Efficacy and Tolerability of Fixed-Combination Acne Treatment in Adolescents

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Acne is common among adolescents and can be difficult to manage. Providing an effective treatment method that offers an early onset of action and a favorable tolerability profile may lead to improved adherence, increased satisfaction, and improved clinical outcomes in this patient population. A post hoc analysis was conducted of 1755 adolescents (age range, 12 to <18 years) with moderate to severe acne who had been enrolled in 2 double-blind, multicenter studies and were randomized to receive either clindamycin phosphate (CP) 1.2%–benzoyl peroxide (BPO) 2.5% gel, CP 1.2%, BPO 2.5%, or vehicle once daily for 12 weeks.

Significantly superior reductions in inflammatory, noninflammatory, and total lesion counts were observed in the CP 1.2%–BPO 2.5% gel group versus the other 3 groups (P≤.002 for all week 12 pairwise comparisons). At week 12, treatment success with CP 1.2%–BPO 2.5% gel was statistically superior to CP 1.2% (P=.004), BPO 2.5% (P=.031), and vehicle (P<.001). Participants observed improvement with CP 1.2%–BPO 2.5% gel treatment as early as week 2, with 31.4% of participants reporting their skin was clear, almost clear, or showed marked improvement. Clindamycin phosphate 1.2%–BPO 2.5% gel was associated with a low incidence of treatment-related adverse events (AEs) and a favorable cutaneous tolerability profile.

Clindamycin phosphate 1.2%–BPO 2.5% gel is an effective, safe, and well-tolerated treatment in adolescents with moderate to severe acne. The once-daily regimen, early signs of improvement, favorable cutaneous tolerability profile, and participant satisfaction may lead to increased adherence and improved clinical outcomes.

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Formulating a therapeutic strategy that aligns with the needs of a specific patient population is the cornerstone of acne management, the goal being combination therapy that targets multiple pathogenic factors of acne. Achieving a balance of good efficacy and acceptable tolerability can be a challenge. Additionally, variations in skin color and cultural practices as well as the attitudes of both patients and their guardians can complicate the clinical picture. Beyond treatment efficacy, physicians also must address a number of factors that can influence treatment success, most importantly adherence. The nature of the treatment regimen (eg, tolerability profile, dosage, vehicle, duration of therapy) can have a profound effect on patient adherence.

Acne is common among adolescents, affecting more than 85% of teenagers.[1] It can appear in children as young as 8 to 10 years of age but typically is more common and severe in adolescents. The prevalence of acne in adolescent boys has been estimated at 81% to 95% compared to 79% to 82% in adolescent girls.[2,3] Acne can cause notable scarring in adolescents and often has considerable social and psychological impacts.[1,4] Studies have linked acne to anxiety, depression, social isolation, interpersonal difficulties, low self-esteem, dissatisfaction with facial appearance, and fewer employment opportunities in adulthood.[4,5] Despite the devastating physical and emotional consequences associated with acne,

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as teenagers gain independence during adolescence, attitudes toward treatment and adherence to the prescribed regimen may be adversely affected.

An effective treatment method that offers an early onset of action and a highly favorable tolerability profile can improve adherence to treatment, patient satisfaction, and overall clinical outcome. Fixed-combination products containing clindamycin phosphate (CP) and benzoyl peroxide (BPO) are widely used for the treatment of acne vulgaris.[6,7] However, a potential limitation of BPO is concentration-dependent dryness and irritation that may impact patient compliance and limit product use.[8] One option is to use fixed combinations of CP and BPO with lower concentrations of BPO. The clinical efficacy and tolerability of CP 1.2%–BPO 2.5% gel in adult patients with moderate to severe acne previously has been reported in the literature.[9-15] This study specifically evaluated its use in treating adolescent acne.

METHODS

Study Population

A post hoc analysis was conducted of 1755 adolescents (age range, 12 to <18 years) with moderate to severe acne who were enrolled in 2 randomized, double-blind, multicenter studies and were treated with either CP 1.2%–BPO 2.5% combination gel, CP 1.2%, BPO 2.5%, or vehicle once daily for 12 weeks. Participants were stratified by Fitzpatrick skin type and acne severity (evaluator global severity score [EGSS], ranging from 0 [clear] to 5 [very severe]). The study group included male and female adolescents of any race or ethnicity who presented with 17 to 40 inflammatory lesions (papules, pustules, and nodules), 20 to 100 noninflammatory lesions (open and closed comedones), and 2 or fewer nodules. A washout period was required for participants who were currently using prescription and over-the-counter acne treatments including topical astringents and abrasives (1 week), topical antiacne products (eg, soaps containing antimicrobials and known comedogenic products)(2 weeks); topical retinoids, retinol, and systemic acne treatments (4 weeks); and systemic retinoids (6 months).

Efficacy Evaluation

Inflammatory, noninflammatory, and total lesion counts from the forehead, cheeks, nose, and chin, as well as EGSS, were evaluated at baseline and weeks 4, 8, and 12. Participant self-assessments also were conducted at baseline and weeks 4, 8, and 12, at which point participants rated their acne severity relative to baseline on a scale ranging from 1 (clear) to 7 (worse). Participant satisfaction was evaluated on a scale ranging from 1 (least satisfied) to 10 (most satisfied) relative to results of prior acne therapies and current study treatment at week 12; participants were considered dissatisfied (score of 1–5) or satisfied (score of 6–10).

Safety Evaluation

Cutaneous safety (ie, erythema, scaling) and tolerability (ie, itching, burning, stinging) were evaluated at each study visit on a scale of 0 (none) to 3 (severe). Safety also was evaluated through reported adverse events (AEs).

Statistical Analysis

The randomized intention-to-treat population comprised all 1755 participants who were enrolled. The safety population included all randomized participants presumed to have used the study medication at least once and provided at least one postbaseline evaluation (N=1695).

Coprimary comparative efficacy end points included absolute change from baseline to week 12 in inflammatory and noninflammatory lesions as well as improvement of 2 or more grades in the EGSS. Supportive analyses of percentage changes in inflammatory and noninflammatory lesion counts and absolute as well as percentage changes in total lesion counts also were conducted. The number of participants who reported that their acne was clear or almost clear at week 12 was evaluated in a post hoc analysis.

Coprimary analysis of the dichotomized EGSS was based on pairwise tests using a logistic regression with factors of treatment, analysis center, and stratification variables (ie, dichotomized skin type, baseline acne severity). Tests of superiority for lesion count analyses were based either on an analysis of covariance or on ranked data submitted to an analysis of covariance.

All missing efficacy data, with the exception of the participant self-assessment, were imputed using the last-observation-carried-forward method. The number of participants who reported that their acne was clear or almost clear at week 12 was evaluated using logistic regression. Adverse events were recorded and classified using Medical Dictionary for Regulatory Activities (MedDRA) terminology. Descriptive statistics were used to summarize cutaneous safety and tolerability scores at baseline and weeks 4, 8, and 12.

RESULTS

Baseline Characteristics

A randomized group of 1755 adolescent participants received treatment with either CP 1.2%–BPO 2.5%

Analysis of Participant Demographics and Baseline Characteristics by Treatment Group

Treatment Variable	CP 1.2%–BPO 2.5% (n=493)	CP 1.2% (n=495)	BPO 2.5% (n=522)	Vehicle (n=245)	Total (N=1755)
Age, y					
Mean	15.4	15.6	15.3	15.3	15.4
Median	15.4	15.6	15.3	15.5	15.4
Range	12.1–18.0	12.1–18.0	12.0–18.0	12.2–18.0	12.0–18.0
Gender, n (%)					
Male	300 (60.9)	306 (61.8)	284 (54.4)	160 (65.3)	1050 (59.8)
Female	193 (39.1)	189 (38.2)	238 (45.6)	85 (34.7)	705 (40.2)
Ethnicity, n (%)					
Hispanic/Latino	61 (12.4)	74 (14.9)	74 (14.2)	34 (13.9)	243 (13.8)
Not Hispanic/Latino	432 (87.6)	421 (85.1)	448 (85.8)	211 (86.1)	1512 (86.2)
Race, n (%)[a]					
White	405 (82.2)	413 (83.4)	412 (78.9)	198 (80.8)	1428 (81.4)
Black/African American	62 (12.6)	59 (11.9)	89 (17.0)	32 (13.1)	242 (13.8)
Native Hawaiian/Pacific Islander	2 (0.4)	0 (0)	3 (0.6)	2 (0.8)	7 (0.4)
Asian	9 (1.8)	13 (2.6)	11 (2.1)	7 (2.9)	40 (2.3)
American Indian/Alaskan native	4 (0.8)	5 (1.0)	1 (0.2)	3 (1.2)	13 (0.7)
Other	18 (3.7)	12 (2.4)	15 (2.9)	9 (3.7)	54 (3.1)
Evaluator global severity score, n (%)					
Moderate	395 (80.1)	391 (79.0)	431 (82.6)	196 (80.0)	1413 (80.5)
Severe	98 (19.9)	104 (21.0)	91 (17.4)	49 (20.0)	342 (19.5)
Median lesion count					
Inflammatory	26.0	26.0	25.0	26.0	26.0
Noninflammatory	48.0	44.0	45.0	42.0	45.0
Total	74.0	74.0	71.0	70.0	73.0

Abbreviations: CP, clindamycin phosphate; BPO, benzoyl peroxide.
[a]Participants were able to report multiple races.

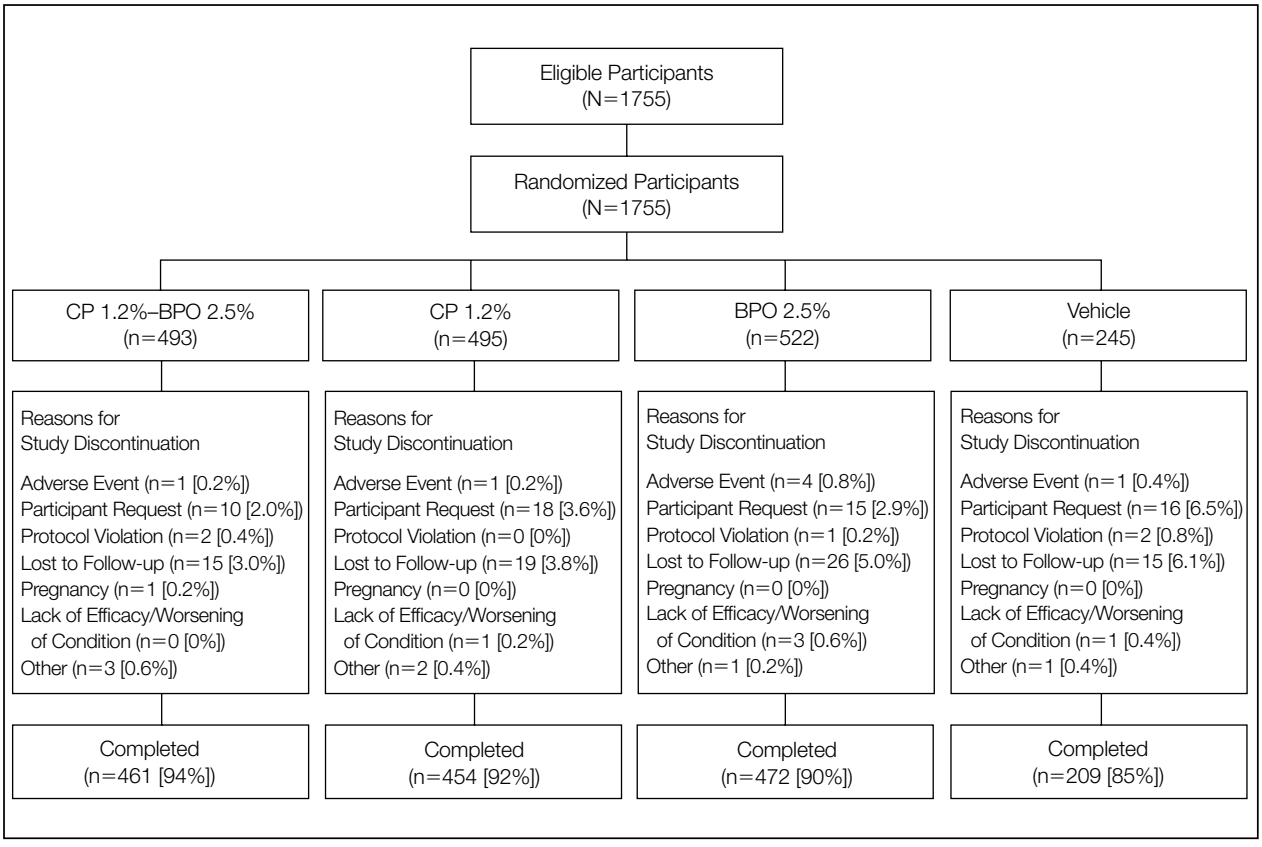

Figure 1. Schematic profile of participant disposition. CP indicates clindamycin phosphate; BPO, benzoyl peroxide.

gel (n=493), CP 1.2% (n=495), BPO 2.5% (n=522), or vehicle (n=245)(Figure 1). Demographic data were similar across treatment groups (Table). At baseline, the median number of inflammatory and noninflammatory lesions was 26.0 and 45.0, respectively.

Efficacy

Lesions Counts—At week 4, the mean absolute reduction in inflammatory, noninflammatory, and total lesion counts relative to baseline for the CP 1.2%–BPO 2.5% gel treatment group was significantly superior to the individual active ingredients and vehicle (inflammatory lesions, $P<.001$ vs CP 1.2% and vehicle and $P=.002$ vs BPO 2.5%; noninflammatory lesions, $P<.001$ vs CP 1.2% and vehicle and $P=.003$ vs BPO 2.5%; total lesions, $P<.001$ vs CP 1.2%, BPO 2.5%, and vehicle), remaining superior at weeks 8 and 12.

By week 12, the mean percentage reduction in inflammatory lesion count was significantly greater in the CP 1.2%–BPO 2.5% gel group (54.1%) versus the CP 1.2% (43.5% [$P<.001$]), BPO 2.5% (45.8% [$P=.001$]), and vehicle (21.1% [$P<.001$]) groups. The mean percentage reduction in noninflammatory lesion count was significantly greater in the CP 1.2%–BPO 2.5% gel group (43.6%) versus the CP 1.2% (33.3% [$P<.001$]), BPO 2.5% (36.2% [$P=.004$]), or vehicle (16.7% [$P<.001$]) groups. The mean percentage reduction in total lesion count was significantly greater in the CP 1.2%–BPO 2.5% gel group (47.7%) versus the CP 1.2% (37.6% [$P<.001$]), BPO 2.5% (39.9% [$P<.001$]), or vehicle (19.0% [$P<.001$]) groups (Figure 2).

Evaluator Global Severity Score—Treatment success (ie, ≥2-grade improvement in the EGSS) was significantly greater in the CP 1.2%–BPO 2.5% gel treatment group versus the CP 1.2% ($P=.002$) and vehicle ($P=.006$) groups at week 4 and versus all 3 treatment groups at weeks 8 ($P<.001$ [CP 1.2%]; $P=.021$ [BPO 2.5%]; $P<.001$ [vehicle]) and 12 ($P=.004$ [CP 1.2%]; $P=.031$ [BPO 2.5%]; $P<.001$ [vehicle]). At week 12, treatment success was reported in 32.9% of participants in the CP 1.2%–BPO 2.5% gel group versus 24.2%, 26.6%, and 12.2% of participants in the CP 1.2%, BPO 2.5%, and vehicle groups, respectively (Figure 3).

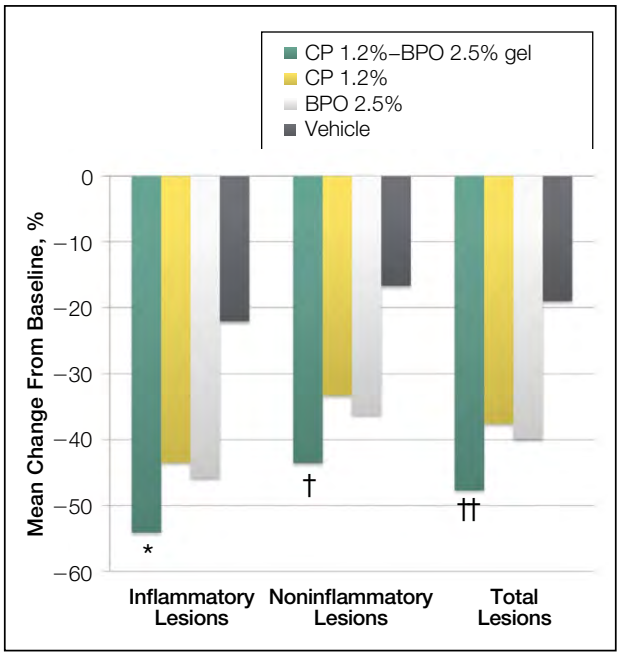

Figure 2. Mean percentage reduction in inflammatory, noninflammatory, and total lesion counts from baseline to week 12 (intention-to-treat population). CP indicates clindamycin phosphate; BPO, benzoyl peroxide. Asterisk indicates *P*<.001 vs CP 1.2% and vehicle, and *P*=.001 vs BPO 2.5%; dagger, *P*<.001 vs CP 1.2% and vehicle, and *P*=.004 vs BPO 2.5%; double dagger, *P*<.001 vs CP 1.2%, BPO 2.5%, and vehicle.

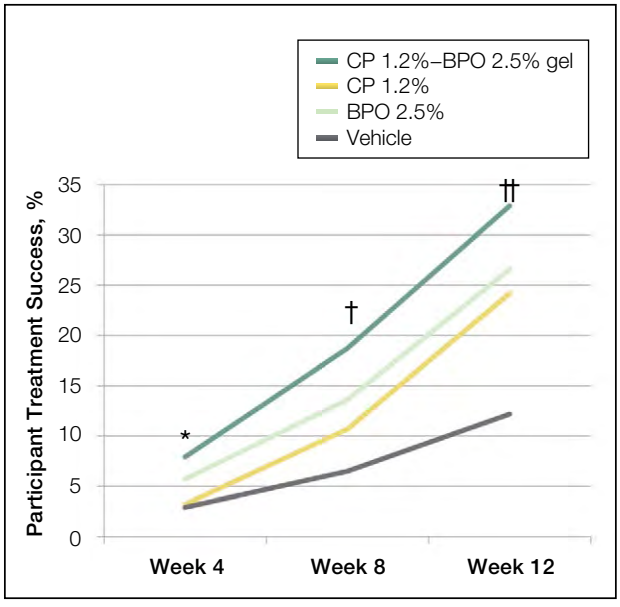

Figure 3. Investigator-assessed treatment success (≥2-grade improvement in the evaluator global severity score) at weeks 4, 8, and 12 (intention-to-treat population; N=1755). CP indicates clindamycin phosphate; BPO, benzoyl peroxide. Asterisk indicates *P*=.002 vs CP 1.2%, *P*=.185 vs BPO 2.5%, and *P*=.006 vs vehicle; dagger, *P*<.001 vs CP 1.2% and vehicle, and *P*=.021 vs BPO 2.5%; double dagger, *P*=.004 vs CP 1.2%, *P*=.031 vs BPO 2.5%, and *P*<.001 vs vehicle.

At week 12, investigators rated acne as clear or almost clear in 26.8% of participants treated with CP 1.2%–BPO 2.5% gel versus 19.8% (*P*=.021), 21.5% (*P*=.019), and 9.0% (*P*<.001) of participants in the CP 1.2%, BPO 2.5%, and vehicle groups, respectively (Figure 4).

Participant Self-assessment—At week 2, the first time point examined, a statistically greater number of participants rated their acne as clear or almost clear with CP 1.2%–BPO 2.5% gel (6.9%) compared with vehicle (1.5%)(*P*=.010). At all time points, CP 1.2%–BPO 2.5% gel remained superior compared with vehicle (week 4, 12.6% vs 6.2% [*P*=.009]; week 8, 23.1% vs 7.4% [*P*<.001]; week 12, 39.0% vs 15.5% [*P*<.001]). At weeks 4, 8, and 12, CP 1.2%–BPO 2.5% gel was superior to CP 1.2% (week 4, 12.6% vs 7.2% [*P*=.007]; week 8, 23.1% vs 15.1% [*P*=.004]; week 12, 39.0% vs 30.2% [*P*=.010]) and BPO 2.5% (week 4, 12.6% vs 6.8% [*P*=.002]; week 8, 23.1% vs 18.0% [*P*=.023]; week 12, 39.0% vs 31.6% [*P*=.005]).

At week 2, more than 31% of participants observed at least marked improvement in their acne with CP 1.2%–BPO 2.5% gel. By week 12, this percentage had increased to almost 70%. More than twice as many participants using CP 1.2%–BPO 2.5% gel reported their acne to be clear at week 12 compared to either active ingredient (Figure 5).

Participant Satisfaction—At baseline, the mean participant satisfaction score based on results of prior acne therapies was 4.4; at week 12, this value increased to 7.5 in participants treated with CP 1.2%–BPO 2.5% gel (*P*<.001), the highest of all 4 treatment groups. Additionally, 81% of participants reported satisfaction with CP 1.2%–BPO 2.5% gel at week 12 compared with 27% at baseline (*P*<.001).

Safety

Adverse Events—The CP 1.2%–BPO 2.5% gel safety profile was comparable to the individual active ingredients and vehicle. The incidence of AEs considered possibly related, probably related, or related to therapy was low (2.2% for CP 1.2%–BPO 2.5% gel; 2.4% for CP 1.2%; 3.8% for BPO 2.5%; 5.3% for vehicle). The majority of reported AEs (≥96%) were mild to moderate in severity; no serious treatment-related AEs were reported. One participant in the

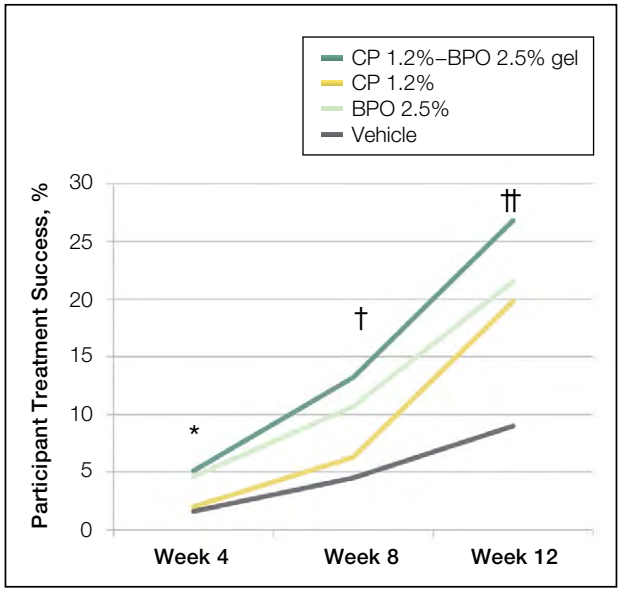

Figure 4. Investigator assessment of acne as clear or almost clear at weeks 4, 8, and 12 (intention-to-treat population; N=1755). CP indicates clindamycin phosphate; BPO, benzoyl peroxide. Asterisk indicates *P*=.017 vs CP 1.2% and vehicle, and *P*=.422 vs BPO 2.5%; dagger, *P*<.001 vs CP 1.2%, *P*=.109 vs BPO 2.5%, and *P*=.001 vs vehicle; double dagger, *P*=.021 vs CP 1.2%, *P*=.019 vs BPO 2.5%, and *P*<.001 vs vehicle.

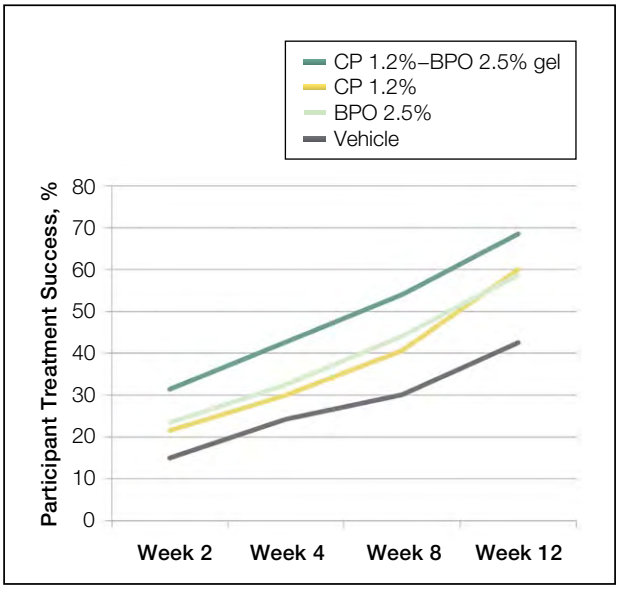

Figure 5. Participant self-assessment of at least marked improvement in acne (clear, almost clear, and marked improvement) from week 2 to week 12 (intention-to-treat population; N=1755). CP indicates clindamycin phosphate; BPO, benzoyl peroxide.

BPO 2.5% group reported application-site irritation that resulted in treatment discontinuation; there were no reports of discontinuation due to application-site reactions in the CP 1.2%–BPO 2.5% gel, CP 1.2%, or vehicle groups.

Cutaneous Tolerability Assessments—Overall mean scores for cutaneous safety (ie, erythema, scaling) and tolerability (ie, itching, burning, and stinging) at baseline and each postbaseline visit were less than 1 (mild) and were comparable between CP 1.2%–BPO 2.5% gel versus the vehicle. Mean scores reported in the CP 1.2%–BPO 2.5% gel group were 0 (none) for burning and stinging, 0.1 for itching and erythema, and 0.2 for scaling. No participants in the CP 1.2%–BPO 2.5% gel group reported severe local signs or symptoms or discontinued the study treatment due to erythema, scaling, itching, burning, or stinging.

COMMENT

Adolescents with acne experience more self-esteem issues, social isolation, depression, and self-consciousness than their peers without acne.[2,16] Despite the psychosocial impact of acne, however, many adolescents do not seek treatment, and unrealistic expectations of therapy or poor tolerability can lead to low adherence in those who were treated.[16,17] Effective therapies that demonstrate early signs of improvement and are well-tolerated may provide improved adherence and yield notable improvements in clinical outcome.[18]

Clinical studies have shown that fixed combinations of CP and BPO applied once or twice daily yield superior results than treatment with either agent alone and also can be used in combination with retinoids.[19-23] Clindamycin phosphate and BPO are widely used to treat acne; however, BPO can result in concentration-dependent skin irritation, dryness, scaling, and erythema, which often affect patient compliance.[24,25] Lower concentrations of BPO (eg, 2.5%) have been shown to exert antimicrobial effects similar to those of higher concentrations with the advantage of enhanced tolerability.[26,27]

Clindamycin phosphate 1.2%–BPO 2.5% gel has been shown to provide comparable bioavailability to fixed-combination CP-BPO products that contain higher concentrations of BPO (eg, 5%).[28] Its potential to provide effective treatment of acne with excellent safety and tolerability has been confirmed in an extensive clinical program.[9]

This analysis revealed that in adolescent participants with moderate to severe acne, a once-daily formulation of CP 1.2%–BPO 2.5% gel was found

to yield superior results compared with individual active ingredients and vehicle at week 12 for all primary and supportive end points. Mean percentage reductions in inflammatory and noninflammatory lesions at week 12 were statistically superior to those yielded by individual active ingredients and vehicle. Local signs and symptoms of erythema, scaling, itching, burning, or stinging were not seen in the majority of participants across all treatment groups and generally were mild when present.

In clinical practice, patient expectations and satisfaction are important aspects of acne management. Additionally, improved adherence and patient outcomes including quality-of-life benefits often are associated with once-daily medications, which are perceived by patients to be as safe and effective as treatments with more frequent dosing regimens.[29,30] For adolescents, a once-daily treatment is especially preferred for its convenience.[24,31]

More than 31% of participants observed at least marked improvements in their acne on treatment with CP 1.2%–BPO 2.5% gel as early as 2 weeks after treatment initiation. Satisfaction rates for CP 1.2%–BPO 2.5% gel were much greater than those reported for prior acne therapies; by the end of the study, overall participant satisfaction was at 81%.

CONCLUSION

Data from this post hoc analysis of adolescent acne participants demonstrate that once-daily treatment with CP 1.2%–BPO 2.5% gel is effective and well-tolerated among adolescents with moderate to severe acne and is associated with remarkably superior reductions in both inflammatory and noninflammatory lesions. Importantly, patients report noticeable improvements within 2 weeks of treatment initiation. Coupled with a simple, once-daily dosing regimen, the high levels of patient satisfaction associated with this treatment may encourage adherence and lead to effective acne resolution in this difficult-to-treat population.

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