A New, Once-daily, Optimized, Fixed Combination of Clindamycin Phosphate 1.2% and Low-concentration Benzoyl Peroxide 2.5% Gel for the Treatment of Moderate-to-Severe Acne

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ABSTRACT

The treatment of acne with combination therapy is commonplace with treatment aimed at sustained efficacy with minimal side effects, maximum adherence, and the avoidance of bacterial resistance. Combinations containing clindamycin and benzoyl peroxide have been shown to be effective, but the irritation caused by the concentration of benzoyl peroxide 5% in the more commonly used, fixed combinations can be limiting. In addition, surfactants, preservatives, and high levels of organic solvents, including alcohols, often used in combination with benzoyl peroxide, are potential irritants. An optimized formulation of clindamycin and benzoyl peroxide using a lower concentration of benzoyl peroxide (clindamycin–benzoyl peroxide 2.5% gel) has been developed without the use of surfactants or alcohol. It was recently introduced for the once-daily treatment of inflammatory and noninflammatory lesions in moderate-to-severe acne. Following a clinical program that studied more than 2,800 patients, clindamycin-benzoyl peroxide 2.5% was found to be highly effective and well tolerated. This review highlights the development of clindamycin-benzoyl peroxide 2.5% gel and the data from clinical trials.(*J Clin Aesthetic Dermatol.* 2009;2(5):44–48.)

Acne vulgaris affects 40 to 50 million people in the United States.[1] Current evidence suggests it is a result of increased sebum production, follicular hyperkeratinization, and 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.

Two commonly used topical acne medications are clindamycin and benzoyl peroxide (BPO). Clindamycin improves acne by reducing the levels of *P. acnes* and decreasing inflammation.[3] BPO is a safe and effective agent and 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] A small subset of patients can also have allergic contact dermatitis in response to BPO.[9]

In addition, surfactants, preservatives, and high levels of organic solvents, including alcohols, often used in combination with BPO, are potential irritants on their own.[10,11] Alcohols and surfactants disrupt membrane lipid bilayers of the epidermal barrier, which affect the permeability barrier leading to xerotic conditions and can also result, with chronic use, in epidermal cytotoxicity and increased irri-

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tancy.[10,12] Preservatives are sensitizing in a subset of the patient population.[13]

DEVELOPMENT OF CLINDAMYCIN-BPO 2.5% GEL

A new, fixed combination of clindamycin phosphate 1.2% and low concentration BPO 2.5% (clindamycin-BPO 2.5%, Acanya™ Gel, Arcutis Pharmaceuticals, Redwood City, California) aqueous gel formulation that does not contain any preservatives, parabens, or surfactants has recently been developed and optimized through *in-vivo*, human-irritation testing and *in-vitro*, human-skin permeation studies. Reducing the concentration of BPO from 5% to 2.5% in this optimized formulation resulted in a 33-percent reduction in mean irritation scores in normal healthy volunteers (Figure 1).[10] Any further reduction in BPO concentration afforded minimal additional benefits in skin irritation scores, and the efficacy benefits of the combination would potentially be compromised.[10]

A low concentration of BPO is generally recommended when initiating treatment to minimize local side effects.[15] Previous clinical studies have shown that a lower concentration of BPO (2.5%) was as effective as higher concentrations (5% and 10%) in reducing inflammatory lesions with a low frequency and severity of skin irritation and allergic reactions.[16,17] However, these studies may not have been powered adequately to detect a statistical difference between BPO 2.5% versus 5% and 2.5% versus 10%. The more recent data support the view that a fixed combination of clindamycin-BPO that uses a low concentration of 2.5% BPO could be optimal provided the formulation is optimized.[14]

Two concerns relating to the use of a low concentration of BPO (2.5%) might be a diminishing, beneficial effect of BPO on *P. acnes* and reduced efficacy of the combination product in treating acne. It has been shown that BPO 2.5% significantly reduced *P. acnes* counts after one week of topical application to the face.[12] In addition, a recent, *in-vitro*, percutaneous-penetration study showed that clindamycin-BPO 2.5% gel achieved comparable skin penetration of BPO to clindamycin-BPO combination products containing higher concentrations of BPO (5%) (Figure 2).[14] These data suggest that clindamycin-BPO 2.5% gel may provide comparable efficacy in treating acne without the troublesome skin irritation seen with higher doses of BPO, but comparative clinical trials are needed to confirm this assertion.

Successful management of acne includes targeting multiple pathogenic factors, providing sustained efficacy using treatment regimens with minimal side-effects, maximizing adherence, avoiding bacterial resistance, and educating patients.[18,19] Patients can often have unrealistic expectations of therapy, and together with the impact of poor tolerability, low adherence can result.[19,20] In addition, improved adherence and patient outcomes, including quality-of-life benefits, are correlated with once-daily medications.[21,22] Effective, once-daily therapies demonstrating early signs of improvement that are well tolerated with lower skin irritation may provide improved adherence and therefore yield significantly improved clinical outcomes.[23]

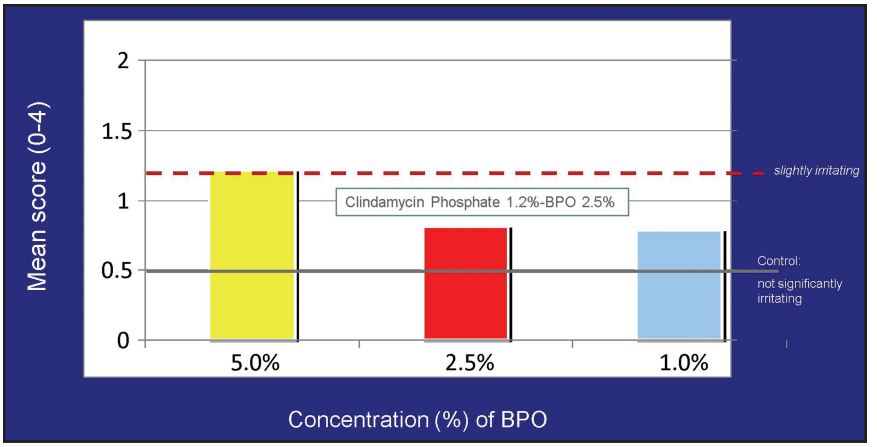

Figure 1. Twenty-one day cumulative irritation study in human volunteers

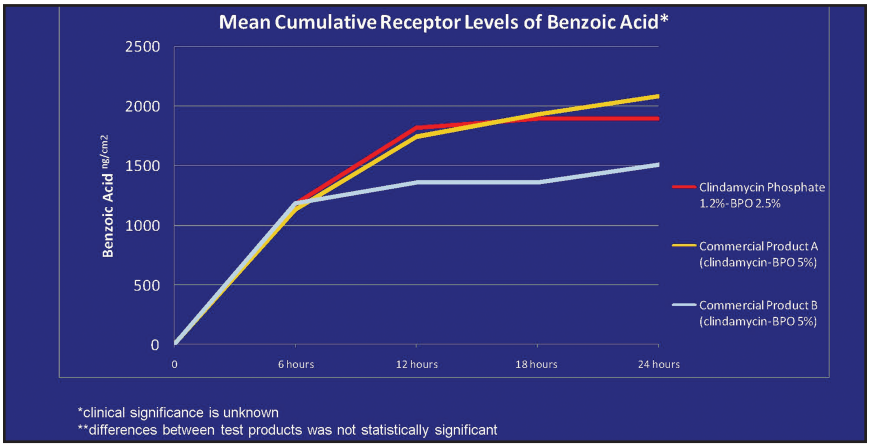

Figure 2. *In-vitro* percutaneous absorption

EFFICACY AND TOLERABILITY OF CLINDAMYCIN-BPO 2.5% GEL

The efficacy and safety of once-daily clindamycin-BPO 2.5% gel has been evaluated in two identical Phase III studies in a total of 2,813 patients with moderate-to-severe acne.[24]

Clindamycin-BPO 2.5% gel was compared with the individual active ingredients (clindamycin phosphate 1.2% and BPO 2.5%) and vehicle over 12 weeks. Clindamycin-BPO 2.5% gel demonstrated statistically superior efficacy over both active ingredients and vehicle for inflammatory, noninflammatory, and total lesion reduction.

After 12 weeks of treatment, inflammatory-lesion counts were reduced by a median of 64.1 percent with

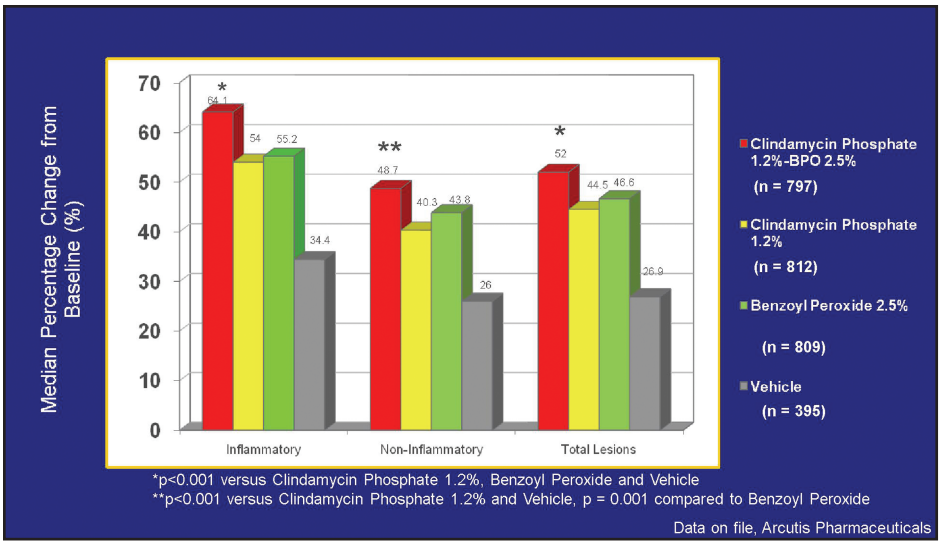

Figure 3. Median percent reduction in lesion count (Week 12)

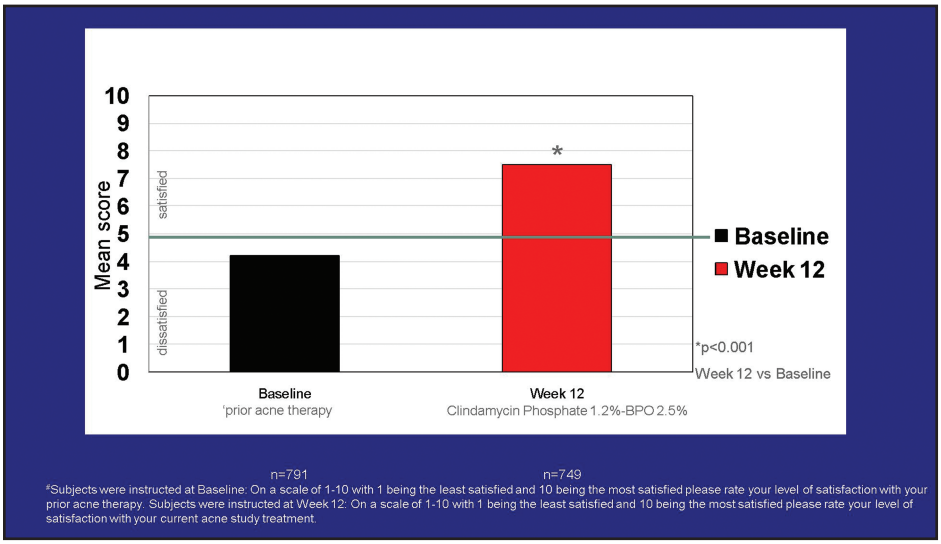

Figure 4. Patient satisfaction survey

clindamycin-BPO 2.5% gel and noninflammatory-lesion counts by a median of 48.7 percent, compared to 54.0-percent and 40.3-percent median reductions with clindamycin phosphate gel ($p<0.001$), 55.2 percent and 43.8 percent with BPO 2.5% gel ($p<0.001$ and $p=0.001$, respectively), and 34.4 percent and 26.0 percent with vehicle gel, respectively ($p<0.001$). Total lesion counts were reduced by a median of 52.0 percent with clindamycin-BPO 2.5% gel compared to 44.5 percent with clindamycin gel, 46.6 percent with BPO 2.5% gel, and 26.9 percent with vehicle gel (all $p<0.001$) (Figure 3).[25]

Treatment success was defined as at least a 2-grade improvement in global severity by the Evaluator Global Severity Score (EGSS)—the EGSS was evaluated on a static scale ranging from 0 (clear) to 5 (very severe). More than one-third of subjects (34.9%) on clindamycin-BPO 2.5% gel were judged to be "treatment successes" by the investigators compared to 16.5 percent on vehicle gel ($p<0.001$).[24] The percent of subjects' acne being "clear" or "almost clear" was also determined. The percent of subjects who were judged as "clear" or "almost clear" by the investigators represented at least a 2-grade improvement in EGSS in subjects who had moderate acne at Baseline and at least a 3-grade improvement in EGSS in the subjects who had severe acne at Baseline. Almost 20 percent of the subjects enrolled in the Phase III studies had severe acne at Baseline. At Week 12, 28.6 percent of subjects were determined as "clear/almost clear" of their acne compared to 12.6 percent on vehicle ($p<0.001$).[24]

In clinical practice, patient expectation of and satisfaction with their acne therapy is an important aspect of management. Subject evaluations of acne improvement were collected using a Subject Self Assessment (SSA) 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 subjects on clindamycin-BPO 2.5% gel (39.2%) judged their acne to be "clear/almost clear" at Week 12 compared to 16.6 percent on vehicle gel ($p<0.001$).[24] Patients can often have unrealistic expectations of therapy. Previous studies have shown that patients expect to see improvements in their acne within one month and even those with severe acne would expect to see improvement within eight weeks.[26,27] What is encouraging in this very large study is that the finding that subjects who reported that their acne was "clear/almost clear" was statistically significantly superior to vehicle as early as Week 2 ($p=0.002$).[24]

Subject satisfaction was assessed at Baseline and Week 12. At Baseline, subjects were given the following instructions: "On a scale of 1 to 10, with 1 being the least satisfied and 10 being the most satisfied, please rate your level of satisfaction with your prior acne therapy." At Week 12, subjects were given the following instructions: "On a scale of 1 to 10, with 1 being the least satisfied and 10 being the most satisfied, please rate your level of satisfaction with your current acne study treatment." In the *post-hoc* analysis, subjects with a Baseline score of 5 or less were considered dissatisfied with their prior acne therapy and subjects with a score of 6 to 10 were considered satisfied with their prior acne therapy. Subjects with a Week-12 score of 5 or less were considered dissatisfied with their current acne study treatment and subjects with a score of 6 to 10 were considered satisfied with their current acne study treatment.

At Baseline, subjects randomized to receive clindamycin-BPO 2.5% gel had a mean satisfaction score of 4.2 (dissatisfied) with prior acne therapies. At Week 12, these subjects had a mean score of 7.5 (satisfied), which was statistically significant compared to Baseline (p<0.001, Week 12 versus Baseline). Therefore, subjects were significantly more satisfied with clindamycin-BPO 2.5% gel than prior acne therapies (Figure 4).[28] In addition, 81.2 percent of clindamycin-BPO 2.5% gel subjects were satisfied with their treatment at Week 12 (Figure 5).[28] An example of the beneficial effects of clindamycin-BPO 2.5% can be seen in Figure 6, where a patient with severe acne (EGSS 4) was treated with clindamycin-BPO 2.5% for 12 weeks. At Week 12, the EGSS score was 2 (mild acne).

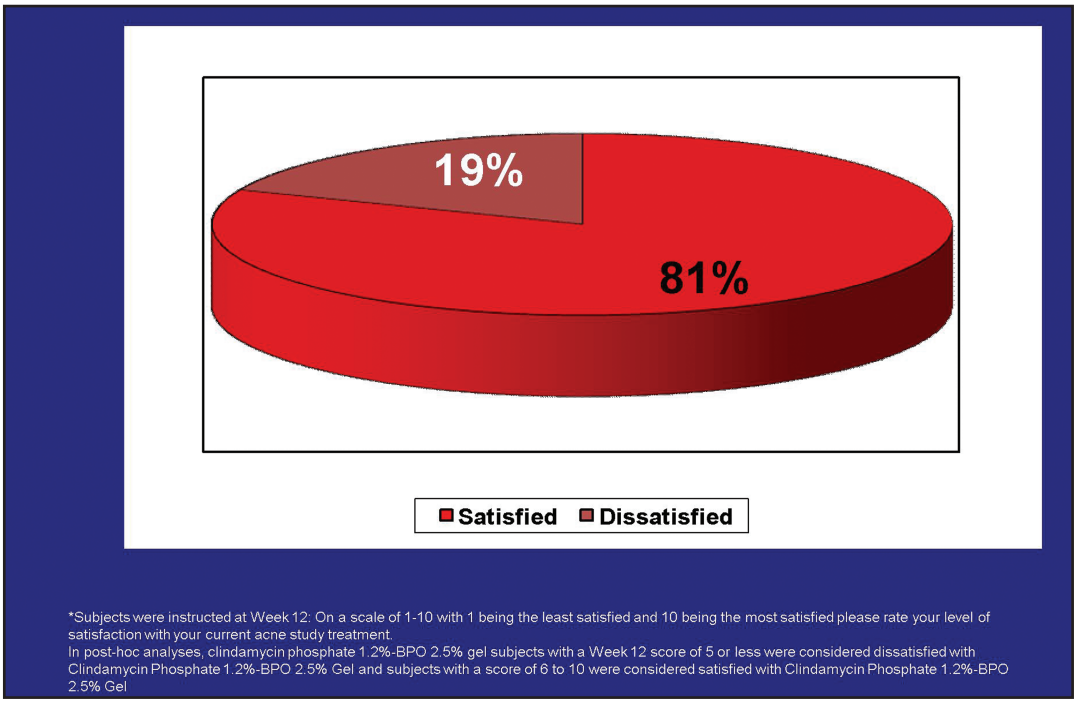

Figure 5. Patient satisfaction survey

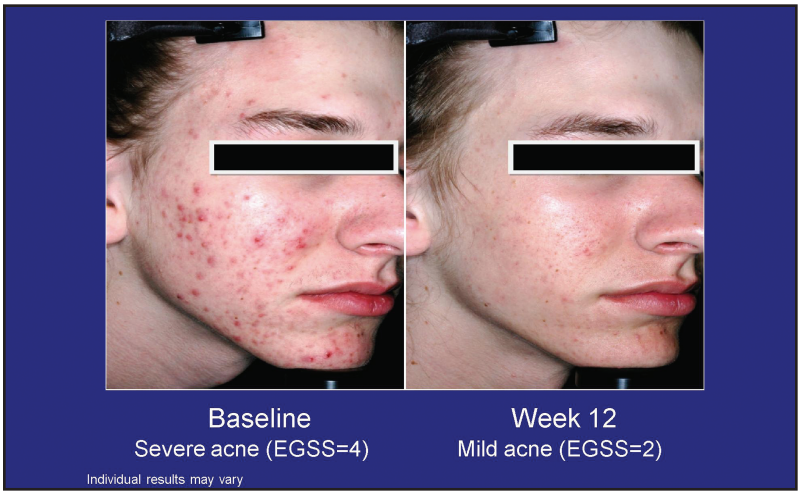

Figure 6. Nineteen-year-old patient with severe acne at Baseline (EGSS = 4) as seen in the photo on the left. Patient was treated with clindamycin phosphate 1.2%-BPO 2.5% aqueous gel once daily for 12 weeks. The patient had mild acne at Week 12 (EGSS = 2) as seen in the photo on the right.

Clindamycin-BPO 2.5% gel was also associated with a low incidence of treatment-related adverse events. The incidence of adverse drug reactions was low and similar across all treatment groups (5.9% for clindamycin-BPO 2.5% gel versus 6.1% for vehicle based on the number of events). The majority (≥97%) were "mild" to "moderate" in severity.[24] Application-site reactions with clindamycin-BPO 2.5% gel were rare (0.1%) and only one patient discontinued due to application-site pain and irritation. Cutaneous tolerability assessments for erythema, scaling, burning, itching, and stinging were performed. No patient on clindamycin-BPO 2.5% gel discontinued treatment because of local signs or symptoms of erythema, scaling, burning, itching, or stinging, and in no patient were these severe. Mean scores for each local sign/symptom were <1 (1=mild) and comparable to individual active ingredients and vehicle.[24]

CONCLUSION

The favorable efficacy and tolerability profile of clindamycin-BPO 2.5% aqueous gel was achieved with the development of a unique formulation that could deliver BPO without the need for surfactants, alcohol, or preservatives that could potentially act as skin irritants. An *in-vitro* percutaneous absorption study demonstrated that the absorption of BPO in human skin from clindamycin-BPO 2.5% gel, measured as benzoic acid, was comparable to that with commercially available fixed-combination preparations containing 5% BPO and clindamycin. These bioavailability results suggest that clindamycin-BPO 2.5% gel might provide comparable efficacy to fixed combination products containing 5% concentrations of BPO; however, comparative clinical studies are needed.[29]

The availability of clindamycin-BPO 2.5% (Acanya™ Gel)—an effective and well-tolerated, fixed combination of clindamycin phosphate 1.2% and BPO 2.5% for the treatment of both inflammatory and noninflammatory lesions of acne—is a welcome addition to the topical armamentarium used to manage moderate-to-severe acne vulgaris.

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