# Study of the Efficacy, Tolerability, and Safety of 2 Fixed-Dose Combination Gels in the Management of Acne Vulgaris

Christos C. Zouboulis, MD, PhD; Tanja C. Fischer, MD; Johannes Wohlrab, MD, PhD; Jo Barnard, PhD; Alessandra B. Alió, MD

*This study investigated the efficacy, tolerability, and safety of 2 fixed-dose combination gels for the treatment of facial acne: clindamycin 1%–benzoyl peroxide 5% gel with hydrating excipients (C/BPO HE) and adapalene 0.1%–benzoyl peroxide 2.5% gel (A/BPO). After 12 weeks of once daily treatment, the mean reduction in inflammatory lesion count was 76.8% and 72.2% in the C/BPO HE group and A/BPO group, respectively (*P=.076*). Significantly more participants achieved treatment success, which was defined as an improvement of 2 grades or more from baseline to week 12 on the investigator's static global assessment (ISGA) scale, with C/BPO HE (30.5% [58/190]) compared with A/BPO (21.8% [42/192])(*P=.046*), and treatment success was achieved more quickly with C/BPO HE (*P=.035*). Both products also reduced noninflammatory (62.2% C/BPO HE vs 61.5% A/BPO) and total lesion counts (69.1% C/BPO HE vs 67.1% A/BPO). Despite the overall similar efficacy profile, C/BPO HE was better tolerated and safer than A/BPO. In the tolerability assessments, erythema, dryness, peeling, pruritus, and burning/stinging were more frequent in the A/BPO group at all time points from week 1 onward (*P<.05*). Treatment-related adverse events (AEs) occurred in 48.4% (92/190) of participants in the C/BPO HE group compared with 78.6% (151/192) of the A/BPO group. We conclude that C/BPO HE and A/BPO have similar efficacy in treating inflammatory and noninflammatory acne lesions, but C/BPO HE achieves better overall treatment success in less time coupled with a significantly better tolerability profile and notably better safety profile.*

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Dr. Zouboulis is from the Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Germany. Dr. Fischer is from the Skin and Laser Center Potsdam, Germany. Dr. Wohlrab is from the University Clinic, Department of Dermatology and Venereology, Martin Luther University Halle-Wittenberg, Halle, Germany. Dr. Barnard is from Stiefel, a GSK company, Maidenhead, United Kingdom. Dr. Alió is from Stiefel, a GSK company, Research Triangle Park, North Carolina.
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Dr. Zouboulis is a consultant and investigator for Galderma Laboratories, LP, and Stiefel, a GSK company, and also is a speaker for Stiefel. Drs. Fischer and Wohlrab report no conflict of interest. Drs. Barnard and Alió are employees of Stiefel, a GSK company.
Correspondence: Christos C. Zouboulis, MD, PhD, Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Auenweg 38, 06847 Dessau, Germany (christos.zouboulis@klinikum-dessau.de).

Topical therapies are the mainstay of treatment of mild to moderate acne. Most topical combination therapies include benzoyl peroxide (BPO) with a retinoid or antibiotic.[1] Benzoyl peroxide has potent antimicrobial effects, does not induce *Propionibacterium acnes* resistance,[1] and has keratolytic and anti-inflammatory properties.[2] The topical combination of BPO with an antibiotic is more effective than monotherapy with either component alone and reduces the risk for *P acnes* developing antibiotic resistance.[1,2]

Currently a number of fixed-dose topical antibiotic-BPO combinations are available. The combination of clindamycin 1% and BPO 5% has been extensively studied.[3-5] Three fixed-dose clindamycin-BPO formulations are available: 2 with

clindamycin 1%–BPO 5% (1 with hydrating excipients [tube gel; C/BPO HE] and 1 without hydrating excipients [jar gel]) and 1 with clindamycin phosphate 1.2%–BPO 2.5%. The vehicle differs in the clindamycin-BPO formulations; C/BPO HE contains the hydrating excipients dimethicone and glycerin while the other formulations do not. The inclusion of dimethicone and glycerin results in less dryness, burning, and peeling.[6-8] Benzoyl peroxide also is available in a fixed-dose combination with the retinoid adapalene (adapalene 0.1%–BPO 2.5% gel [A/BPO]), which is more effective than either agent used alone.[9] It also includes glycerin in the vehicle base.

The current study examined the efficacy, tolerability, and safety of 2 fixed-dose combination gels for the treatment of facial acne: C/BPO HE and A/BPO.

## METHODS

This prospective, randomized, investigator-blind, parallel-group trial was performed in 17 centers in Germany. Participants were randomized in a 1:1 ratio to receive either C/BPO HE or A/BPO for 12 weeks. Because of packaging differences between the 2 formulations, participants were not blinded to their treatment allocation. Treatment was applied once daily in the evening to a clean face (washed with a gentle facial cleanser), and participants were instructed not to wash their face for 4 hours following application. An oil-free moisturizer could be used, provided the participant documented its use. Compliance was assessed using a participant diary, questioning during study visits, and inventory of the amount of medication dispensed and returned. Participants were evaluated at baseline and weeks 1, 2, 4, 8, and 12.

The study was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

### Participants

Male and female participants with facial acne (25–80 inflammatory lesions [including the nose]; 12–100 noninflammatory lesions [excluding the nose]; no facial nodular cystic lesions) who were aged 12 to 45 years, provided signed informed consent, and were willing to avoid the use of any other topical or systemic acne therapies were enrolled in the study. Washout periods were required for other topical or systemic acne medications. Female participants were excluded if they were pregnant, lactating, or not using a medically acceptable form of birth control. Additional exclusion criteria included use of medications that were known to exacerbate acne or might interfere with treatment efficacy.

### End Points

*Efficacy*—The primary end point was the percentage change in inflammatory lesion count (papules and pustules, including nasal lesions) from baseline to week 12. Key secondary end points included the following: the proportion of participants achieving treatment success, which was defined as an improvement of 2 grades or more from baseline to week 12 on the investigator's static global assessment (ISGA) scale (a 6-point scale [0=clear skin with no inflammatory or noninflammatory lesions; 5=severe acne with many inflammatory and noninflammatory lesions and more than a few nodular lesions]); time to treatment success from baseline; and percentage change in total lesion count from baseline to week 12. Other secondary end points included the percentage change in noninflammatory lesion count; absolute change in total, inflammatory, and noninflammatory lesion counts; and time to 50% reduction in total, inflammatory, and noninflammatory lesion counts from baseline.

*Tolerability*—Local tolerability was assessed using a 5-point scale (0=none; 4=strong or severe). Erythema, drying, and peeling were assessed by an investigator, and pruritus and burning/stinging were assessed by the participant.

*Safety*—Safety was determined by monitoring adverse events (AEs) and withdrawals, which were classified using MedDRA (Medical Dictionary for Regulatory Activities) terminology.

### Statistical Analysis

Based on an assumption of a standard deviation of 32% for percentage change in inflammatory lesion count and a 10% dropout rate, it was estimated that 200 participants per treatment arm would have more than 80% power to detect the clinically important difference of 10% at $\alpha=.05$ (2-tailed type I error).

All analyses were based on the intention-to-treat population of all randomized participants who applied a study drug. All statistical analyses were performed using SAS Version 9, and, with a few exceptions, all tests were 2-tailed and interpreted at the .05 level of significance. Time-to-event data were summarized using Kaplan-Meier survival estimates or life table methods, with log-rank statistics. Appropriate inferential and summary statistics were used as necessary. The last observation carried forward method was used to account for missing continuous data. For binary response data, missing values were considered failures. The primary end point was analyzed at $\alpha=.05$ using analysis of covariance, with treatment, center, treatment by center, and baseline lesion count in the model. Cochran-Mantel-Haenszel methodology was used to

analyze the proportion of ISGA success, with center as the stratification variable.

## RESULTS

### Baseline Demographics

Three hundred eighty-two participants entered the study—190 in the C/BPO HE group and 192 in the A/BPO group—and 337 participants completed the study. Eighteen participants in the C/BPO HE group and 27 in the A/BPO group discontinued due to withdrawal of consent (8 and 6 participants, respectively), lost to follow-up (5 and 10 participants, respectively), AEs (3 and 9 participants, respectively), or other reasons (2 participants in each group). Baseline demographic characteristics were similar between the groups (Table).

**Baseline Demographic Characteristics**

| | C/BPO HE | A/BPO | Total | *P* Value |
|---|---|---|---|---|
| ITT population, n (%) | 190 (50) | 192 (50) | 382 (100) | |
| Male, n (%) | 95 (50) | 97 (51) | 192 (50) | .947 |
| Female, n (%) | 95 (50) | 95 (49) | 190 (50) | |
| Age, y | | | | |
| Mean (SD) | 20.8 (7.3) | 20.9 (6.8) | 20.9 (7.0) | .797 |
| 12–17, n (%) | 79 (42) | 73 (38) | 152 (40) | .437 |
| 18–45, n (%) | 111 (58) | 119 (62) | 230 (60) | |
| Race, n (%) | | | | |
| White | 183 (96) | 186 (97) | 369 (97) | .635 |
| Asian | 4 (2) | 2 (1) | 6 (2) | |
| Multiracial | 3 (2) | 3 (2) | 6 (2) | |
| Native Hawaiian or other Pacific Islander | 0 (0) | 1 (<1) | 1 (<1) | |
| Ethnicity, n (%) | | | | |
| Non-Hispanic/Latino | 190 (100) | 189 (98) | 379 (99) | .080 |
| Hispanic/Latino | 0 (0) | 3 (2) | 3 (<1) | |
| Mean inflammatory lesion count, n (SD) | 39.0 (13.7) | 40.8 (16.0) | N/A | .182 |
| Mean noninflammatory lesion count, n (SD) | 52.7 (25.7) | 51.1 (26.5) | N/A | .479 |
| Mean total lesion count, n (SD) | 91.7 (31.4) | 92.0 (33.5) | N/A | .905 |
| ISGA acne severity, n (%) | | | | |
| Almost clear | 1 (<1) | 1 (<1) | 2 (<1) | .960 |
| Mild | 54 (28) | 57 (30) | 111 (29) | |
| Moderate | 130 (68) | 128 (67) | 258 (68) | |
| Severe | 5 (3) | 6 (3) | 11 (3) | |

Abbreviations: ITT, intention to treat; C/BPO HE, clindamycin 1%–benzoyl peroxide 5% gel with hydrating excipients; A/BPO, adapalene 0.1%–benzoyl peroxide 2.5% gel; SD, standard deviation; N/A, not available; ISGA, investigator's static global assessment.

## Efficacy

*Primary End Point*—After 12 weeks of treatment, the mean reduction in inflammatory lesion count was 76.8% in the C/BPO HE group compared with 72.2% in the A/BPO group (Figure 1). The between-group difference approached statistical significance ($P$=.076).

*Secondary End Points*—Significantly more participants in the C/BPO HE group versus the A/BPO group achieved treatment success at week 12 on the ISGA scale (30.5% [58/190] vs 21.8% [42/192]; $P$=.046). Time to treatment success was significantly shorter in the C/BPO HE group ($P$=.035). The mean reduction in total lesion count from baseline to week 12 was 69.1% in the C/BPO HE group compared with 67.1% in the A/BPO group ($P$=.420)(Figure 1). Assessments at individual time points did not reveal any significant between-group differences in percentage change in lesion counts, except that there was a significantly greater reduction in inflammatory lesions at week 4 in the C/BPO HE group (63.9%) versus the A/BPO group (58.0%)($P$=.021). Both treatments effectively reduced inflammatory and noninflammatory lesions over 12 weeks. Improvement occurred rapidly with a pronounced reduction in lesion counts observed within the first 2 weeks of application, particularly for inflammatory lesions. There were no significant differences between the agents in the absolute change in total, inflammatory, and noninflammatory lesion counts at any time point, and there were no significant differences with respect to the time to achieve a 50% reduction in total, inflammatory, and noninflammatory lesion counts.

Figure 2 demonstrates the effect of treatment on skin appearance from baseline to week 1 and week 12.

## Tolerability

Tolerability assessments revealed a significantly greater incidence of local reactions across weeks 1 through 12 in the A/BPO group versus the C/BPO HE group ($P$<.03). Most participants experienced none or mild local signs or symptoms (grade 0 to 1); however, by week 12, the number of grade 1 (mild) reactions was roughly double that of the C/BPO HE treatment group. In participants who experienced tolerability reactions, C/BPO HE was significantly better tolerated at all grades than A/BPO from week 1 onward with respect to all investigator-rated (erythema, dryness, peeling) and participant-rated (pruritus, burning/stinging) outcomes ($P$<.05). Participants in the A/BPO group experienced more grade 2 to 3 reactions during the first 2 to 4 weeks of treatment ($P$<.05).

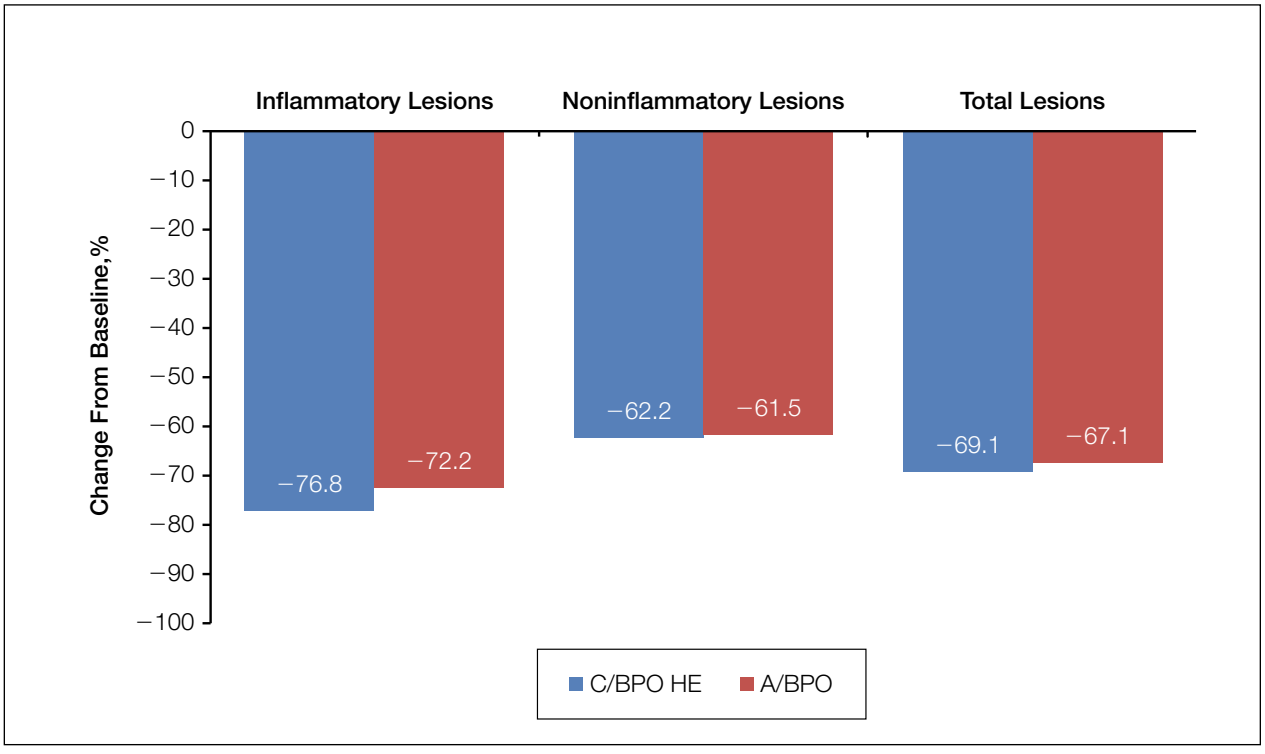


**Figure 1.** Mean percentage change in lesion counts from baseline to week 12 following treatment with clindamycin 1%–benzoyl peroxide 5% gel with hydrating excipients (tube gel)(C/BPO HE) or adapalene 0.1%–benzoyl peroxide 2.5% gel (A/BPO)(N=382).

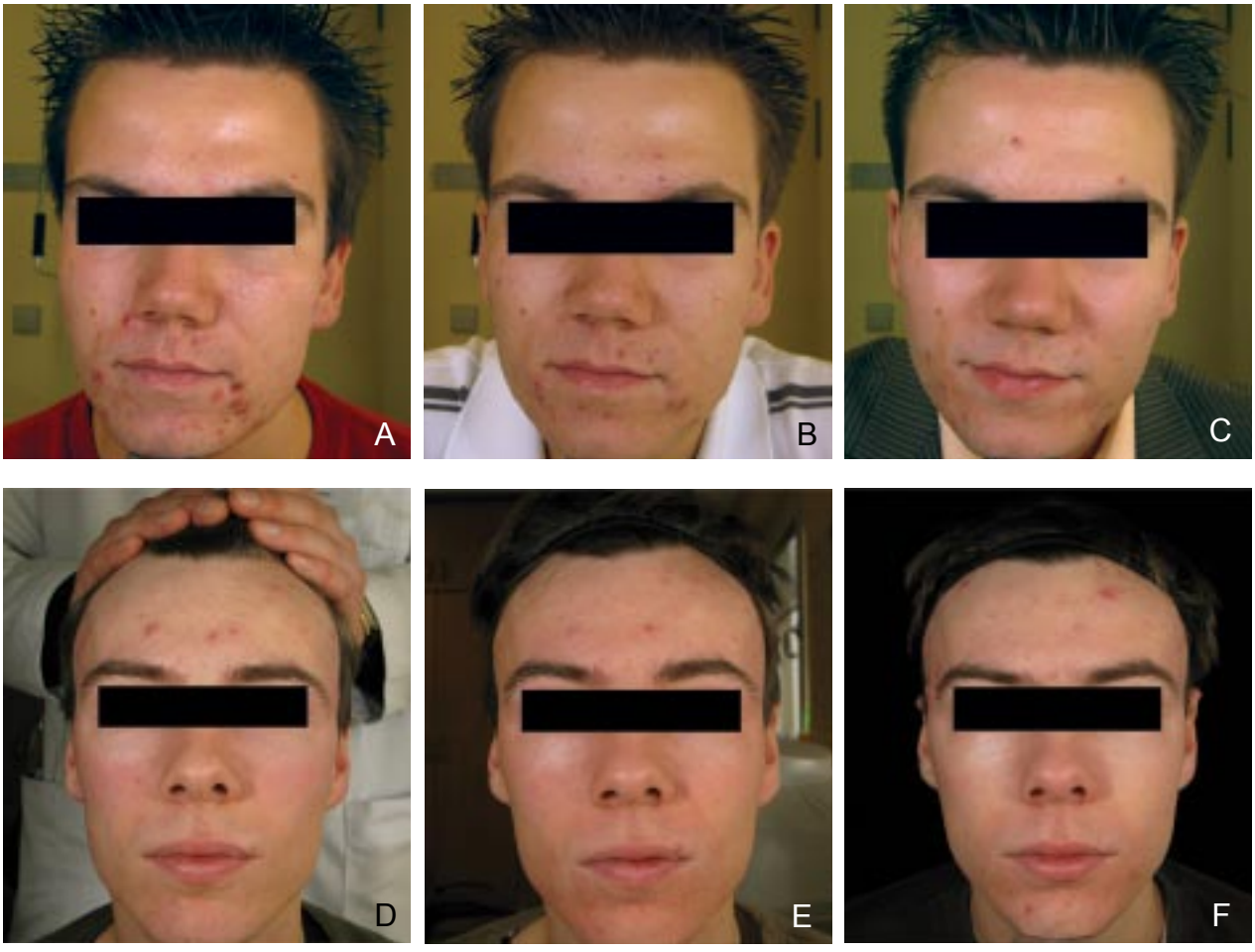


**Figure 2.** Treatment efficacy in a participant treated with clindamycin 1%–benzoyl peroxide 5% gel with hydrating excipients at baseline (A), week 1 (B), and week 12 (C), and a participant treated with adapalene 0.1%–benzoyl peroxide 2.5% gel at baseline (D), week 1 (E), and week 12 (F).

### Safety

Treatment-related AEs occurred in 48.4% (92/190) and 78.6% (151/192) of participants in the C/BPO HE group and A/BPO group, respectively. They were mostly mild to moderate application site reactions; however, severe AEs were reported in 7.4% (14/190) and 21.4% (41/192) of participants, respectively. Three participants in the C/BPO HE group developed severe AEs that were unrelated to treatment (contusion and joint sprain [n=1], abortion [n=1], and benign ovarian tumor [n=1]). Overall, 1.6% (3/190) and 4.7% (9/192) of participants, respectively, withdrew from the study due to AEs.

### Compliance

More missed applications were noted in the A/BPO group (429 applications) during the first 4 weeks of the study versus the C/BPO HE group (150 applications). These differences occurred from week 1 when 38.0% (73/192) of participants in the A/BPO group missed an application due to tolerability issues or an AE compared with 5.8% (11/190) of the C/BPO HE group. During weeks 2 through 4, 33.3% (64/192) of participants in the A/BPO group missed an application for these reasons versus 1.6% (3/190) of the C/BPO HE group.

## COMMENT

The guidelines of the Global Alliance to Improve Outcomes in Acne promote topical therapies as the mainstay of treatment of mild to moderate acne.[1] Because acne is a multifaceted skin condition, it is best treated with a combination of agents to target multiple aspects of its pathology, and all currently available fixed-dose combinations have proven to be effective.[3,9-12]

This study demonstrates that C/BPO HE and A/BPO have comparable efficacy in the topical treatment of acne, though some parameters significantly favored C/BPO HE. For example, significantly more participants in the C/BPO HE group achieved treatment success on the ISGA scale compared with the

A/BPO group (*P*=.046). Both agents produced consistent reductions in inflammatory lesion count over 12 weeks; the percentage change in inflammatory lesions was greater with C/BPO HE than A/BPO, but the difference did not reach statistical significance (*P*=.076). Interestingly, C/BPO HE had similar efficacy to A/BPO for reductions in noninflammatory lesions, despite the fact that retinoids have greater activity against microcomedone formation.[1] Time to treatment success was significantly shorter with C/BPO HE than A/BPO (*P*=.035), suggesting that although BPO augments the efficacy of adapalene, there is a delay in achieving visible results, which may make patients impatient and affect compliance.

The choice of outcome measures is an important element of any clinical trial. Lesion counts are typically the primary outcome measure in acne studies because they are evaluated numerically, but they do not necessarily reflect a patient's perception of the overall skin condition. The Global Alliance to Improve Outcomes in Acne notes that the impact of acne on quality of life is related to the patient's self-assessment of disease severity rather than the physician's objective clinical assessment.[13] Although both treatments in this study achieved similar reductions in lesion counts, significantly more participants in the C/BPO HE group met the global criteria for treatment success (*P*=.046), which occurred more quickly (*P*=.035). The between-group difference in ISGA score may reflect a physician perception of improved appearance, with C/BPO HE resulting from less erythema and peeling compared with the A/BPO group.

A notable finding from our study was that C/BPO HE had a more favorable tolerability and safety profile than A/BPO. Between-group differences in investigator- and participant-rated tolerability assessments were in favor of C/BPO HE at all severity grades and time points. Participants in the C/BPO HE group had fewer incidences of application site AEs, severe AEs, and AE-related study withdrawals. These factors probably impacted compliance, as our adherence investigations indicated that one-third of participants in the A/BPO group missed applications during the first 4 weeks of treatment because of tolerability issues or AEs.

Surveys of dermatology outpatients indicate that patient satisfaction with efficacy, regimen simplicity, and tolerability is a major determinant of patient adherence.[14,15] It is pertinent to consider if the physician's perception of a favorable balance between efficacy and tolerability is in alignment with the patient's expectations. Physicians may judge effects such as erythema and scaling to be an acceptable compromise for a drug's efficacy, whereas a patient may not perceive the drug to be working as well or as quickly as expected and may not be prepared to endure tolerability issues, leading to reduced compliance with therapy. Data from our study on the impact of treatment on quality of life and patient perceptions of product acceptability may help to elucidate other factors that may impact adherence with therapy.[16]

Our study has some limitations. The lack of participant blinding may have led to bias in the participant-rated outcomes if they had perceptions of which combination may be more effective or better tolerated. However, investigator blinding and use of lesion counts and the validated ISGA scale for key efficacy end points should have helped to limit any bias in the visual assessment of acne. Because most participants were white, our results may not be representative of the acne populations seen in different regions with other skin types.

## CONCLUSION

Our results indicate that C/BPO HE and A/BPO reduce total, inflammatory, and noninflammatory lesion counts to a similar degree when applied once daily to the face in participants with acne, but C/BPO HE achieves better overall treatment success with a faster onset of action. Although both fixed-dose combinations were generally well tolerated and safe, C/BPO HE exhibited a significantly better tolerability profile and notably better safety profile.

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