Randomized, Observer-Blind, Split-Face Study to Compare the Irritation Potential of 2 Topical Acne Formulations Over a 14-Day Treatment Period

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This randomized, observer-blind, split-face study assessed the irritation potential and likelihood of continued use of clindamycin phosphate 1.2%–benzoyl peroxide (BPO) 2.5% gel or adapalene 0.1%–BPO 2.5% gel once daily over a 14-day treatment period in 21 participants (11 males; 10 females) with acne who were 18 years or older. Investigator clinical assessment (erythema and dryness) and self-assessment (dryness and burning/stinging) were performed at baseline and each study visit (days 1–14) using a 4-point scale (0=none; 3=severe). Transepidermal water loss (TEWL) and corneometry measurements were performed at baseline and days 3, 5, 7, 9, 11, and 14. Lesions were counted at baseline and on day 14. Participant satisfaction questionnaires were completed on days 7 and 14.

At the end of the study, investigators reported none or only mild erythema in 86% (18/21) of participants treated with clindamycin phosphate 1.2%–BPO 2.5% gel compared with 62% (13/21) of participants treated with adapalene 0.1%–BPO 2.5% gel. No severe erythema was reported with clindamycin phosphate 1.2%–BPO 2.5% gel. Adapalene 0.1%–BPO 2.5% gel was prematurely discontinued due to severe erythema in 1 participant on day 5 and a second participant on day 9. Additionally, 2 more participants reported severe erythema on day 14. Mean erythema scores were 0.9 (mean change from baseline, 0.7) with clindamycin phosphate 1.2%–BPO 2.5% gel and 1.4 (mean change from baseline, 1.3) with adapalene 0.1%–BPO 2.5% gel on day 14 (P<.05 for days 6–14). Similar results were seen with dryness. Mean scores were 0.5 (mean change from baseline, 0.4) and 1.0 (mean change from baseline, 1.0), respectively (P<.05 for days 6–14). Self-assessment, TEWL, and corneometry results underscored the investigator clinical assessment. Participant preference and likelihood of continued usage was greater with clindamycin phosphate 1.2%–BPO 2.5% gel.

Continued use and efficacy results for the treatment of acne were influenced by the potential of the product to cause irritation and the participant preferences. Irritation potential was more pronounced and severe with adapalene 0.1%–BPO 2.5% gel. Undoubtedly, as a result more participants preferred treatment with clindamycin phosphate 1.2%–BPO 2.5% gel and were more likely to continue to use the product.

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Fixed-combination therapy is the standard of care for acne, targeting the major pathogenic factors in its development.[1,2] Topical retinoid therapy is considered the cornerstone of most acne regimens.[1] However, topical retinoids are potentially irritating to the skin, and the most common adverse effects are dryness, erythema, stinging, and pruritus.[3] Irritation,

especially over the first few weeks of treatment, can be a limiting factor for treatment adherence in several patients.[4] Fixed combinations of topical antibiotics—combination of benzoyl peroxide (BPO) and clindamycin phosphate or erythromycin—also are commonly used.[1] Similar to topical retinoids, antibiotics such as BPO also can cause skin irritation, peeling, dryness, pruritus, erythema, and burning.[5]

Combining multiple therapies that are all potentially irritating can be a challenge. Recent research has focused on reducing the concentration of BPO. In one study (N=200), one-third of acne patients who used a clindamycin–BPO 5% fixed-combination product developed dryness, which caused them to reduce usage, switch products, or stop using the medication.[6] Advances made in formulation research allowing for the removal of potentially irritating surfactants, preservatives, alcohol, and parabens, as well as lowering the concentration of BPO to 2.5%, have led to reductions in irritation in a fixed-combination product containing clindamycin and BPO 2.5%.[7] The ideal treatment regimen involves selection of the least potentially irritating treatments without sacrificing efficacy. The combination enhances adherence and improves outcomes.[6]

Currently, 2 fixed-combination products are available that combine a low concentration of BPO (2.5%) with either clindamycin phosphate or adapalene. A meta-analysis that compared clindamycin 1%–BPO 2.5% gel with a fixed combination containing clindamycin 1%–BPO 5% found comparable efficacy in reducing total acne lesions with the possibility that the clindamycin 1%–BPO 2.5% gel may be superior in treating noninflammatory lesions.[8] There are no head-to-head studies comparing the efficacy of clindamycin phosphate 1.2%–BPO 2.5% gel and adapalene 0.1%–BPO 2.5% gel in acne patients. Their efficacy has been independently demonstrated through large pivotal studies.[9,10] In these studies, clindamycin phosphate 1.2%–BPO 2.5% gel and adapalene 0.1%–BPO 2.5% gel appeared comparable in reducing both inflammatory and noninflammatory lesions in patients with moderate acne.[10,11] The current randomized, observer-blind, split-face study compared the irritation potential of these 2 products.

Methods

Study Design and Population—Experience has shown that a 2-week treatment period is adequate for comparison of dermal tolerability, as medications used to treat acne usually show skin irritation reactions during the first 2 weeks before subsiding.[4,5]

A 14-day, randomized, observer-blind, split-face study was performed comparing 2 once-daily formulations: clindamycin phosphate 1.2%–BPO 2.5% gel and adapalene 0.1%–BPO 2.5% gel. Twenty-one acne patients (11 males; 10 females) with Fitzpatrick skin types I to III who met the inclusion/exclusion criteria were enrolled. All participants received both treatments, one applied to each side of the face as randomly assigned, over 14 days. Test areas were compared intraindividually. Basic Dove® bar soap was provided for cleansing to be used on the entire face throughout the trial.

Eligible participants included males and females of any race and ethnicity 18 years or older with acne who presented with a minimum of 10 inflammatory lesions (eg, papules, pustules, nodules) and 10 noninflammatory lesions (eg, open and closed comedones). Women of childbearing potential were required to have a negative urine pregnancy test result and had to agree to use an effective contraception method for the duration of the study. A washout period of up to 1 month was required for participants who used prior prescription and over-the-counter acne treatments. Mandatory washout periods and restrictions were applied to the following topical (eg, face) and systemic treatments: topical astringents and abrasives, 1 week; soaps containing antimicrobials, 1 week; antibiotics and other topical antiacne products, 4 weeks; topical retinoids, retinol, and systemic acne treatments (excluding systemic retinoids), 4 weeks.

Efficacy Evaluations—Investigator clinical assessment (erythema and dryness) and self-assessment (dryness and burning/stinging) were performed at baseline and each study visit (days 1–14) using a 4-point scale (0=none; 3=severe)(Table 1). Transepidermal water loss (TEWL) and corneometry were used to assess water loss, skin hydration, and barrier function. Transepidermal water loss measurements assess the rate of water that is lost through the skin. The measurements are expressed in grams per hour per square meter and estimate the skin's ability to retain moisture. Additionally, TEWL measurements are used as an index of the extent of possible damage to the skin's water barrier function.[12] Corneometry provides information on the extent of skin hydration under various physiologic conditions in response to topical therapies. Corneometry measurements assess a 10- to 20-μm thickness of the stratum corneum and determine the capacitance of the skin because of its behavior as a dielectric medium. It measures skin hydration and also can be used as an indirect measure of barrier function.[13] Transepidermal water loss and corneometry measurements were performed at baseline and on days 3, 5, 7, 9, 11, and 14. Lesion counts were performed at baseline and on day 14. VISIA® photographs of the face were taken in ambient light at baseline and on days 7 and 14 for documentation

Table 1.

Investigator Clinical Assessment and Self-assessment of Erythema, Dryness, and Burning/Stinging

Score	Erythema[a]	Dryness[a,b]	Burning/Stinging[b]
0	None: no erythema present (might have been minor discoloration)	None: no dryness present	None: no burning/stinging
1	Mild: light pink and noticeable	Mild: slight but definite roughness	Mild: slight warm burning/stinging sensation; not really bothersome
2	Moderate: pink/red and easily noticeable	Moderate: moderate roughness	Moderate: definite warm burning/stinging sensation that was somewhat bothersome
3	Severe: deep or bright red and might have been warm to the touch	Severe: marked roughness	Severe: hot tingling/stinging sensation that caused definite discomfort and might have interrupted daily activities and/or sleep

[a]Investigator clinical assessment of erythema and dryness.
[b]Participant self-assessment of dryness and burning/stinging.

of acne lesions. Participant satisfaction questionnaires also were completed on days 7 and 14.

Safety Evaluation—Safety was evaluated on each study day through reported adverse events (AEs), which were summarized by the treatment group, the level of severity, and the relationship of the AE to the study treatment. Skin irritation other than erythema in the treatment areas, skin irritation outside of the treatment area, and vital signs were descriptively summarized.

Statistical Analysis—Investigator clinical assessment scores of erythema and dryness were performed separately at each trial visit. Absolute scores, including the changes from baseline, were summarized by treatment and day using descriptive statistical methods. Pooled analyses are provided. Differences between the treatments for each postbaseline assessment were tested with respect to the changes from baseline using the Wilcoxon signed rank test. The participant self-assessment of dryness and burning/stinging was analyzed separately to the primary parameters. Transepidermal water loss and corneometry data were analyzed by applying the 2-tailed paired *t* test comparing the mean differences between the treatments in changes from baseline. Lesion count data were summarized by mean, standard deviation, median, interquartile range, minimum, and maximum.

Results

Twenty-one participants were included in the safety and intention-to-treat analyses. Participants were aged 18 to 29 years (mean, 21.3 years). All participants were white.

Investigator Clinical Assessment—Although erythema scores increased after treatment with both formulations, the increase was less prominent with clindamycin phosphate 1.2%–BPO 2.5% gel. Mean erythema scores were 0.9 (mean change from baseline, 0.7) with clindamycin phosphate 1.2%–BPO 2.5% gel and 1.4 (mean change from baseline, 1.3) with adapalene 0.1%–BPO 2.5% gel on day 14 ($P<.05$ for days 6–14)(Figure 1).

A similar result was seen with dryness. The mean scores were 0.5 (mean change from baseline, 0.4) with clindamycin phosphate 1.2%–BPO 2.5% gel and 1.0 (mean change from baseline, 1.0) with adapalene 0.1%–BPO 2.5% gel on day 14 ($P<.05$ for days 6–14)(Figure 2). At the end of the study (day 14), 86% (18/21) of participants treated with clindamycin phosphate 1.2%–BPO 2.5% gel reported none or only mild erythema compared with

62% (13/21) of participants treated with adapalene 0.1%–BPO 2.5% gel (Figure 3).

No severe erythema was reported with clindamycin phosphate 1.2%–BPO 2.5% gel. Treatment with adapalene 0.1%–BPO 2.5% gel was prematurely discontinued due to severe erythema in 1 participant on day 5 and another participant on day 9, and 2 more participants reported severe erythema on day 14.

Participant Self-assessment—The participant self-assessment of dryness underscored the results of the investigator clinical assessment. At the end of the study (day 14), the mean dryness score had increased to 0.7 for clindamycin phosphate 1.2%–BPO 2.5% gel and 1.1 for adapalene 0.1%–BPO 2.5% gel (mean changes from baseline, 0.4 and 0.8, respectively). Participants noted no severe irritation reactions with clindamycin phosphate 1.2%–BPO 2.5% gel, but 2 participants recorded irritation reactions following treatment with adapalene 0.1%–BPO 2.5% gel.

The number of participants who assessed burning/stinging on the side of the face treated with clindamycin phosphate 1.2%–BPO 2.5% gel remained approximately constant, whereas the number of participants who assessed burning/stinging from treatment with adapalene 0.1%–BPO 2.5% gel increased during the first week of treatment (mean change from baseline, 0.1 and 0.5, respectively)($P<.05$ for days 5–14)(Figure 4).

Transepidermal Water Loss and Corneometry—Transepidermal water loss and corneometry measurements also underscored the investigator clinical assessment with a significantly lower mean change from baseline using TEWL for clindamycin phosphate 1.2%–BPO 2.5% gel versus adapalene 0.1%–BPO 2.5% gel at days 5, 7, 9, 11, and 14 ($P<.02$). In addition, the treatment comparisons showed a statistically significantly higher mean change from baseline with corneometry measurements for clindamycin phosphate 1.2%–BPO 2.5% gel compared with adapalene 0.1%–BPO 2.5% gel on day 3 ($P<.05$).

Lesion Counts—Lesion counts showed similar decreases in the mean number of papules and pustules with clindamycin phosphate 1.2%–BPO 2.5% gel and adapalene 0.1%–BPO 2.5% gel (change from baseline, 3.2 and 3.0, respectively). Only slight changes in the number of open and closed comedones, in favor of clindamycin phosphate 1.2%–BPO 2.5% gel, were noted (change from baseline, 2.4 and 0.4, respectively; not statistically significant). Although isolated nodules remained or disappeared with clindamycin phosphate 1.2%–BPO 2.5% gel, a new nodule appeared on 1 participant who was treated with adapalene 0.1%–BPO 2.5% gel.

Participant Satisfaction—After 2 weeks of treatment, results of the participant satisfaction questionnaire showed that more participants preferred clindamycin phosphate 1.2%–BPO 2.5% gel than adapalene 0.1%–BPO 2.5% gel for overall facial application and from an overall appearance standpoint. Participants rated that clindamycin phosphate 1.2%–

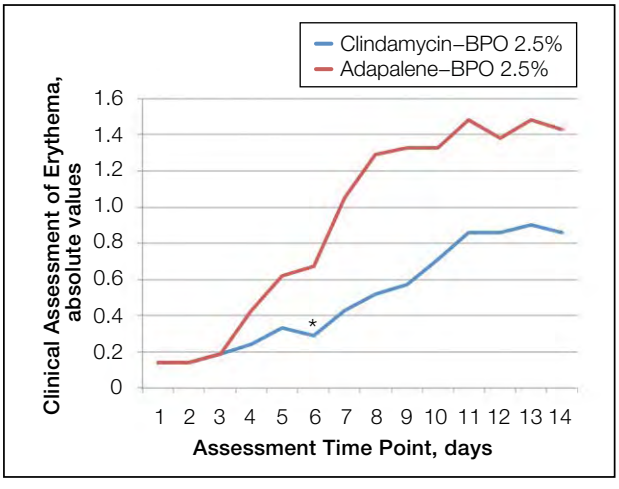

Figure 1. Mean scores of the investigator clinical assessment of erythema (N=21)(absolute values; intention-to-treat analysis) from treatment with clindamycin phosphate 1.2%–benzoyl peroxide (BPO) 2.5% gel and adapalene 0.1%–BPO 2.5% gel. Asterisk indicates $P<.05$ for days 6 through 14. Erythema was graded on a scale of 0 (none) to 3 (severe).

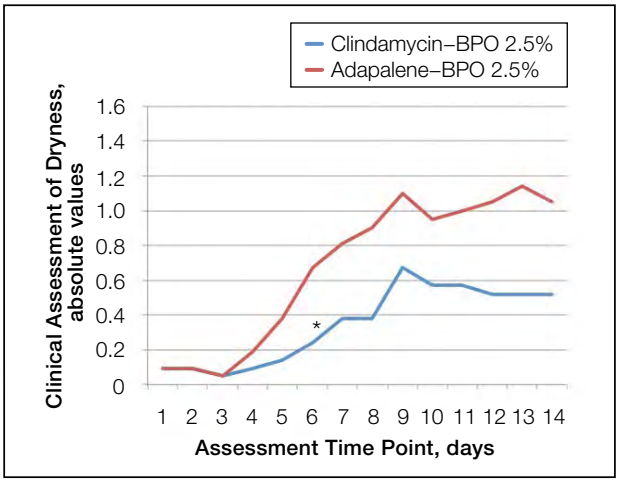

Figure 2. Mean scores of the investigator clinical assessment of dryness (N=21)(absolute values; intention-to-treat analysis) from treatment with clindamycin phosphate 1.2%–benzoyl peroxide (BPO) 2.5% gel and adapalene 0.1%–BPO 2.5% gel. Asterisk indicates $P<.05$ for days 6 through 14. Dryness was graded on a scale of 0 (none) to 3 (severe).

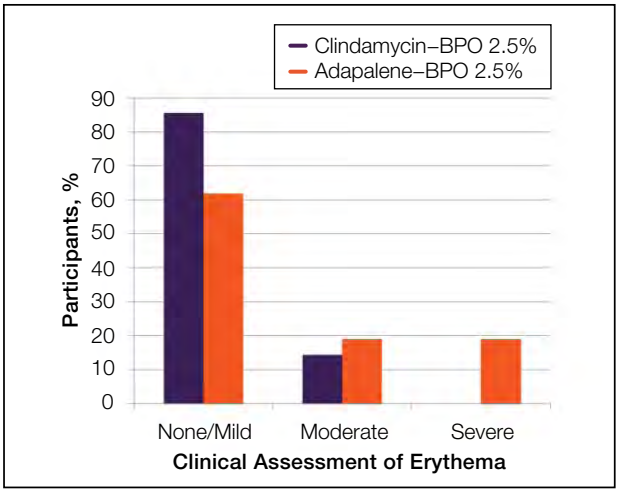

Figure 3. Comparative severity of erythema at day 14 (N=21)(intention-to-treat analysis) from treatment with clindamycin phosphate 1.2%–benzoyl peroxide (BPO) 2.5% gel and adapalene 0.1%–BPO 2.5% gel.

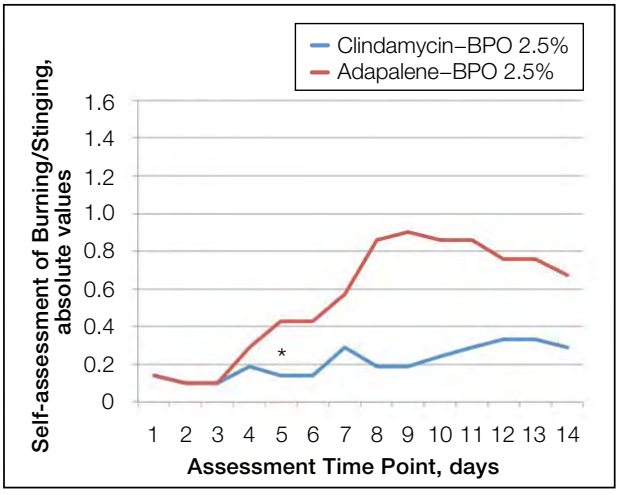

Figure 4. Mean scores of the participant self-assessment of burning/stinging (N=21)(absolute values; intention-to-treat analysis) from treatment with clindamycin phosphate 1.2%–benzoyl peroxide (BPO) 2.5% gel and adapalene 0.1%–BPO 2.5% gel. Asterisk indicates $P<.05$ for days 5 through 14. Burning/stinging was graded on a scale of 0 (none) to 3 (severe).

Table 2.

Comparative Participant Satisfaction Questionnaire (Day 14)(N=20)[a]

Participant Satisfaction Question	Participants, n (%)	
	Clindamycin Phosphate 1.2%–BPO 2.5% Gel	Adapalene 0.1%–BPO 2.5% Gel
Which side of your face did the medication absorb or dry more quickly?	12 (60)	8 (40)
Which side of your face feels more moisturized or hydrated?	15 (75)	5 (25)
Which side of your face stings or burns more?	0 (0)	19 (95)
Immediately following product application, which side of your face do you prefer from an overall appearance standpoint?	13 (65)	6 (30)
Which side of your face feels smoother or softer?	13 (65)	7 (35)
Which product (side of your face) do you prefer for facial application overall?	13 (65)	7 (35)
Which product are you more satisfied with in relation to the improvement of your acne?	11 (55)	9 (45)
Which product (side of your face) are you most likely to continue using in the future?	13 (65)	7 (35)

Abbreviation: BPO, benzoyl peroxide.
[a]Some participants were undecided on some questions.

BPO 2.5% gel was absorbed or dried more quickly, moisturized or hydrated better, stung or burned less, and left the face smoother or softer (Table 2).

More participants were satisfied with the improvement of their acne after 2 weeks of treatment with clindamycin phosphate 1.2%–BPO 2.5% gel and nearly twice as many participants were likely to continue using clindamycin phosphate 1.2%–BPO 2.5% gel (65% [13/20]) compared with adapalene 0.1%–BPO 2.5% gel (35% [7/20])(Table 2).

Safety Evaluation—In total, 6 nonserious mild treatment-emergent AEs were reported in 4 (19%) participants (headache, 3; nasopharyngitis, 2; oral herpes, 1). All 6 treatment-emergent AEs were considered to be unlikely related to the drug. Five AEs recovered without sequelae and 1 was ongoing at the end of the trial but follow-up was not deemed necessary.

Comment

The efficacy of 2 fixed-combination products used to treat acne has been demonstrated in large pivotal studies.[9,10] In separate studies, clindamycin phosphate 1.2%–BPO 2.5% gel and adapalene 0.1%–BPO 2.5% gel showed similar efficacy in reducing both inflammatory and noninflammatory lesions in patients with moderate acne.[10,11] Adherence is an important aspect in acne management. Continued use and efficacy results for the treatment of acne are influenced by the potential irritation of a product and the patient's preferences, especially within the first 2 weeks of treatment. In our study of 21 participants, irritation potential was significantly ($P<.05$ from day 6) more prominent and severe with adapalene 0.1%–BPO 2.5% gel. Undoubtedly, as a result more of the participants preferred and also were more likely to continue treatment with clindamycin phosphate 1.2%–BPO 2.5% gel.

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