Clindamycin Phosphate 1.2% and Benzoyl Peroxide 2.5%: A New, Once-Daily, Fixed Combination Treatment for Moderate to Severe Acne

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Fixed combination products containing clindamycin and benzoyl peroxide (BPO) 5% have been shown to be effective in treating acne. However, the 5% concentration of BPO combined with inactive ingredients, such as surfactants, preservatives, and alcohols in these formulations, may contribute to skin irritation and dryness.

An optimized formulation of clindamycin phosphate (CDP) and BPO using a low concentration of BPO (CDP 1.2% and BPO 2.5% gel) was developed without the use of preservatives, surfactants, or alcohol. Results of clinical studies in more than 2800 participants with moderate to severe acne demonstrated that using a once-daily, CDP 1.2% and BPO 2.5% gel is effective in the treatment of inflammatory and noninflammatory lesions of acne and is very well tolerated.

Acne vulgaris affects 40 to 50 million people in the United States.[1] Current evidence suggests it is a result of increased sebum production and follicular hyperkeratinization, proliferation of *Propionibacterium acnes* compounded by host responses to the proinflammatory activities of *P acnes*.[2] As a result, combination therapy targeting the multiple components of acne is now commonplace.

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Two commonly used topical acne medications are clindamycin and benzoyl peroxide (BPO). Clindamycin phosphate (CDP) improves acne by reducing the levels of *P acnes* and decreasing inflammation,[3] and BPO is a safe, effective agent that is not associated with antimicrobial resistance.[2] In addition, BPO has anticomedogenic and keratolytic properties.[4,5]

Fixed combination products of clindamycin 1% and BPO 5% have been widely accepted and used for the treatment of acne. Many studies have shown that the combination of clindamycin 1% with BPO 5% is superior to each individual active ingredient.[6-8] The primary limitation of the BPO component in these fixed combinations is that in certain patients it may cause concentration-dependent cutaneous irritation and dryness.[2] As a result, it is generally recommended to initiate treatment with a low concentration of BPO to minimize local side effects.[9] A small subset of patients can also have allergic contact dermatitis in response to BPO.[10] Concentrations of BPO

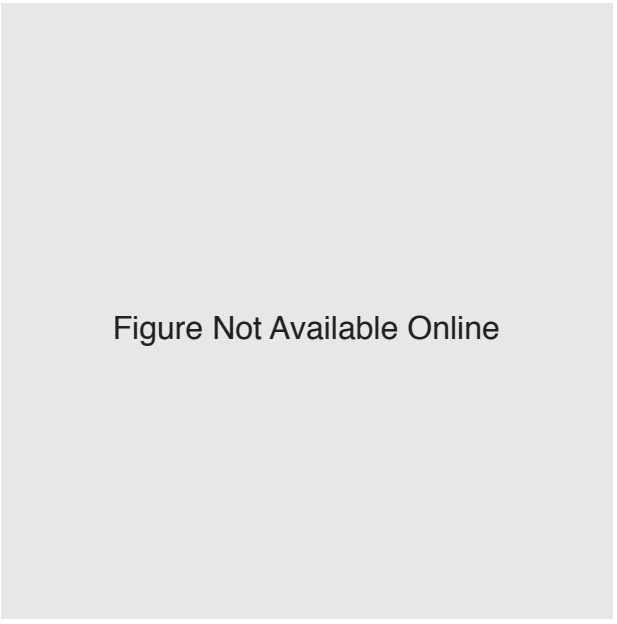

Figure 1. Mean percent reduction in lesion count at week 12. Asterisk indicates $P<.001$ versus clindamycin, benzoyl peroxide, and vehicle; dagger, $P<.001$ versus clindamycin and vehicle, $P=.001$ compared to benzoyl peroxide. Reprinted with permission from Thiboutot D, Zaenglein A, Weiss J, et al. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% for the once-daily treatment of moderate to severe acne vulgaris: assessment of efficacy and safety in 2813 patients. *J Am Acad Dermatol.* 2008;59:792-800.[13]

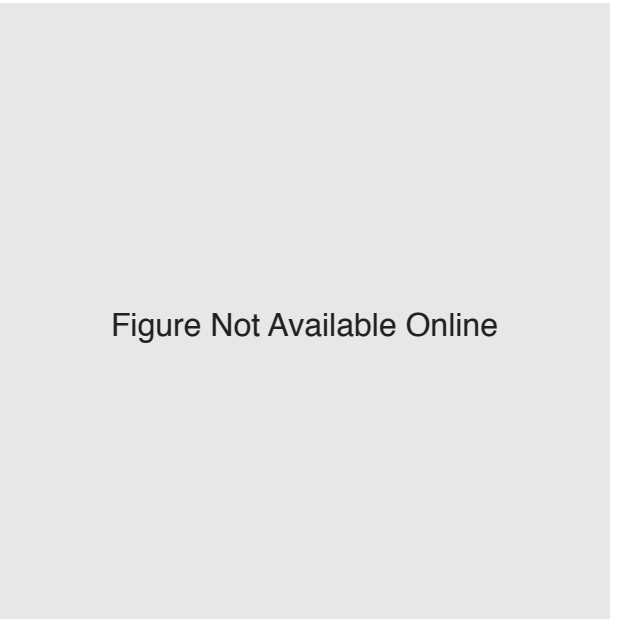

Figure 2. Treatment success and Evaluator Global Severity Score. Asterisk indicates $P=.002$ versus clindamycin, .009 versus benzoyl peroxide; dagger, $P<.001$ versus clindamycin, .002 versus benzoyl peroxide; double dagger, $P<.001$ versus clindamycin and benzoyl peroxide, all clindamycin phosphate 1.2%/benzoyl peroxide 2.5% results $P<.001$ versus vehicle. Adapted with permission from Thiboutot D, Zaenglein A, Weiss J, et al. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% for the once-daily treatment of moderate to severe acne vulgaris: assessment of efficacy and safety in 2813 patients. *J Am Acad Dermatol.* 2008;59:792-800.[13]

2.5% may be as effective as a 5% concentration in reducing the number of inflammatory lesions of acne and significantly reducing *P acnes* counts after one week of topical application to the face.[11]

It has also been suggested that a once-daily treatment for acne that is effective and well tolerated may contribute to improved patient compliance.[12] Consequently, a fixed dose, once-daily combination product containing CDP 1.2% (equivalent to clindamycin 1%) and a low concentration of BPO 2.5% (clindamycin/BPO 2.5%) in a gel vehicle was developed.

The efficacy and safety of CDP 1.2% and BPO 2.5% gel was evaluated in 2 identical phase III studies in a total of 2813 participants with moderate to severe acne and demonstrated statistically superior efficacy over both active ingredients and vehicle for both inflammatory and noninflammatory lesions.[13] After 12 weeks of treatment, mean inflammatory lesion counts were reduced by 54.6% and mean noninflammatory lesion counts by 43.2% with CDP 1.2% and BPO 2.5% gel, as compared with 29% and 24% with vehicle alone, respectively ($P<.001$) (Figure 1).[13] Treatment success was defined as at least a 2-grade improvement in global severity by the Evaluator Global Severity Score (EGSS), which was evaluated on a static scale ranging from 0 (clear) to 5 (very severe). Over one-third of participants (35%) on CDP 1.2% and BPO 2.5% gel were judged to be treatment successes by the investigators as compared with 16.5% on vehicle alone ($P<.001$) (Figure 2).[13] The percentage of participants who were clear or almost clear represented at least a 2-grade improvement in EGSS in participants who had moderate acne at baseline and at least a 3-grade improvement in EGSS in the 20% of participants who had severe acne at baseline. Twenty-nine percent of participants were determined as clear or almost clear of their acne at week 12 as compared with 13% with vehicle alone ($P<.001$).

Participant evaluations of acne improvement were collected using a self-assessment scale. Severity and the degree of improvement were evaluated relative to baseline on a scale ranging from 1 (clear) to 7 (worse). A significantly greater percentage of participants on CDP 1.2% and BPO 2.5% gel (39%) judged their acne to be clear or almost clear at week 12 as compared with 17% on vehicle alone, and the percentage of participants who reported that their acne was clear or almost clear was superior to vehicle as early as week 2 (Figure 3).[13]

In addition, participants were instructed at week 12 to rate their level of satisfaction with their current acne study treatment on a scale of 1 to 10, with 1 being

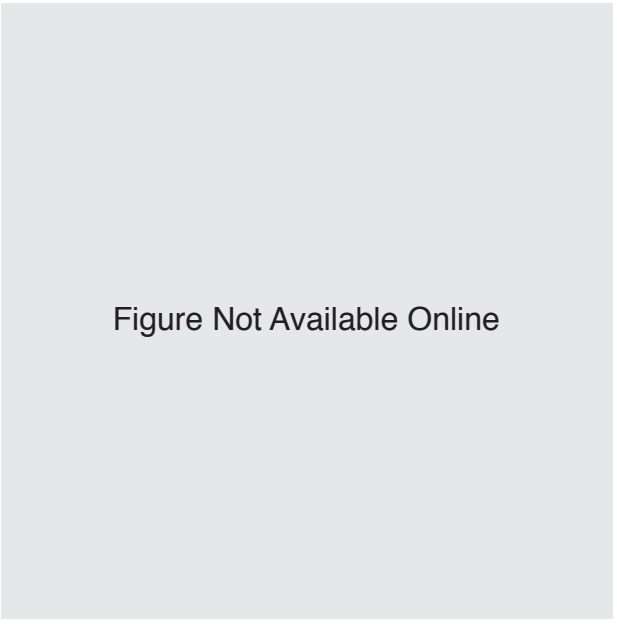

Figure 3. Participant self-assessment. Asterisk indicates $P=.045$ versus benzoyl peroxide and .002 versus vehicle; dagger, $P=.001$ versus clindamycin, .002 versus benzoyl peroxide, .005 versus vehicle; double dagger, $P<.001$ versus clindamycin and vehicle, .003 versus benzoyl peroxide; section sign, $P<.001$ versus clindamycin, benzoyl peroxide, and vehicle. Reprinted with permission from Thiboutot D, Zaenglein A, Weiss J, et al. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% for the once-daily treatment of moderate to severe acne vulgaris: assessment of efficacy and safety in 2813 patients. *J Am Acad Dermatol.* 2008;59:792-800.[13]

the least satisfied and 10 being the most satisfied. The mean participant satisfaction score with CDP 1.2% and BPO 2.5% gel at week 12 (7.5) was significantly greater than with their prior acne therapy (4.2) ($P<.001$). In a posthoc analysis, 81% of participants were satisfied with CDP 1.2% and BPO 2.5% gel at the end of 12 weeks of treatment (participants with a score of 6–10 were considered satisfied with their current acne study treatment).

The CDP 1.2% and BPO 2.5% gel was also associated with a low incidence of treatment-related adverse effects and highly favorable cutaneous tolerability profile. The incidence of adverse drug reactions was low and similar across all treatment groups (5.9% for the CDP 1.2% and BPO 2.5% gel versus 6.1% for vehicle based on the number of events). The majority (≥97%) were mild to moderate in severity. Application site reactions were rare (0.1%) and only one participant discontinued use due to application site pain and irritation. No participants discontinued treatment because of local signs or symptoms of erythema, scaling, burning, itching, or stinging, and in no participant were these severe. Mean scores for each local sign/symptom were less than 1 (1=mild) and comparable to individual active ingredients and vehicle (Figure 4).[13]

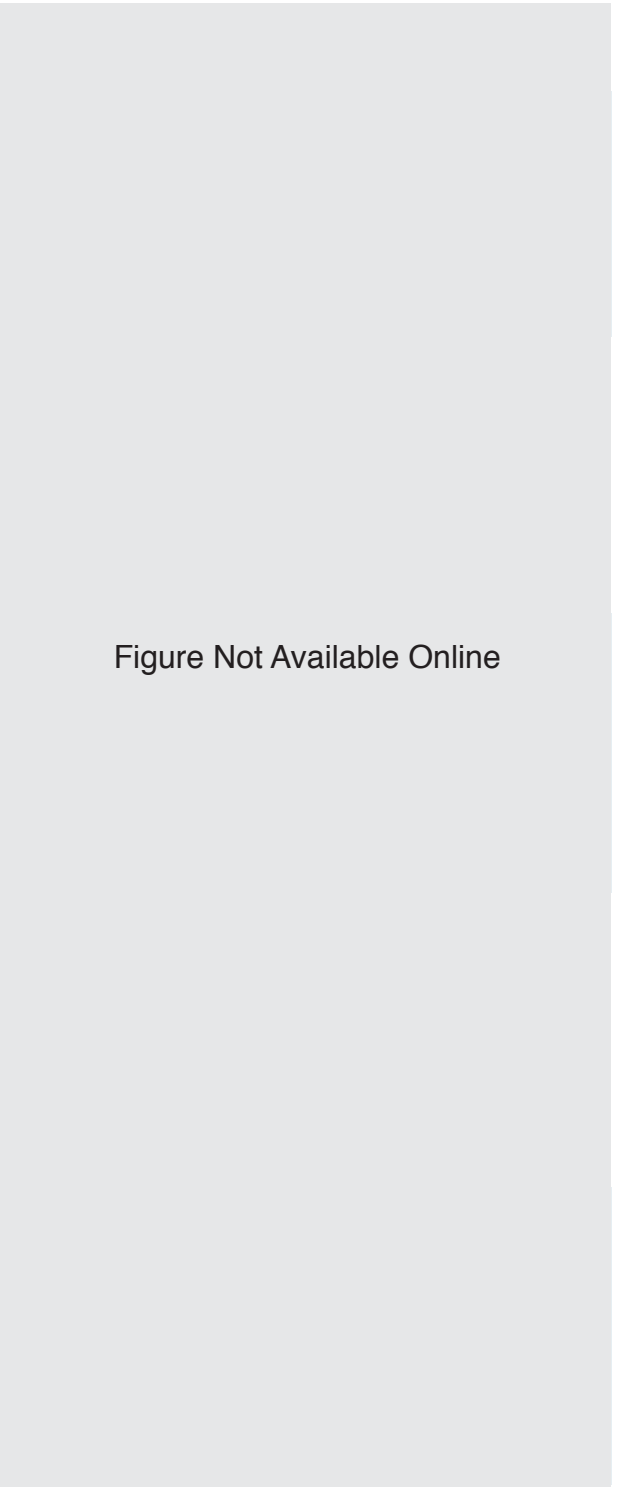

Figure 4. Cutaneous tolerability mean scores (scale 0–3) for erythema (A), scaling (B), stinging(C), itching (D), and burning (E). Asterisk indicates differences between test products were not statistically significant. Reprinted with permission from Thiboutot D, Zaenglein A, Weiss J, et al. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% for the once-daily treatment of moderate to severe acne vulgaris: assessment of efficacy and safety in 2813 patients. *J Am Acad Dermatol.* 2008;59:792-800.[13]

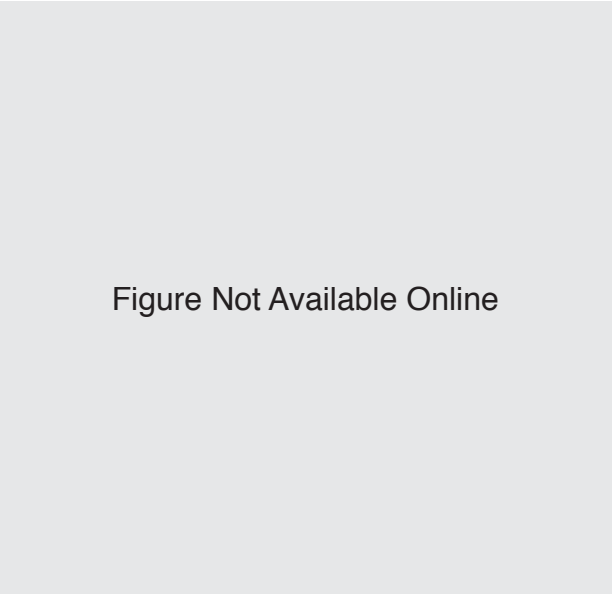

Figure 5. In vitro percutaneous absorption. Asterisk indicates differences between test products were not statistically significant. Reprinted from Bucks D, Yu K, Angel A, et al. Can delivery be enhanced and skin irritation minimized using a lower concentration of benzoyl peroxide in a fixed combination product? Poster presented at: 67th Annual Meeting of the American Academy of Dermatology; March 6, 2009; San Francisco, CA. P717.[15]

The favorable efficacy and tolerability profile of CDP 1.2% and BPO 2.5% gel was achieved with the development of an aqueous gel formulation that could deliver BPO levels into the skin comparable to fixed combination products containing BPO 5% without the need for surfactants, alcohol, or preservatives that could potentially act as skin irritants.[14] An in vitro percutaneous absorption study demonstrated that the absorption of BPO in human skin from the CDP 1.2% and BPO 2.5% gel, measured as benzoic acid, was comparable to that with commercially available fixed combination preparations containing BPO 5% (Figure 5).[15] These bioavailability results suggest that the CDP 1.2% and BPO 2.5% gel might provide comparable efficacy to fixed combination products containing 5% concentrations of BPO; however, comparative clinical studies would need to be carried out to confirm this.[14]

The availability of CDP 1.2% and BPO 2.5% gel, an effective and well-tolerated fixed combination of CDP 1.2% and BPO 2.5% for the treatment of both inflammatory and noninflammatory lesions, is a welcome addition to the topical armamentarium used to manage moderate to severe acne vulgaris.

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