Original Contribution

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# The tolerability profile of clindamycin 1%/benzoyl peroxide 5% gel vs. adapalene 0.1%/benzoyl peroxide 2.5% gel for facial acne: results of a randomized, single-blind, split-face study

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## Summary

*Background* Topical combination therapy, such as that with fixed-dose clindamycin/benzoyl peroxide (BPO) or adapalene/BPO, is the recommended first-line approach for the treatment of facial acne.

*Aims* To compare the tolerability of clindamycin 1%/BPO 5% gel *vs.* adapalene 0.1% BPO 2.5% gel for the first 2 weeks of treatment in patients with facial acne.

*Patients/Methods* Using a randomized, single-blind, split-face method, 48 patients with acne received both clindamycin/BPO and adapalene/BPO once daily for 2 weeks. The primary endpoint was investigator-assessed tolerability. Treatment efficacy, patient-assessed tolerability and satisfaction, and safety were also investigated.

*Results* Forty-five patients completed treatment. Investigator-rated scores for erythema, dryness, and peeling were significantly higher with adapalene/BPO than clindamycin/BPO. Patients rated clindamycin/BPO as significantly more tolerable than adapalene/BPO for redness, dryness, burning, itching, and scaling. Investigator Static Global Assessment scores and lesion counts improved with both products, with no significant difference between treatments. Patients' Global Change Assessment showed a statistically significant difference in favor of clindamycin/BPO at week 1, but not week 2. Overall, >80% of patients were "satisfied" or "very satisfied" with treatment at week 2, but 63% of patients stated that they preferred clindamycin/BPO. Both products were well tolerated, with no serious adverse events (AEs), but a *post hoc* analysis indicated that treatment-related AEs, including irritation, dryness and erythema, were significantly less common with clindamycin/BPO.

*Conclusions* Clindamycin/BPO had a better tolerability profile than adapalene/BPO during 2 weeks of split-face treatment. Treatment satisfaction was highest with clindamycin/BPO.

*Keywords*: clindamycin, benzoyl peroxide, adapalene, acne, combination, topical

## Introduction

Acne is a multifactorial disease with four primary pathogenic processes: sebum production, *Propionibacterium acnes* colonization, altered keratinization, and release of inflammatory mediators into the skin.[1] These

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processes interact in a complex manner to produce acne lesions,[1] so treatment targeting multiple pathogenic processes is recommended as first-line therapy for most patients with acne.[1]

Topical combination therapy, comprising a retinoid and antimicrobial agent, is the current standard of care in patients with mild-to-moderate acne.[1] The Global Alliance to Improve Outcomes in Acne recommends the combination of a topical retinoid with an antimicrobial, preferably benzoyl peroxide (BPO), as a first-line approach for almost all patients with acne.[1] Global Alliance members also acknowledge that topical antibiotics have an important role in acne management, particularly in patients with an inflammatory component, but recommend that they are used in combination with BPO to minimize the development of *P. acnes* resistance and that, when possible, duration of use should be limited to approximately 3–4 months.[1]

A number of fixed-dose combination topical products are available for the treatment of acne, including clindamycin-BPO (C/BPO) combinations and adapalene-BPO (A/BPO) combinations.[1,2] Both C/BPO and A/BPO are once-daily formulations, making them convenient for patients to use. Patients often do not use multiple medications as prescribed,[2] and it is thought that poor adherence to medication may be a major contributor to treatment failure in patients with acne.[1] As well as being effective and well-tolerated, fixed-dose combination products are more convenient for patients than multiple individual agents,[2] and, by simplifying treatment regimens, fixed-dose combination products may improve patient adherence[2] and thereby have a positive influence on treatment outcomes.[1,3]

Adapalene is the only topical retinoid to be formulated with BPO,[1] and the fixed combination has proven to be faster acting and more effective than either agent alone.[3] Local irritation, including erythema, peeling, dryness, burning and itching, is a common adverse effect of topical retinoids,[4] although the potential for irritation appears to be lower with adapalene than with other retinoids such as tretinoin.[5,6] BPO can also cause cutaneous irritation,[7] but it appears that potential for local irritation with combination A/BPO is comparable to that with adapalene alone.[3,7]

C/BPO has been shown to have a more rapid anti-acne effect than adapalene monotherapy,[8] to be at least as effective as A/BPO[9] and to be better tolerated than adapalene, both as monotherapy and in combination with BPO.[8,9] Treatment advantages have also been observed with C/BPO relative to combination clindamycin/tretinoin.[10] There is potential for minor local irritation with clindamycin,[11] but C/BPO has been formulated with increased levels of hydrating excipients to improve tolerability and patient acceptance of therapy.[12] It has also been suggested that the direct anti-inflammatory action of clindamycin could alleviate irritation associated with BPO.[8]

The primary objective of the current study was to compare the tolerability of C/BPO and A/BPO during the first 2 weeks of treatment in patients with facial acne. A randomized, investigator-blind, split-face design was used to compare the agents during the first 2 weeks of treatment, thereby minimizing potential for variation by having patients act as their own control. This was followed by 6 weeks of open-label treatment with C/BPO over the entire face. Treatment efficacy, quality of life, and patient satisfaction with treatment were also investigated.

## Materials and methods

### Study design

A multicenter (3), 8-week study was conducted in Argentina. For the first 2 weeks of the study, a randomized, investigator-blinded, split-face study design was employed, whereby patients applied C/BPO gel containing 1% clindamycin (as 1.2% clindamycin phosphate) and 5% BPO (Clindoxyl®) and A/BPO gel containing 0.1% adapalene and 2.5% BPO (Epiduo®) in a bilateral split-face fashion, with randomized allocation of C/BPO and A/BPO to the left or right side. For the remaining 6 weeks, patients applied open-label C/BPO to the entire face.

The study was approved by local Institutional Review Boards and Ethics Committees and was conducted in accordance with the guidelines of the International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the ethical principles of the Declaration of Helsinki.

### Patients

Male and female patients, $\geq 21$ years of age, who were in good general health with a documented diagnosis of acne vulgaris (15–60 inflammatory and noninflammatory facial lesions, excluding the nose, nasogenian, and upper and lower eyelids), and who were willing to avoid all other topical or systemic acne therapies for the duration of the study were eligible for inclusion.

Female patients who were pregnant, planning to become pregnant or breastfeeding were excluded from the study, and sexually active female subjects had to be using a medically acceptable form of contraception

(oral contraception, injectable or implantable methods or intrauterine devices). Patients receiving estrogens, androgens or anti-androgens for >12 weeks before the study were allowed to enter the study as long as they did not expect to alter hormonal treatment during the study.

Other exclusion criteria included severe systemic diseases or diseases of the facial skin other than acne; presence of facial hair that could obscure accurate assessment of acne severity; history or presence of regional enteritis or inflammatory bowel disease; use of topical antibiotics on the face (in the preceding 2 weeks) or systemic antibiotics (in the preceding 4 weeks), topical corticosteroids on the face or systemic corticosteroids (in the preceding 4 weeks), systemic retinoids (preceding 6 months) or other topical anti-acne medications (preceding 2 weeks); concomitant use of photosensitizing or neuromuscular blocking agents, or medications known to exacerbate acne, including vitamins; concomitant use of the following types of facial products: astringents, toners, abradents, hair removal wax, facials, acid-containing peels, masks, nonmild cleansers, washes or soaps (containing BPO, sulfacetamide sodium or salicylic acid), moisturizers (containing retinol, salicylic or $\alpha$- or $\beta$-hydroxy acids); facial procedures (chemical peel, laser therapy, photodynamic therapy, microdermabrasion, or UV light therapy) within the past 4 weeks; use of an investigational drug or treatment within 4 weeks of study entry.

Use of a facial emollient was not permitted during the first 2 weeks of the study and only if absolutely necessary thereafter. Oil-free make-up was permitted but had to be removed $\geq 1$ h before a study visit, and changes in make-up were not permitted during the study.

All patients provided written informed consent before entering the study.

### Procedures and study endpoints

At baseline, data were collected regarding demographics and medical/medication histories, and lesion counts and facial photography were performed. Investigator Static Global Assessment (ISGA) and SKINDEX-29 quality-of-life (QOL) assessments were also conducted. Each patient received one tube of C/BPO, one tube of A/BPO, two units of soap-free facial cleanser (Physiogel®) and two units of a noncomedogenic sunscreen (Spectraban® SPF 20). After patients gave informed consent and met inclusion criteria, treatment was randomly allocated to either side of the face by a computer-generated randomization schedule. Patients and study-center staff were instructed not to reveal the treatment allocation to the investigator, and patients were instructed not to apply the product in their presence.

For the first 2 weeks of the study, patients were instructed to wash their face in the evening with Physiogel® cleanser, rinse thoroughly with warm water and pat dry with a soft towel before applying a thin film of C/BPO and A/BPO to either side of the face, as per the randomization schedule, thoroughly washing and drying their hands between application of the two products. The study product was to be left on for $\geq 4$ h, preferably 8 h. In the morning, subjects were instructed to wash their face with Physiogel® and apply Spectraban® SPF 20. Starting at week 2, patients were instructed to apply C/BPO gel to the entire face each evening for the next 6 weeks and to follow the same procedures for cleansing and sunscreen application as used during the 2-week split-face phase of the study.

After the baseline visit, subsequent study visits were at weeks 1, 2, 5, and 8. At these visits, patients returned used product tubes and provided updated information about concomitant medication. In addition, compliance was queried, and study medication was dispensed (one tube of C/BPO and one tube of A/BPO at week 1, and two tubes of C/BPO at weeks 2 and 5) during these visits. At each visit, investigators assessed tolerability, conducted facial photography, and performed lesion counts and ISGA assessments of acne severity. Patients completed the Global Change Assessment (GCA), the Product Acceptability and Preference questionnaire (weeks 1, 2, and 8), and the SKINDEX-29 QOL assessment (weeks 2 and 8). Adverse events (AEs) were monitored at each visit. Patient diary cards were dispensed at baseline and week 1 and collected at weeks 1 and 2.

The primary endpoint was the investigator assessment of the signs and symptoms of local tolerability (erythema, peeling, dryness, and irritant/allergic contact dermatitis) during the first 2 weeks of treatment, measured using a 4-point scale ranging from 0 = no signs/symptoms to 3 = intense signs/symptoms. Secondary endpoints were the investigator assessment of the signs and symptoms of local tolerability at weeks 5 and 8; lesion counts; ISGA assessments of acne severity using a 6-point scale ranging from 0 (clear) to 5 (very severe); patient's GCA using a 7-point scale ranging from $-3$ (very much worse) to $+3$ (very much improved); SKINDEX-29 QOL assessments using standard SKINDEX-29 scoring; Product Acceptability and

Preference. As part of the Product Acceptability and Preference Questionnaire, patients assessed local tolerability (redness, dryness, burning, itching, and scaling). Each side of the face was assessed separately at weeks 1 and 2, and the whole face was assessed at week 8 using a 6-point scale ranging from 0 = none to 5 = very severe. The Product Acceptability and Preference Questionnaire also asked patients to rate decrease in acne breakouts (1 = highly favorable to 5 = highly unfavorable), general comfort of the skin (1 = very comfortable to 6 = very uncomfortable), ease of application (1 = very easy to 5 = very difficult), compliance (0 = not compliant to 2 = very compliant), and satisfaction with treatment (1 = very satisfied to 5 = very unsatisfied).

Safety was assessed by recording all AEs that were observed or spontaneously reported during the study by patients, investigators, or designees. AE reports were reviewed by the investigator to determine causality.

### Data analysis and statistical methods

Assuming a standard deviation (SD) of two in tolerability scores, it was estimated that 45 patients per treatment arm would detect a 1.2 difference with 80% power using a two-sided type I error rate of 0.05.

Data analysis was undertaken on the intent-to-treat population (all patients who received $\geq 1$ application of study medication). At weeks 1 and 2 (split-face), the individual differences between both sides of the face in terms of tolerability scores, ISGA, CGA, and each question of the Product Acceptability and Preference Questionnaire were analyzed using the Wilcoxon signed-rank test at an alpha level of 0.05. No adjustments were made for multiplicity. Differences between the two sides of the face regarding lesion counts at weeks 1 and 2 were analyzed using paired *t*-tests at an alpha level of 0.05. The assumption of normality was tested using a Shapiro–Wilk test at an alpha level of 0.01, and if not verified, a nonparametric method (Wilcoxon signed-rank test) was used. All endpoint data at weeks 5 and 8 were presented in a descriptive fashion. AE data were analyzed in terms of frequencies and percentages.

## Results

### Patients

Forty-eight patients were enrolled in the study, with 45 patients completing the study (Fig. 1). The first patient was enrolled in February 2009, and the last patient completed the study in April 2009. Demographic and disease characteristics are listed in Table 1. Most patients were women (79%), all were White, 69% were of Hispanic or Latino ethnicity, and the median age was 26 years. The majority of patients (>90%) had mild-to-moderate scores on ISGA; mean

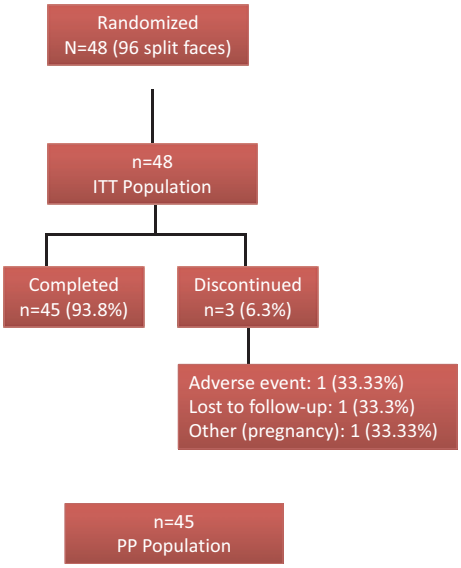


**Figure 1** Patient flow through the study.

**Table 1** Baseline demographics and disease characteristics

| Characteristic | Patient cohort (*n* = 48) |
|---|---|
| Age, years | |
| Mean (SD) | 27.6 (5.5) |
| Median | 26 |
| Range | 21.6–45.6 |
| Sex, *n* (%) | |
| Male | 10 (20.8) |
| Female | 38 (79.2) |
| Race, *n* (%) | |
| White | 48 (100) |
| Black | 0 |
| Asian | 0 |
| Ethnicity, *n* (%) | |
| Hispanic or Latino | 33 (68.8) |
| No Hispanic or Latino | 15 (31.3) |
| ISGA score, *n* (%) | |
| 2 – Mild | 14 (29.2) |
| 3 – Moderate | 31 (64.6) |
| 4 – Severe | 3 (6.3) |
| Lesion count, mean (SD) | |
| Inflammatory | 14.2 (9.1) |
| Noninflammatory | 24.8 (12.8) |
| Total | 39.1 (13.0) |

ISGA, Investigator Static Global Assessment.

total lesion count was 39.1 at baseline, with a mean inflammatory lesion count of 14.2. The mean (SD) number of days patients were exposed to study products was 52.3 (9.3).

### Local tolerability

With the exception of peeling at week 2, mean investigator-rated scores for erythema, dryness and peeling were significantly higher on the side of the face treated with A/BPO relative to the side treated with C/BPO during the 2-week split-face phase of the study (Fig. 2). Mean scores for irritant/allergic dermatitis were 0.04 for both sides of the face at weeks 1 and 2, and the problem was not reported thereafter. At week 8, after 6 additional weeks' full-face treatment with C/BPO, mean scores for erythema, dryness, and peeling were also negligible (Fig. 2), with 85–98% of patients assessed as not having any of these local symptoms.

Mean patient ratings for redness, dryness, burning, and scaling were also significantly lower with C/BPO than with A/BPO at weeks 1 and 2, as was itching at week 1 (Fig. 3). Patient ratings continued to decrease during full-face treatment with C/BPO, such that at week 8, the mean score for each parameter was <1 (very minimal) (Fig. 3).

### Acne severity

Compared with baseline, mean ISGA scores improved for both sides of the face, and there was no significant difference between the two treatments during the split-face portion of the study (Table 2). Over the course of the study, there was an improvement in full-face ISGA ratings from a mean of 2.8 at baseline to 1.6 at week 8.

Similarly, total lesion count decreased during the first 2 weeks of therapy with C/BPO and A/BPO, with no significant difference between the two treatments (Table 2). At week 8, mean total lesion count was 13.8, compared with 39.1 at baseline. Both treatments effectively reduced inflammatory and noninflammatory lesion counts, with a particularly pronounced effect on inflammatory lesions. Baseline total inflammatory lesion count was 14.2, compared with 4.3 at week 8, and noninflammatory lesion counts were reduced from 24.8 at baseline to 9.5 at week 8.

At week 1, patient's GCA showed a statistically significant difference in favor of C/BPO *vs.* A/BPO, which was no longer evident at week 2 (Table 2). At week 8, mean GCA score was 2.3, with 87% of patients considering themselves "much" (32%) or "very much" (55%) improved.

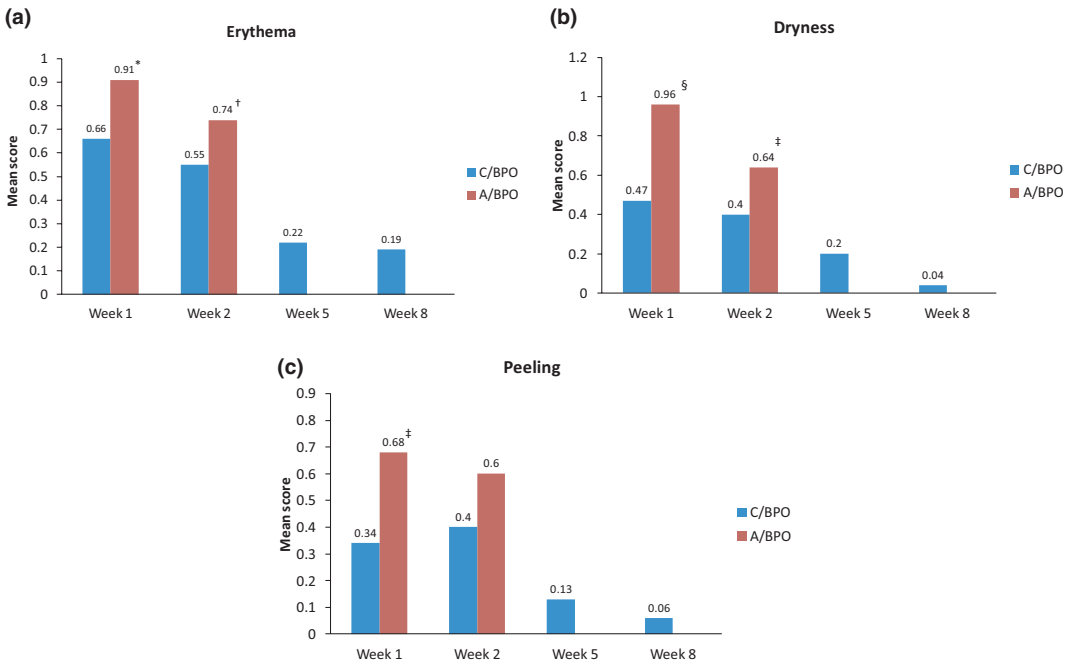


**Figure 2** Mean scores for (a) erythema, (b) dryness, and (c) peeling as rated by investigators using a 4-point scale (0 = no signs/symptoms to 3 = intense signs/symptoms) at weeks 1 and 2 (split-face application of C/BPO and A/BPO) and weeks 5 and 8 (whole-face application of C/BPO). *$P = 0.01$ *vs.* C/BPO, †$P < 0.05$ *vs.* C/BPO; ‡$P < 0.005$ *vs.* C/BPO, §$P < 0.0001$ *vs.* C/BPO. BPO, benzoyl peroxide.

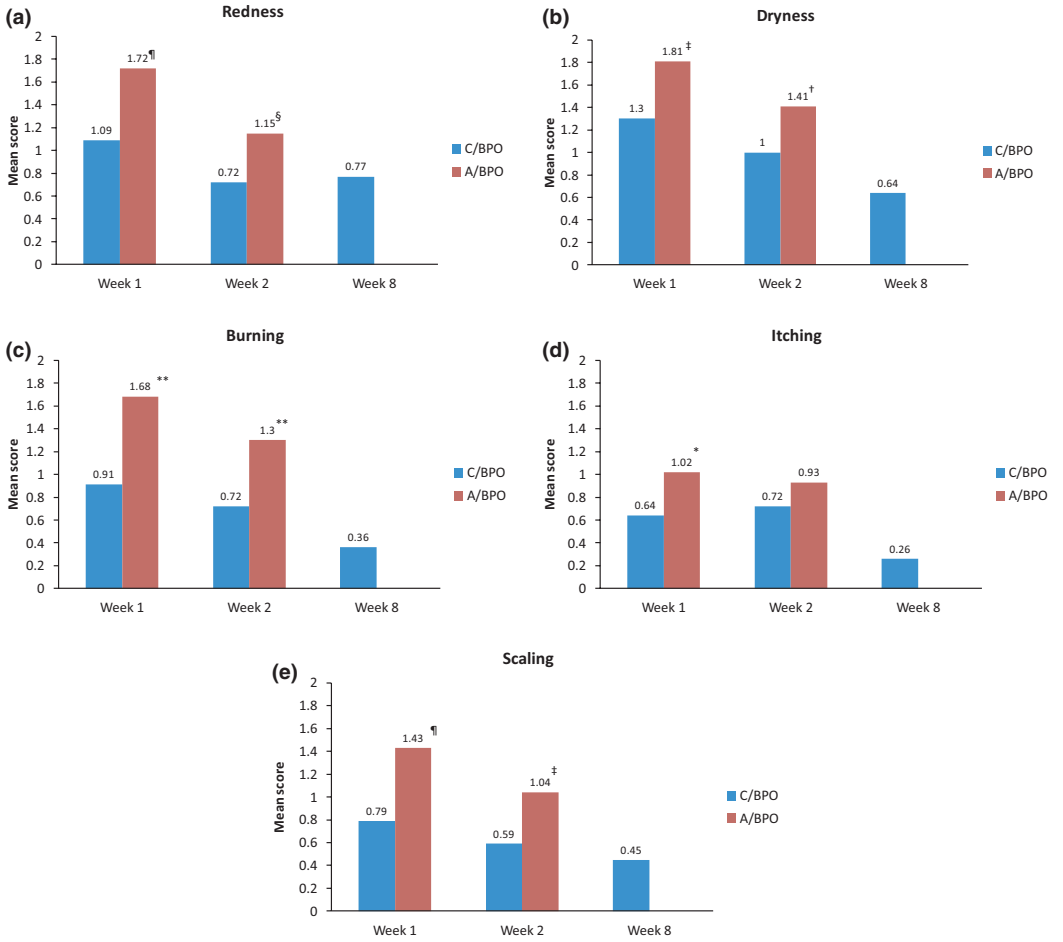


**Figure 3** Mean scores for (a) redness, (b) dryness, (c) burning, (d) itching, and (e) scaling as rated by patients using a 6-point scale (0 = none to 5 = very severe) at weeks 1 and 2 (split-face application of C/BPO and A/BPO) and 8 (whole-face application of C/BPO). *$P < 0.05$ *vs.* C/BPO, †$P < 0.01$ *vs.* C/BPO; ‡$P < 0.005$ *vs.* C/BPO, §$P \leq 0.001$ *vs.* C/BPO; ¶$P \leq 0.0005$ *vs.* C/BPO; **$P < 0.0001$ *vs.* C/BPO. BPO, benzoyl peroxide.

**Table 2** Investigator Static Global Assessment (ISGA), lesion counts and patient's Global Change Assessment (GCA) over the course of the study

| | ISGA† | | Total lesion count | | Patient's GCA‡ | |
|---|---|---|---|---|---|---|
| Mean (SD) | C/BPO | A/BPO | C/BPO | A/BPO | C/BPO | A/BPO |
| Baseline§ | 2.8 (0.6) | | 39.1 (13) | | – | |
| Week 1¶ | 2.2 (0.7) | 2.4 (0.7) | 14.6 (7.5) | 14.5 (7.4) | 1.8 (0.8) | 1.5 (1.0)* |
| Week 2¶ | 1.9 (0.8) | 1.9 (0.8) | 9.9 (5.9) | 10.7 (7.0) | 1.9 (1.0) | 1.9 (1.1) |
| Week 5†† | 1.9 (0.8) | – | 16.0 (10.4) | – | 2.0 (1.2) | – |
| Week 8†† | 1.6 (0.9) | – | 13.8 (11.5) | – | 2.3 (1.0) | – |

BPO, benzoyl peroxide.
*$P < 0.05$ *vs.* C/BPO.
†ISGA = a 6-point scale ranging from 0 (clear) to 5 (very severe).
‡GCA = a 7-point scale ranging from −3 (very much worse) to +3 (very much improved).
§Full-face analysis.
¶Split-face treatment.
††Full-face C/BPO treatment.

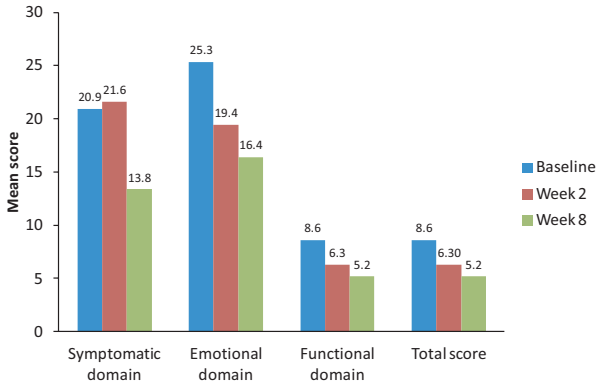


**Figure 4** Skindex-29 quality of life questionnaire scores at baseline and weeks 2 and 8. A reduction in score reflects improvement in quality of life.

### Patient preference and quality of life

Compared with baseline, patient quality of life improved over the course of the study, as indicated by reductions in SKINDEX-29 domain and total scores (Fig. 4). Reductions in scores for the Emotional and Functional domains, as well as the total score, occurred at weeks 2 and 8. A mean reduction in the Symptomatic domain was only noted at week 8.

Patients rated the two treatments to be equally effective at reducing acne breakouts, with >80% of patients in both groups rating product efficacy as favorable or highly favorable at week 2. Mean patient ratings for comfort of skin were, however, significantly better with C/BPO than A/BPO at week 1 (2.8 *vs.* 3.2; $P < 0.05$) and week 2 (2.4 *vs.* 2.7; $P < 0.005$). Overall skin comfort continued to improve over the next 6 weeks, with 83% of patients rating their skin as comfortable or very comfortable at week 8 (mean score 1.8). Fewer than 40% of patients in each group reported a sense of skin hydration at week 1 or 2 with either product (30–34% with C/BPO and 24–26% with A/BPO), but at week 8, 61% of patients felt that their skin was hydrated and moisturized.

During the split-face phase of the study, almost all patients (96–98%) rated C/BPO and A/BPO as "easy" or "very easy" to use, even with make-up, with no significant between-group differences. Patients reported high compliance with both products: during the first week of the study, 92% of patients reported that they were "very compliant" with treatment, dropping to 87% of patients at week 2, and at week 8, 94% of patients reported using C/BPO every day.

Overall treatment satisfaction was high, with 72% of patients rating themselves as "satisfied" or "very satisfied" with C/BPO and 68% with A/BPO at week 1, and corresponding rates at week 2 were 89% with C/BPO and 83% with A/BPO. At week 8, after an additional 6 weeks of full-face C/BPO treatment, 85% of patients rated themselves as "satisfied" or "very satisfied" with treatment. When asked which product they preferred at weeks 1 and 2, 63–64% of patients chose C/BPO, 32–35% chose A/BPO, and 2–4% had no preference. At the end of weeks 1 and 2 of treatment, more patients said they would use C/BPO again if given the choice to continue acne treatment (94% *vs.* 55% of patients who said they would use A/BPO again after 1 week of therapy, and 85% *vs.* 70% of patients, respectively, after 2 weeks of therapy). At week 8, after an additional 6 weeks of full-face treatment with C/BPO, 89% of patients said that they would use the product in the future.

### Safety

Treatment-related AEs occurred in 41/48 (85.4%) patients. All treatment-related AEs were application site reactions, most commonly irritation. The majority of AEs were of mild-to-moderate severity. Almost all treatment-related AEs occurred during the split-face phase of the study, with only 11 patients (22.9%) having a treatment-related AE during full-face treatment with C/BPO. Three patients developed severe cutaneous AEs during the split-face phase of the study, all of which subsided during continued treatment, treatment interruption or dose reduction. One patient discontinued treatment due to moderate application site irritation. There were no serious AEs. A *post hoc* analysis, which was conducted to determine on which side of the face AEs occurred, indicated that treatment-related AEs, including irritation, dryness and erythema, were significantly less common with C/BPO than A/BPO ($P \leq 0.01$) (Table 3).

**Table 3** Treatment-related adverse events (AEs) occurring during the course of the split-face phase (weeks 1 and 2) of the study

| | Patients with AEs, *n* (%) | | |
|---|---|---|---|
| | C/BPO ($n = 48$) | A/BPO ($n = 48$) | *P*-value |
| Any AE | 31 (64.6) | 40 (83.3) | 0.0067 |
| Application site conditions | | | |
| Irritation | 23 (47.9) | 33 (68.8) | 0.0124 |
| Erythema | 13 (27.1) | 19 (39.6) | 0.0143 |
| Dryness | 10 (20.8) | 18 (37.5) | 0.0114 |
| Exfoliation | 8 (16.7) | 10 (20.8) | 0.1573 |
| Pruritus | 8 (16.7) | 10 (20.8) | 0.3173 |
| Dermatitis | 2 (4.2) | 1 (2.1) | 0.3173 |

BPO, benzoyl peroxide.

## Discussion

This study has demonstrated that topical C/BPO is better tolerated than A/BPO during the initial 2 weeks of treatment for facial acne, with significantly lower overall scores for investigator- and patient-rated tolerability parameters. Although C/BPO was better tolerated than A/BPO, both C/BPO and A/BPO were well tolerated during the 2-week split-face phase of our study, with low investigator-rated scores for erythema, dryness and peeling, which continued to decline during full-face treatment with C/BPO from week 2 to 8. This was also the case for patient-rated redness, dryness, burning, itching, and scaling.

The gel formulation of C/BPO used in our study contains the hydrating excipients dimethicone and glycerin, and the A/BPO gel formulation includes glycerin in the vehicle base. It has been suggested that inclusion of hydrating excipients in the gel may contribute to the relatively good tolerability of C/BPO.[8] In a study comparing C/BPO gel containing hydrating excipients with a C/BPO gel without excipients, scaling, erythema, dryness and pruritus occurred less frequently in patients with facial acne using the C/BPO gel containing the hydrating excipients.[12] Patients were most satisfied with the excipient-containing formulation, which also provided a more consistent reduction in total inflammatory lesions than C/BPO gel without excipients.[12]

During the initial 2-week split-face phase of our study, neither C/BPO nor A/BPO rated very well in terms of leaving the skin feeling hydrated and moisturized, but C/BPO performed slightly better than A/BPO (30–34% of patients reporting a sense of hydration with C/BPO *vs.* 24–26% with A/BPO). After an additional 6 weeks of full-face C/BPO treatment, the proportion of patients who felt that their skin was hydrated and moisturized had doubled. The inclusion of hydrating excipients in the C/BPO gel may have contributed to this result.

Our results are consistent with those of a previous 12-week randomized, investigator-blind, parallel-group study by Zouboulis *et al.*[9] comparing the same two fixed-combination C/BPO and A/BPO gel products. These researchers reported that C/BPO was significantly better tolerated than A/BPO from weeks 1 through 12 with respect to investigator-rated (erythema, dryness, peeling) and patient-rated (pruritus, burning/stinging) tolerability outcomes.[9]

Also in line with our observations, Zouboulis *et al.*[9] found that C/BPO had a more favorable safety profile than A/BPO, with a reduced incidence of application site AEs. Albeit in a *post hoc* analysis, we also observed a significantly higher rate of application site AEs with A/BPO than with C/BPO. The *post hoc* analysis was undertaken because, unlike patients in the study by Zouboulis *et al.*, who received 12 weeks' treatment with either C/BPO or A/BPO, our split-face study protocol did not ask investigators to ascribe AEs to one agent or another. However, because all AEs were local, it was possible to use the case report forms to identify which side of the face the reaction occurred on and therefore which product was the likely causative agent. Although *post hoc* analyses can be subject to selection bias, we believe this did not occur in our AE analysis because the data were taken from the case report forms, and investigators were blinded to treatment allocation during the split-face treatment phase of the study.

Also consistent with the previous comparative data by Zouboulis *et al.*[9] is the finding that C/BPO and A/BPO were rapidly and similarly effective in reducing acne lesions, particularly inflammatory lesions. However, Zouboulis *et al.*[9] did report a significantly higher treatment success rate ($\geq$ 2-grade improvement in ISGA) and significantly quicker time to treatment success with C/BPO. It was suggested that this difference may have reflected a physician perception of improved appearance, resulting from less erythema and peeling associated with C/BPO compared with A/BPO.[9]

The Global Alliance to Improve Outcomes in Acne notes that the impact of acne on quality of life of adult patients is related to the patient's self assessment of disease severity rather than the physician's clinical assessment.[1] Although, in our study, both C/BPO and A/BPO achieved similar improvements in ISGA and reductions in investigator-assessed lesion counts, patients' GCA showed a statistically significant, although clinically nonsignificant, difference in favor of C/BPO *vs.* A/BPO at week 1, and by week 8, the vast majority of patients considered themselves "much" or "very much" improved. Improvements in QOL also occurred during the course of our study, with patients reporting improvements on the Emotional, Functional and Symptomatic SKINDEX-29 QOL domains.

Overall, patient satisfaction with treatment was high in our study, but patients reported being more satisfied with C/BPO at a ratio of approximately 2–1. At the end of week 1, almost all patients said they would use C/BPO again if given the choice to continue acne treatment, whereas just over half of the patient population said they would continue with A/BPO. Patient satisfaction with treatment and QOL are both associated with improved adherence to treatment, and the presence of side effects is associated with poor adherence,[1] so it seems reasonable to assume that better

patient-rated tolerability of C/BPO *vs.* A/BPO contributed to improved satisfaction with treatment and greater willingness to continue treatment with C/BPO, particularly during its initial stages.

In the previous comparison of C/BPO and A/BPO by Zouboulis *et al.*,[9] the number of missed applications during the first 4 weeks of treatment was almost 3-fold higher with A/BPO than C/BPO, with one-third of A/BPO recipients missing an application because of tolerability issues or an AE. The study authors noted that although physicians may think that local AEs such as erythema, dryness, and peeling are an acceptable compromise for an effective acne medication, these local AEs may detract from the patient's perception of efficacy, leading to reduced adherence and a disappointing overall response to treatment.[9]

In general, physicians need to counsel patients to have realistic expectations of treatment, including time to lesion clearance and potential for irritation, and educate them regarding how to apply treatments effectively.[1,13] Patients who are not taught to apply topical therapy to the entire face typically spot treat, and application site reactions can also result in products being used less than optimally.[1,13]

Regimen simplicity is another determinant of patient adherence to therapy,[1] but in our study, almost all patients (>95%) rated C/BPO and A/BPO as "easy" or "very easy" to use, with no differences between the treatment groups. Both C/BPO and A/BPO are gel-fixed combinations that can be stored at room temperature and are applied once daily, all of which are patient-preferred treatment characteristics.[1]

Reducing the BPO dosage to 2.5% is an option for patients who cannot tolerate combination C/BPO containing 5% BPO, as used in the current study and the study by Zouboulis *et al.* Indeed, a meta-analysis of randomized controlled trials that treated patients with combination C/BPO products containing 2.5% or 5% BPO has shown that C/BPO 2.5% has similar efficacy to C/BPO 5%.[14] The 2.5% BPO product appeared to have an advantage over the 5% BPO product with regard to noninflammatory lesions, and it was suggested that better adherence because of decreased irritation may have contributed to this observation.[14]

Our study is not without limitations. It was a single-blind analysis, and the fact that patients were not blinded to treatment allocation may have introduced some bias with regard to patient-rated outcomes, especially if they had perceptions as to which combination may be better tolerated. However, the primary endpoint was the investigator rating of local tolerability, and investigators were blinded to treatment allocation, thereby minimizing the impact of any bias on the primary results. Similarly, investigator blinding limited any bias introduced by the *post hoc* analysis of AEs. Finally, our study was of relatively short duration, and no conclusions can be drawn about the comparative efficacy of the two products during longer-term treatment. However, the focus of the study was on acute tolerability, and as potential for irritation is highest during the first 2 weeks of treatment, we believe the study duration was appropriate.

## Conclusions

In conclusion, although C/BPO gel and A/BPO gel were both generally well tolerated and safe, C/BPO demonstrated a better tolerability profile than A/BPO during 2 weeks of split-face treatment. Continued use of C/BPO for the entire face was associated with amelioration of local irritation. Both agents effectively reduced overall acne severity and achieved high levels of patient satisfaction, but satisfaction was highest with C/BPO, and patients were more inclined to continue treatment with this product. Ultimately, as a result of improved tolerability, and better patient satisfaction and willingness to adhere to therapy, C/BPO gel may be a more appropriate option than A/BPO gel for the treatment of facial acne.

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