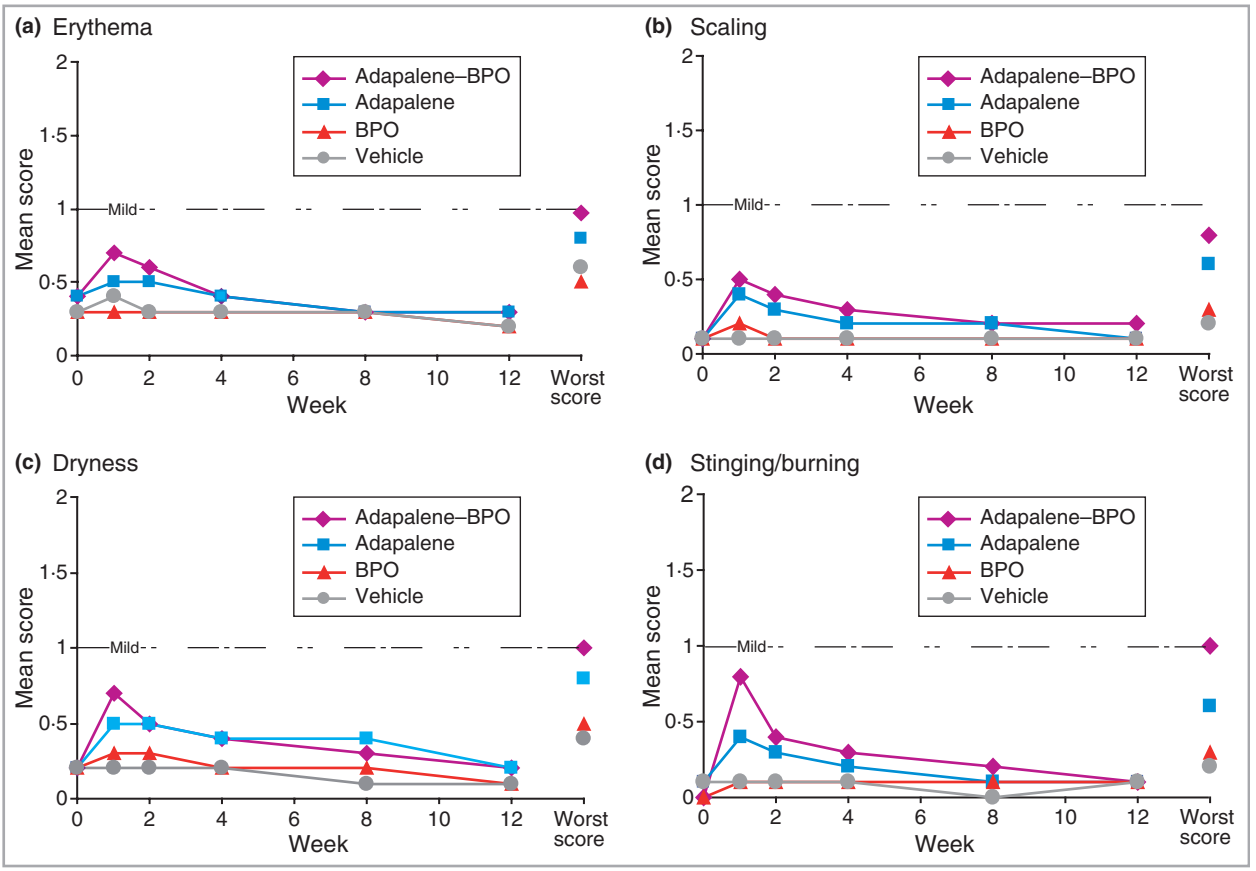

Fig 7. Local tolerability. Effects of adapalene–benzoyl peroxide (BPO) combination therapy on skin tolerance variables: (a) erythema; (b) scaling; (c) dryness; (d) stinging/burning. Skin tolerability variables were assessed according to the following scoring scale: 0, none; 1, mild, 2, moderate; 3, severe. Mean scores at each visit and mean worst scores (worst observation recorded for a subject during the postbaseline period) are shown.

tolerated topical retinoid. Peak scores were observed at week 1 and were generally higher for adapalene–BPO, but were then comparable at subsequent visits. Consistent with previous studies evaluating adapalene–BPO, local tolerability scores were ≤ 1, consistent with low or mild cutaneous irritation (1 = mild).[18,19] Adverse event frequency was slightly higher with the combination therapy relative to the monotherapies studied, mainly due to an increase in mild-to-moderate 'dry skin', occurring early in the study and resolving during the course of the study. The frequency of adverse events for adapalene–BPO in a previous study[18] was similar to that of adapalene monotherapy and lower than in the current study. Potential explanations for the varying results could include the overall lighter phototypes of subjects entering into the present study, as these patients may be more sensitive to topical medications. As with other retinoid acne therapies, educating patients on the concomitant use of a noncomedogenic moisturizer may help avoid potential irritation, especially during the first 2 weeks. Compared with the previous study, fewer subjects in the current study were requested to use a moisturizer due to skin dryness, which may have also contributed to the increase in treatment-related adverse events such as 'dry skin'. Importantly, subjects who received adapalene–BPO in this study were more satisfied with the overall treatment experience and felt better about themselves relative to other study therapies, despite more subjects indicating that they were somewhat bothered by side-effects with the combination.

The use of combination therapy is consistent with current consensus guidelines, which recommend early initiation of therapy with topical retinoids and antimicrobials.[3] The availability of additional fixed-dose formulations, such as adapalene–BPO, that target multiple pathogenetic factors of acne will provide patients and clinicians greater opportunity for customizing care and improving outcomes for patients with acne. Fixed-dose once-daily combination products may also increase patient adherence to treatment. Reductions in the complexity of acne treatment regimens, shortening the time for visible signs of success, and improving overall patient outcomes are all factors that may encourage patients to maintain their treatment regimens.

Results of the present study are consistent with previous studies that have evaluated the combination of topical retinoids with a topical antimicrobial for reducing inflammatory lesions and comedones.[18,22–25] The results are also consistent

with a recently completed study in over 1600 patients in North America, which demonstrated that adapalene–BPO is superior to adapalene and BPO monotherapies and the vehicle, with an early onset of therapeutic effect, and a good tolerability profile (Stein-Gold L, Tan J, Werschler W *et al.* Adapalene–benzoyl peroxide, a unique fixed dose combination gel for the treatment of acne: a North American, multicenter, randomized, double-blind, controlled, phase III trial in 1668 patients. Submitted to Cutis). Compared with already existing fixed-dose combinations,[26–28] adapalene–BPO provides a logical complementary mode of action and offers the advantage of being antibiotic free and may therefore be expected to decrease the incidence of epidermal bacterial resistance relative to antibiotics.[3,13–16]

In summary, the fixed-dose combination of adapalene and BPO is safe, well tolerated, and provides significantly greater efficacy for the treatment of acne vulgaris and a faster onset of action relative to adapalene and BPO monotherapy.

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