A 3-Step Acne System Containing Solubilized Benzoyl Peroxide Versus Clindamycin–Benzoyl Peroxide

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A 3-step acne system has been developed to enhance the bioavailability and follicular penetration of benzoyl peroxide (BPO). Participants with mild to moderate facial acne vulgaris were randomly assigned to 10 weeks' facial treatment with the 3-step acne system (proprietary salicylic acid cleanser 2% twice daily, proprietary salicylic acid toner 2% once daily, and solubilized BPO gel 5% twice daily) or with control cleanser twice daily plus clindamycin 1%–BPO 5% gel (jar formulation) twice daily. Among 139 participants enrolled, the 3-step acne system was at least as effective as clindamycin-BPO in reducing noninflammatory lesion counts in the early weeks of treatment in the absence of an antibiotic (mean reductions were 27% vs 13%, 39% vs 25%, 40% vs 33%, and 42% vs 42% at weeks 2, 4, 6, and 10, respectively)(all not significant). Both regimens were associated with comparable reductions in inflammatory lesion counts at all time points. Both regimens also were generally well-tolerated with mean scores for erythema, dryness, peeling, burning/stinging, and itching less than mild in both groups at all time points. The 3-step acne system is at least as effective as clindamycin-BPO in reducing noninflammatory lesion counts in the early weeks of treatment in the absence of an antibiotic, which is likely attributed to the solubilized BPO formulation.

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Benzoyl peroxide (BPO) can be highly effective in the treatment of both comedonal (noninflammatory) and inflammatory acne.[1] Importantly, it has a key advantage over antibiotics in that it is not associated with the development of antibacterial resistance in *Propionibacterium acnes*

or other bacteria.[2-4] However, BPO is poorly water soluble and can be difficult to stabilize in vehicles with high water content. This can facilitate aggregation of crystalline clusters that can reduce both bioavailability and follicular penetration. Furthermore, prior attempts to enhance the solubility of BPO using different solvents have been hindered by stability challenges.[5] In an attempt to circumvent treatment issues resulting from poor solubility, many commercial BPO products are formulated as oil-in-water emulsions. These formulations consist of macrocrystals and microcrystals of various sizes, some too large to penetrate the follicular opening, suspended in a water-based emulsion.

The mean diameter of a hair follicle on the surface of the forehead has been reported to be 66 μm, with the hair shaft having a mean diameter of approximately 17 μm.[6] In comparison, an evaluation of BPO clusters in a sample of 3 commercially available BPO formulations revealed their diameters to be 5 to 50 μm, 10 to 100 μm, and 50 to 100 μm, respectively.[7]

The combined effect of the above-mentioned factors—poor BPO water solubility and inaccessible BPO trapped in the interior of clusters in a water-based emulsion vehicle—pose a therapeutic challenge, especially when trying to optimize efficacy.

However, using Soluzyl Technology™, a novel solubilized formulation of BPO has been developed that is stable. This technology has allowed the production of a homogeneous solution of BPO molecules with a diameter of approximately 0.0001 μm, which facilitates enhanced bioavailability and maximizes follicular penetration. Early research has demonstrated that this formulation penetrates the skin more readily than commercial formulations containing BPO and achieves relatively greater bactericidal activity, both on the surface of the skin and in follicles.[8] Therefore, it is possible that this formulation also could enhance the clinical efficacy of BPO. Early clinical data have shown that a 5% formulation of the solubilized BPO may result in a greater mean reduction in noninflammatory lesion counts in the early weeks of treatment than a combination antibiotic-BPO product. In addition, the solubilized BPO 5% formulation has been shown to result in a comparable reduction in inflammatory lesion counts relative to the combination antibiotic-BPO product.[9]

This solubilized BPO 5% formulation is available as part of a 3-step acne system. For patients with normal to oily skin, solubilized BPO 5% is formulated as a gel and is designed to be used in conjunction with a proprietary salicylic acid cleanser 2% and a proprietary salicylic acid toner 2%. For patients with normal to dry skin, solubilized BPO 5% is formulated as a lotion and is designed to be used in conjunction with a gentle nonsoap cleanser and a noncomedogenic therapeutic moisturizer containing 20% glycerin and 1% dimethicone.[10]

Results from a study evaluating the 3-step acne system for normal to dry skin have been previously presented.[11] We report the results from a study evaluating the 3-step acne system for normal to oily skin in a larger group of participants and over a longer time span than prior studies.

Methods

Participants—Participants aged 12 to 45 years were eligible for enrollment in the study if they had mild to moderate facial acne vulgaris (10–100 noninflammatory lesions; 17–60 inflammatory lesions; ≤2 nodulocystic lesions on the face, excluding the nose) and were willing to refrain from excessive sun exposure; use of tanning beds; and use of any nonstudy acne medications, moisturizers, sunscreens, fragrances, or aftershaves. Females of childbearing potential were required to have a negative urine pregnancy test result and to use an acceptable method of contraception throughout the study.

No participants were allowed to enter the study if they were using other medicated products on their face or had used a medicated facial cleanser in the preceding week; a topical α-hydroxy acid or antiacne medication in the preceding 2 weeks; a topical retinoid, topical or systemic antibiotic, or topical or systemic steroid in the preceding 4 weeks; estrogen/birth control pills for less than 3 months immediately before the baseline visit; or systemic retinoids in the preceding 6 months. Other exclusion criteria included participation in an investigational study in the preceding 30 days; having received a facial cosmetic procedure (eg, laser resurfacing, chemical peel, dermabrasion) in the preceding 6 months; allergy to BPO, clindamycin, lincomycin, salicylic acid, sunscreens, or substances to be used in the study; uncontrolled systemic disease; infection with human immunodeficiency virus; a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis; a beard or sideburns that could interfere with study evaluations; and pregnancy, breastfeeding, or planning of a pregnancy during the study. The study was approved by the relevant institutional review boards. All adult participants signed informed consent and participants younger than 18 years signed an assent for the study with informed consent signed by a parent or legal guardian.

Treatment Regimen—Participants were randomly assigned in a 1:1 ratio to 10 weeks of facial treatment with either the 3-step acne system for normal

to oily skin or clindamycin-BPO treatment. The participants assigned to the 3-step acne system group were instructed to apply the proprietary salicylic acid cleanser 2% twice daily, the proprietary salicylic acid toner 2% once daily, and the solubilized BPO gel 5% twice daily. The participants in the clindamycin-BPO group were instructed to use the control cleanser twice daily and apply the clindamycin 1%–BPO 5% gel (jar formulation) twice daily.

All participants were provided with a moisturizer and sunscreen for use on an as-needed basis.

Outcome Measures—Efficacy was assessed as reductions in noninflammatory (open and closed comedones) and inflammatory (papules, pustules, and nodules/cysts) lesion counts. Tolerability was assessed in terms of erythema, dryness, peeling, burning/stinging, and itching using a 4-point scale (Table) both in the overall study population and in the subgroup of participants with Fitzpatrick skin types I or II. Efficacy was assessed at baseline and weeks 2, 4, 6, and 10, and tolerability was assessed at baseline and weeks 1, 2, 4, 6, and 10. All assessments were evaluated by a blinded investigator or blinded expert grader, except burning/stinging and itching for which the participants were asked for their grading.

Statistical Analyses—The determination of sample size was not based on a power analysis, but the size was expected to be large enough to show a clinical difference between treatments. The data were analyzed using SAS® software. The 2-tailed tests were considered statistically significant at $\alpha=.05$.

Between-group differences were analyzed using a 2-tailed χ^2 test or Fisher exact test for gender and race; a 2-tailed *t* test or Wilcoxon rank sum test for age and baseline lesion counts; Wilcoxon rank sum test for Fitzpatrick skin type and mean tolerability scores; and analysis of covariance or Wilcoxon rank sum test for percentage change from baseline in lesion counts.

Results

Participants—A total of 139 participants were enrolled (69 assigned to 3-step acne system, 70 assigned to clindamycin-BPO); 128 participants (92%) completed the study. The primary reason for premature discontinuation was reported to be lack of efficacy (clindamycin-BPO, 1 participant), voluntary withdrawal (clindamycin-BPO, 4 participants; 3-step acne system, 3 participants), pregnancy (3-step acne system, 1 participant), and other (1 participant in each group).

Most participants were white (79%); female (64%); and had Fitzpatrick skin types II, III, or IV (23%, 35%, and 27%, respectively). The mean age was 20 years (range, 12.4–45.7 years), with a mean of 52 noninflammatory and 28 inflammatory

Tolerability Assessments

Score	Erythema	Dryness	Peeling	Burning/Stinging	Itching
0 (none)	No erythema present (may be minor discoloration)	No dryness present	No peeling present	No burning/ stinging	No itching
1 (mild)	Light pink, noticeable	Slight but definite roughness	Slight peeling	Light warm, tingling sensation; not really bothersome	Occasional, slight itching
2 (moderate)	Pink-red, easily noticeable	Moderate roughness	Definitely noticeable peeling	Definite warmth, tingling/stinging sensation that is somewhat bothersome	Constant or intermittent itching that is somewhat bothersome
3 (severe)	Deep or bright red, may be warm to the touch	Marked roughness	Extensive peeling	Hot tingling/stinging sensation that is disturbing normal activity	Bothersome itching that is disturbing normal activity

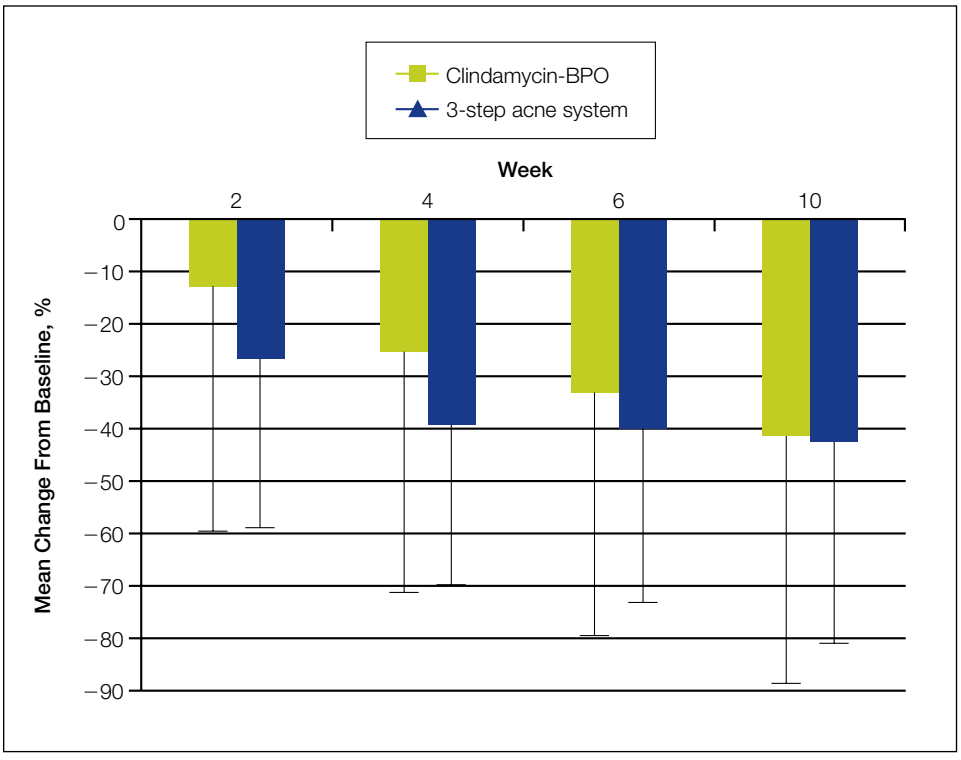

Figure 1. Mean percentage reduction in noninflammatory lesion counts in participants using a 3-step acne system containing solubilized benzoyl peroxide (BPO) gel 5% or a treatment regimen containing clindamycin 1%–BPO 5% gel for facial acne vulgaris. Error bar indicates standard deviation.

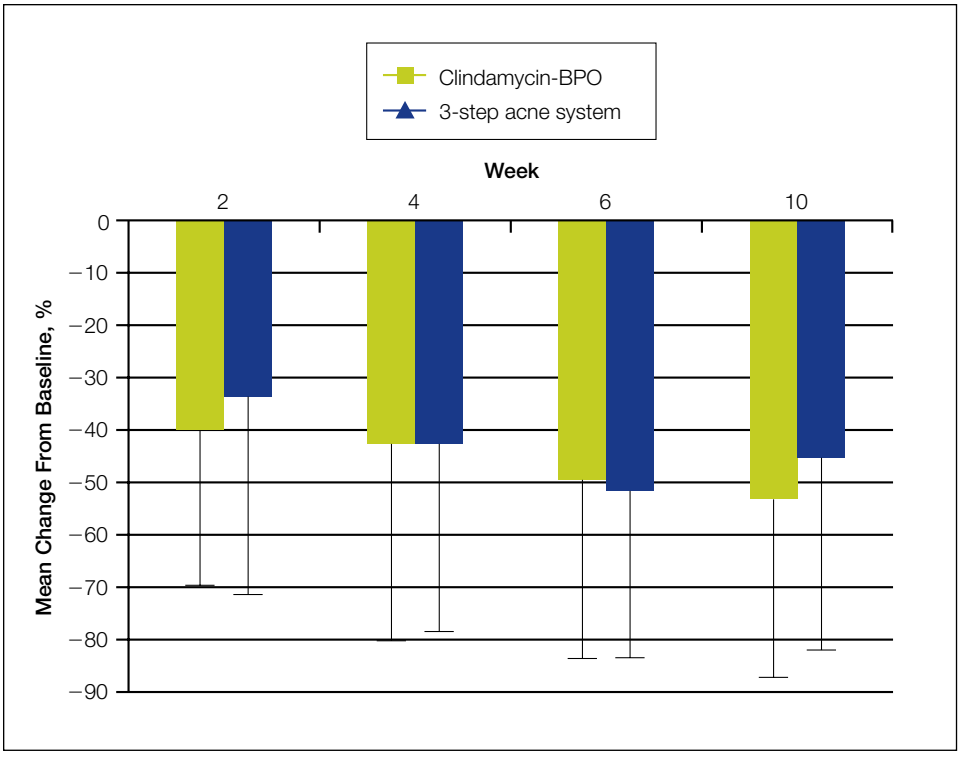

Figure 2. Mean percentage reduction in inflammatory lesion counts in participants using a 3-step acne system containing solubilized benzoyl peroxide (BPO) gel 5% or a treatment regimen containing clindamycin 1%–BPO 5% gel for facial acne vulgaris. Error bar indicates standard deviation.

lesions at baseline. There were no significant between-group differences in any of these parameters at baseline.

Efficacy—The 3-step acne system was associated with a numerically greater reduction in noninflammatory lesion counts than clindamycin-BPO at weeks 2, 4, and 6, with a mean reduction of 27% versus 13%, 39% versus 25%, and 40% versus 33%, respectively, and a comparable reduction at week 10 (42% vs 42%)(Figure 1). Both regimens were associated with comparable reductions in inflammatory lesion counts at all time points (Figure 2).

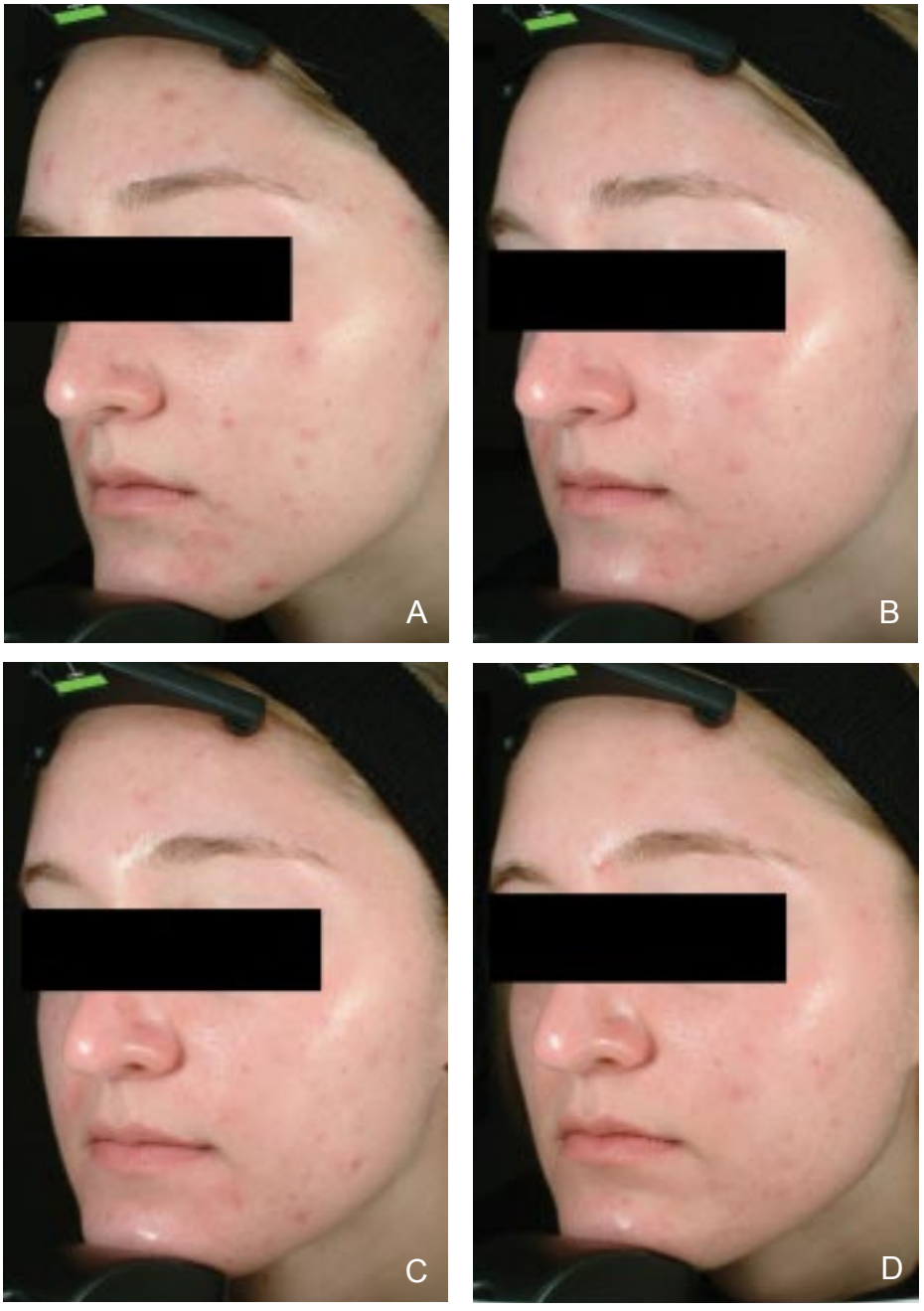

Figure 3. Clinical improvement of facial acne vulgaris in a patient using a 3-step acne system containing solubilized benzoyl peroxide gel 5% (baseline, A; week 2, B; week 4, C; week 10, D).

None of these between-group differences was statistically significant for either noninflammatory or inflammatory lesions. The clinical improvement in acne with the 3-step acne system is demonstrated in Figure 3.

Tolerability—Both regimens generally were well-tolerated with mean scores for erythema, dryness, peeling, burning/stinging, and itching less than mild in both groups at all time points (Figure 4). Mean scores for erythema, dryness, and peeling were comparable between groups at all time points except week 1 when they were transiently significantly higher in the 3-step acne system group than the clindamycin-BPO group ($P \leq .05$, $P \leq .001$, $P \leq .001$, respectively). Mean scores for burning/stinging were significantly higher in the 3-step acne system group than the clindamycin-BPO group at all time points except week 10 (week 1, $P \leq .001$; week 2, $P \leq .001$; week 4, $P \leq .05$; week 6, $P \leq .01$). There were no significant between-group differences in mean scores for itching. Among the subgroup of participants with Fitzpatrick skin types I or II (n=36), the only significant between-group difference in any of the above-mentioned tolerability parameters was burning/stinging at week 1 ($P = .0056$).

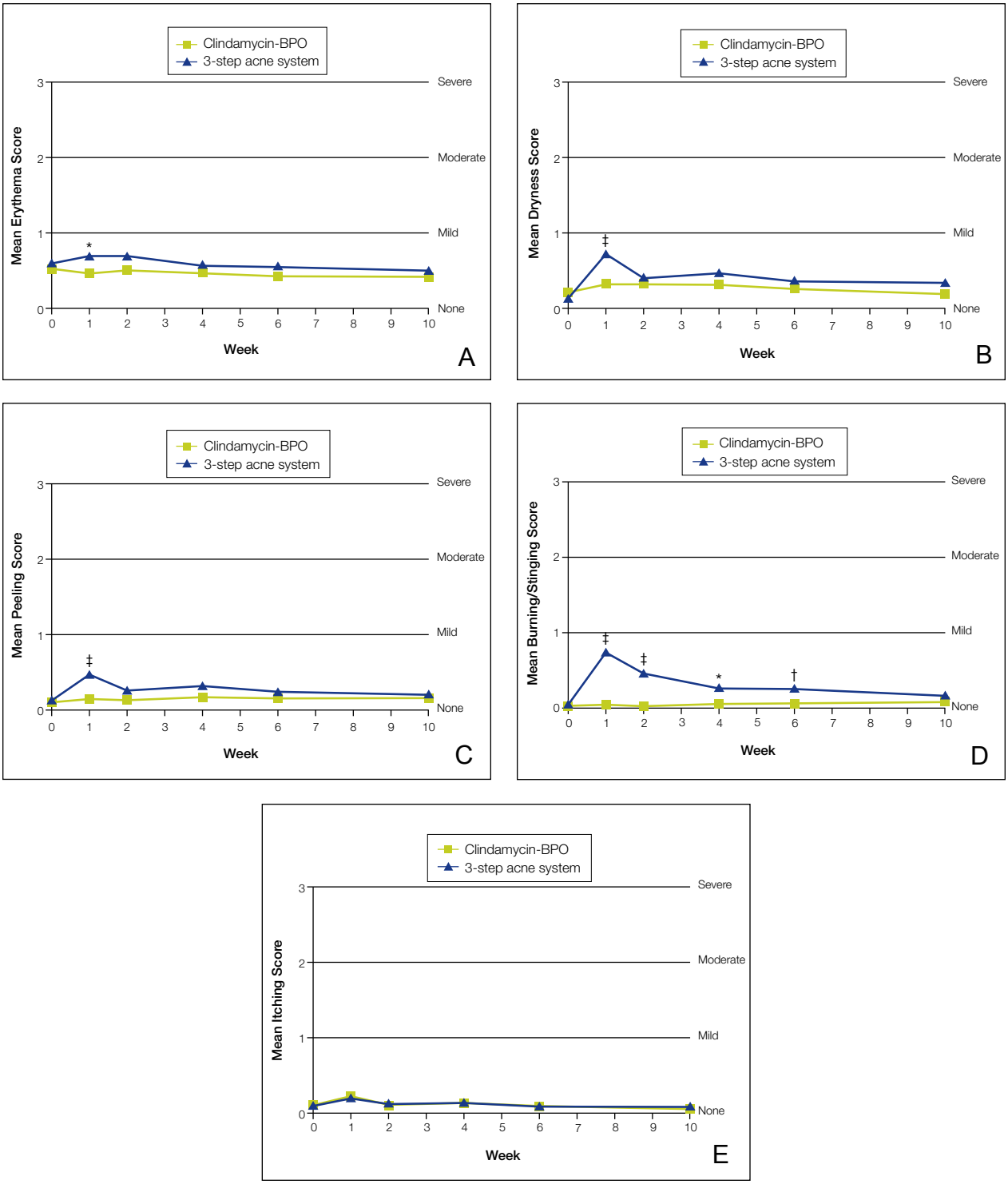

Figure 4. Mean erythema (A), dryness (B), peeling (C), burning/stinging (D), and itching (E) scores in participants using a 3-step acne system containing solubilized benzoyl peroxide (BPO) gel 5% or a treatment regimen containing clindamycin 1%–BPO 5% gel for facial acne vulgaris. Asterisk indicates $P \leq .05$ vs clindamycin-BPO; dagger, $P \leq .01$ vs clindamycin-BPO; double dagger, $P \leq .001$ vs clindamycin-BPO.

Comment

The results of this study highlight the efficacy of the solubilized BPO 5% formulation in reducing noninflammatory lesion counts. The study was not powered to detect statistically significant differences in lesion counts (sample size was not formally calculated, though it was expected to be large enough to show clinical differences), but the early differences in

noninflammatory lesion count reductions appear to be clinically significant in favor of the 3-step acne system compared with clindamycin-BPO. Importantly, the data also suggest that the 3-step acne system may have a more rapid onset of action than clindamycin-BPO. Both treatments resulted in comparable reductions in noninflammatory lesion counts beyond week 6 and at all time points for inflammatory lesion counts.

Both treatments generally were well-tolerated with both groups exhibiting mean scores for erythema, dryness, peeling, and burning/stinging less than mild throughout the study. Although the mean scores for these parameters were initially transiently significantly higher in the 3-step acne system group than the clindamycin-BPO group, the between-group differences lessened rapidly and significance was lost with continued treatment.

The results from this study are consistent with earlier research.[9] Del Rosso[9] reported that the 3-step acne system (not all participants used the proprietary salicylic acid cleanser that is part of the 3-part acne system) was associated with a numerically greater mean reduction in noninflammatory lesion counts than clindamycin-BPO (37% vs 16%, respectively, at week 2 [compared with 27% vs 13% in this study]; and 47% vs 28%, respectively, at week 4 [compared with 39% vs 25% in this study]). Furthermore, both sets of research showed the 2 regimens to be associated with comparable reductions in inflammatory lesion counts and comparable tolerability profiles. In addition, the results of a split-face study by Tanghetti et al[12] showed that the solubilized BPO gel 5% alone resulted in a significantly greater reduction in noninflammatory lesion count at week 1 than clindamycin-BPO ($P \leq .05$). It is likely that the patented solubilized BPO formulation, which incorporates a unique solvent technology, may be responsible for these effects on comedonal acne.

Although both oral and topical antibiotics have been a mainstay in the treatment of acne, their widespread use has contributed to the development of bacterial strains that are resistant to antibiotics. The use of BPO with topical antibiotics helps to reduce but does not fully eliminate the development of antibiotic-resistant bacterial strains,[13] which is a concern because of the propensity of resistance mechanisms to be transferable to a range of other bacteria, including different species and genera.[14,15] Antibiotics used in the treatment of acne already have been shown to increase antibacterial resistance, not only of *P acnes*[16] but also other bacteria such as coagulase-negative staphylococci[15,17] and *Streptococcus pyogenes*.[18] Moreover, the use of antibiotics can have other effects. For example, antibiotic treatment of acne is associated with oropharyngeal colonization with *S pyogenes* (an organism associated with pharyngitis)[18] and may be linked to an increase in the incidence of upper respiratory tract infections.[19] With increasing concerns regarding the development of resistant strains of bacteria such as *Staphylococcus aureus*, there clearly is a need in dermatology for effective acne regimens that do not rely on antibiotics.

The 3-step acne system may represent an effective antibiotic-free approach to treatment for patients with mild to moderate acne that, unlike antibiotic-containing regimens,[3] avoids the need to discontinue or switch treatment once clinical improvement becomes evident. Therefore, patients can continue using the 3-step acne system without interruption for maintenance treatment.

Dermatologists are familiar with the popularity of acne treatment systems among patients. Acne systems can increase treatment adherence by providing patients with a defined routine for skin care and acne treatment that can be followed on a daily basis. However, a variety of factors may impair the bioavailability and follicular penetration of BPO in many commercially available formulations. In contrast, the solubilized BPO in the 3-step acne system facilitates the follicular penetration of BPO, which may enhance its speed of action and its efficacy against noninflammatory acne lesions. This, in turn, may lead to improved patient satisfaction.

Kligman[20] has stated, "No prescription antibiotic can begin to match the antibacterial efficacy of benzoyl peroxide." It is gratifying to know that by revisiting this agent and optimizing its formulation, its usefulness can be enhanced still further even after it has been in common use for decades. Perhaps there are other areas of dermatology to which this concept also may be successfully applied in the future.

Conclusion

The 3-step acne system is an effective antibiotic-free approach to the treatment of acne. Compared with a combination clindamycin-BPO product, the 3-step acne system is at least as effective in reducing noninflammatory lesion counts and may enhance the speed at which these lesions are reduced. The 3-step acne system also demonstrates comparable efficacy against inflammatory lesions and comparable tolerability. Its potential for a more rapid onset of action against noninflammatory lesions is likely attributed to the improved solubilization of BPO, enhancing the bioavailability and follicular penetration of the BPO.

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