Clindamycin Phosphate 1.2%–Benzoyl Peroxide (5% or 2.5%) Plus Tazarotene Cream 0.1% for the Treatment of Acne

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Acne is a multifactorial chronic dermatosis that can be effectively treated with adjuvant medications. The objective of our study was to compare the tolerability and efficacy of 2 adjuvant therapies combining clindamycin phosphate 1.2%–benzoyl peroxide 5% (CLNP-BPO5) or clindamycin phosphate 1.2%–benzoyl peroxide 2.5% (CLNP-BPO2.5) fixed-dose gels with tazarotene (TZ) cream 0.1% (CLNP-BPO5/TZ vs CLNP-BPO2.5/TZ) when applied topically once daily for 12 weeks in participants with moderate to severe facial acne. Forty participants were randomized to receive CLNP-BPO5/TZ or CLNP-BPO2.5/TZ in a parallel-group study and were evaluated at baseline as well as weeks 1, 2, 4, 8, and 12 (or at early termination). In both groups, tolerability assessments increased by week 1 but gradually returned toward baseline levels by week 12. At week 4, the mean change in burning/stinging was significantly higher in the CLNP-BPO5/TZ group compared with the CLNP-BPO2.5/TZ group (P<.05). No other significant differences were observed for the tolerability, efficacy, quality of life (QOL), or participant preference assessments. Our study shows that CLNP-BPO5 or CLNP-BPO2.5 fixed-dose gels in combination with TZ cream 0.1% are generally well-tolerated and effective treatments of moderate to severe facial acne when applied once daily for up to 12 weeks.

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Acne vulgaris is a chronic inflammatory dermatosis characterized by the formation of comedones, papules, pustules, nodules, and cysts that generally manifest on the face, chest, and back. Topical retinoids such as tazarotene (TZ) cream 0.1% are recommended as one of the first-line therapies for acne, as they inhibit the formation of microcomedones and reduce the number of inflammatory and noninflammatory lesions,[1] both preventing and treating the disease. Topical retinoids also may help normalize abnormal desquamation of follicular epithelium in the pilosebaceous unit[2] but are limited by irritation profiles that could negatively impact adherence to therapy in some patients.[3]

Tazarotene cream 0.1% has been shown to have greater efficacy in acne than other topical retinoids,[2] but its efficacy may be further enhanced if combined with other antiacne agents, such as antibiotics and benzoyl peroxide (BPO).[4] Fixed-dose combination products containing an antibiotic such as clindamycin phosphate (CLNP) 1.2% with varying concentrations of BPO are known to be more effective in reducing both inflammatory[5] and noninflammatory lesions compared to either component alone.[6] Furthermore, the use of BPO is recommended in conjunction with an antibiotic to minimize the development of antibacterial resistance.[4]

Adjuvant therapies containing CLNP-BPO fixed-dose combination products have demonstrated an

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ability to enhance the efficacy of retinoids even further[2,4,7] and may overcome the limitations associated with retinoid monotherapies, such as TZ cream 0.1%, namely poor response and tolerability.[3] Moreover, improving tolerability may be important to enhance the patient's adherence to treatment.[3] Several studies have demonstrated the tolerability and efficacy benefits of using retinoids with either CLNP 1.2%[8,9] or BPO monotherapies, or with CLNP-BPO gel fixed-dose combination therapies.[3,10]

The aim of our study was to compare the tolerability and efficacy of 2 adjunctive therapies combining CLNP 1.2%–BPO 5% (CLNP-BPO5)(Duac Gel, Stiefel, a GSK company) or CLNP 1.2%–BPO 2.5% (CLNP-BPO2.5)(Acanya Gel, Valeant Dermatology, a division of Valeant Pharmaceuticals North America LLC) fixed-dose gel formulations with TZ cream 0.1% (Tazorac Cream, Allergan, Inc) when applied topically once daily for 12 weeks in participants with moderate to severe facial acne. Our study also evaluated the influence of acne on quality of life (QOL) and how changes in QOL may influence clinical severity indices used to assess the treatment of acne.

METHODS

Participant Eligibility

This 12-week phase 4, single-center, single-blind, randomized, parallel-group study was conducted in participants with moderate to severe facial acne to compare the tolerability and efficacy of therapy combining CLNP-BPO5 or CLNP-BPO2.5 gel formulations with TZ cream 0.1% (CLNP-BPO5/TZ and CLNP-BPO2.5/TZ, respectively).

The study was conducted from October 19, 2009, to April 7, 2010. Male and female participants were eligible if they were aged 12 to 45 years with 20 to 50 papules and pustules (inflammatory lesions), 30 to 100 open and closed comedones (noninflammatory lesions), 1 or fewer small nodular lesions, no facial cystic lesions, and an investigator static global assessment (ISGA) grade of 3 or higher (0=clear; 1=almost clear; 2=mild; 3=moderate; 4=severe; 5=very severe). The study was performed in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and the Declaration of Helsinki.

Treatment Regimen

Eligible participants were randomly assigned to receive CLNP-BPO5/TZ or CLNP-BPO2.5/TZ formulations in a 1:1 ratio using a computer-generated randomization schedule. All participants were instructed to wash their face with a gentle cleanser and pat dry before each product application. In the mornings, participants were instructed to apply a thin film (pea-sized amount) of either CLNP-BPO5 or CLNP-BPO2.5 gel to the entire affected area of the face; in the evenings, participants were instructed to apply TZ cream 0.1% to the entire affected area of the face. During the 12-week treatment period, participants were assessed at baseline (week 0/day 1) and at weeks 1, 2, 4, 8, and 12 (or sooner in the event of an early withdrawal).

Outcome Measures

Primary End Points—Primary tolerability end points were measured at each visit from baseline to week 12 including erythema, dryness, and peeling assessed by the investigator as well as burning/stinging, itching, and oiliness assessed by participants using a 6-point scale (0=none; 1=trace; 2=mild; 3=moderate; 4=marked; 5=severe) for all. The overall comfort of skin was assessed by the participants on a 5-point scale (−2=uncomfortable; −1=somewhat uncomfortable; 0=neutral; +1=comfortable; +2=very comfortable).

Secondary End Points—Secondary end points included the following: (1) efficacy measured by mean change from baseline in lesion counts (inflammatory, noninflammatory, total) at each visit; (2) proportion of participants who had improvement of 2 grades or more based on ISGA score from baseline to week 12; (3) QOL assessed by the participants using the Skindex-29 (QOL index) 5-point scale (0=never; 1=rarely; 2=sometimes; 3=often; 4=all the time) as well as the product acceptability and preference questionnaire using a 5-point scale (1=very satisfied; 2=satisfied; 3=neutral; 4=unsatisfied; 5=very unsatisfied); and (4) safety measured by adverse events (AEs), which was defined as any untoward medical occurrence in a study participant regardless if the event had a causal relationship with the gel formulations, concomitant medications (classified using the Medical Dictionary for Regulatory Activities, version 11.1), and reasons for study withdrawal.

Statistical Analyses

The intention-to-treat analysis set included all eligible participants who were randomized to receive at least 1 application of the combination therapy. All statistical analyses were performed using SAS version 9.2, and except where noted, all tests were 2 sided at $\alpha=.05$.

Appropriate summary statistics (eg, number of participants, mean, standard deviation [SD], median, 25th and 75th percentiles, minimum and maximum, percentages, frequencies) were used as necessary. Investigator and participant assessments of tolerability were determined by the Wilcoxon rank sum test. Continuous parameters were examined using an

analysis of covariance with terms of treatment and baseline values. If the assumptions of normality were not met, then the Wilcoxon rank sum test was used. Additionally, the Student *t* test was applied if the baseline value did not have an influence on analysis of covariance, and the χ^2 test or the Fisher exact test was used for the proportion of participants with a minimum 2-grade improvement.

Each question of the product acceptability and preference questionnaire was summarized at week 12 and compared using the Wilcoxon rank sum test. Skindex-29 scores were summarized at baseline as well as weeks 4 and 12, and compared using the Student *t* test or Wilcoxon rank sum test if the normality assumption was not met. Analysis of covariance was used to compare changes from baseline between groups.

RESULTS

Baseline Demographics

Of the 40 participants who were initially included in the intention-to-treat analysis set (20 participants in each group), 35 (87.5%) completed the study. Five participants discontinued due to withdrawal of consent (n=4) or lost to follow-up (n=1). The participants were primarily not Hispanic or Latino (33/40 [82.5%])(Table 1). There were no significant differences between the 2 study groups for any demographic or disease characteristics at baseline.

Table 1.

Demographic and Disease Characteristics at Baseline (Day 1): Intention-to-Treat Population

	CLNP-BPO5/TZ (n=20)	CLNP-BPO2.5/TZ (n=20)
Gender, n (%)		
Male	7 (35)	11 (55)
Female	13 (65)	9 (45)
Age, y		
Mean (SD)	21.2 (9.0)	22.6 (7.8)
Median (P25, P75)	17.0 (14.9, 25.7)	22.3 (16.6, 25.6)
Minimum, maximum	12.3, 45.9	13.1, 45.0
Race, n (%)		
Asian	8 (40)	15 (75)
Black	1 (5)	1 (5)
White	9 (45)	4 (20)
Other	2 (10)	0 (0)
Ethnicity, n (%)		
Hispanic or Latino	4 (20)	3 (15)
Not Hispanic or Latino	16 (80)	17 (85)
Lesion counts, mean (SD)		
Inflammatory lesions	27.2 (5.3)	26.5 (6.0)
Noninflammatory lesions	46.6 (16.3)	49.5 (20.0)
Total lesions	73.8 (20.4)	76.0 (24.4)

Abbreviations: CLNP-BPO5/TZ, clindamycin phosphate 1.2%–benzoyl peroxide 5% gel combined with tazarotene cream 0.1%; CLNP-BPO2.5/TZ, clindamycin phosphate 1.2%–benzoyl peroxide 2.5% gel combined with tazarotene cream 0.1%; SD, standard deviation; P25, 25th percentile; P75, 75th percentile.

Tolerability

Primary Analysis—No significant differences in change from baseline were observed for the local tolerability investigator assessments of erythema, dryness, and peeling between the 2 study groups at any end point (weeks 1, 2, 4, 8, and 12). Increases from baseline in the investigator tolerability assessments were observed in both groups, with the greatest value generally observed at week 1. In all cases, the values observed at week 1 were reduced toward baseline levels after 12 weeks of treatment (Table 2).

Secondary Analysis—Participant assessments of tolerability—burning/stinging, itching, oiliness, and overall comfort of skin—were similar to investigator assessments with increases noted at week 1 that gradually returned toward baseline levels over the course of the study (Table 2). A difference was observed between groups at week 4 when the mean (SD) increase in burning/stinging from baseline was 1.25 (1.92) in the CLNP-BPO5/TZ group compared with 0.55 (0.76) in the CLNP-BPO2.5/TZ group ($P<.05$). By week 8, the levels of burning/stinging returned to less than trace for both groups. There were no other clinically relevant differences between groups in the participants' tolerability assessments.

Efficacy

A mean change in inflammatory, noninflammatory, and total lesions was observed at week 12 (−66.1% vs −53.8%, −67.8% vs −75.0%, and −67.7 vs −67.9%, respectively, for CLNP-BPO5/TZ

Table 2.

Tolerability Assessments From Baseline to Week 12: Intention-to-Treat Population

	CLNP-BPO5/TZ (n=20)	CLNP-BPO2.5/TZ (n=20)
Investigator Local Assessments		
Erythema, mean (SD)[a]		
Baseline/day 1	0.05 (0.22)	0.15 (0.49)
Week 12	0.30 (0.57)	0.25 (0.55)
Change[b]	0.25 (0.64)	0.10 (0.79)
Dryness, mean (SD)[a]		
Baseline/day 1	0.05 (0.22)	0.15 (0.37)
Week 12	0.25 (0.64)	0.10 (0.31)
Change[b]	0.20 (0.70)	−0.05 (0.51)
Peeling, mean (SD)[a]		
Baseline/day 1	0.05 (0.22)	0.15 (0.37)
Week 12	0.25 (0.64)	0.10 (0.31)
Change[b]	0.20 (0.70)	−0.05 (0.51)
Participant Assessments		
Burning/stinging, mean (SD)[a]		
Baseline/day 1	0.25 (0.79)	0.05 (0.22)
Week 12	0.75 (0.97)	0.45 (0.89)
Change[b]	0.50 (1.40)	0.40 (0.82)
Itching, mean (SD)[a]		
Baseline/day 1	0.50 (1.00)	0.25 (0.79)
Week 12	0.85 (0.93)	0.70 (1.17)
Change[b]	0.35 (1.42)	0.45 (1.47)
Oiliness, mean (SD)[a]		
Baseline/day 1	1.60 (1.57)	1.60 (1.39)
Week 12	1.25 (1.52)	0.85 (1.39)
Change[b]	−0.35 (1.84)	−0.75 (1.97)
Overall comfort of skin, mean (SD)[c]		
Baseline/day 1	0.20 (1.01)	0.50 (0.76)
Week 12	0.65 (0.93)	1.10 (0.72)
Change[b]	0.45 (1.39)	0.60 (0.99)

Abbreviations: CLNP-BPO5/TZ, clindamycin phosphate 1.2%–benzoyl peroxide 5% gel combined with tazarotene cream 0.1%; CLNP-BPO2.5/TZ, clindamycin phosphate 1.2%–benzoyl peroxide 2.5% gel combined with tazarotene cream 0.1%; SD, standard deviation.

[a]Mean scores assessed on a 6-point scale: 0=none; 1=trace; 2=mild; 3=moderate; 4=marked; 5=severe.

[b]Change from baseline to week 12.

[c]Mean scores assessed on a 5-point scale: −2=uncomfortable; −1=somewhat uncomfortable; 0=neutral; +1=comfortable; +2=very comfortable.

vs CLNP-BPO2.5/TZ). At week 12, the mean (SD) change in ISGA scores from baseline was −1.45 (0.60) for the CLNP-BPO5/TZ group and −1.50 (0.89) for the CLNP-BPO2.5/TZ group. At week 12, the proportion of participants reporting a 2-grade improvement in ISGA was 35% (7/20) in the CLNP-BPO5/TZ group compared with 50% (10/20) in the CLNP-BPO2.5/TZ group. No significant differences were observed between treatment groups at any visit.

QOL and Participant Preference Results

At week 12, the mean (SD) change in Skindex-29 global scores from baseline was −6.1 (11.6) and −3.7 (8.4) for the CLNP-BPO5/TZ and CLNP-BPO2.5/TZ groups, respectively. Based on the product acceptability and preference questionnaire, mean (SD) satisfaction scores received from the participants in the mornings were 1.76 (1.15) for the CLNP-BPO5/TZ group and 1.75 (0.72) for the CLNP-BPO2.5/TZ group. Similar results were obtained in the evenings when mean (SD) satisfaction scores were 1.59 (1.00) for the CLNP-BPO5/TZ group and 1.70 (0.92) for the CLNP-BPO2.5/TZ group. The proportion of participants who were satisfied or very satisfied was 88.2% (15/17) in the CLNP-BPO5/TZ group and 85.0% (17/20) in the CLNP-BPO2.5/TZ group.

Safety

A total of 18 participants (11 in the CLNP-BPO5/TZ and 7 in the CLNP-BPO2.5/TZ group) reported experiencing at least 1 treatment-emergent AE, mostly related to infections and infestations with nasopharyngitis being the most common. Other emergent AEs including respiratory, thoracic, and mediastinal disorders; general disorders and administration-site conditions; and reproductive system and breast disorders were less common (≤3 cases). In the CLNP-BPO5/TZ group, 1 participant experienced 2 treatment-related AEs: application-site erythema and irritation apparent after 2 days of study medication. This participant withdrew consent and discontinued from the study. No serious AEs were reported.

COMMENT

Our study compared the tolerability and efficacy of 2 adjuvant fixed-dose gel therapies—CLNP-BPO5 or CLNP-BPO2.5—in combination with TZ cream 0.1% (CLNP-BPO5/TZ or CLNP-BPO2.5, respectively) for 12 weeks in participants with moderate to severe facial acne. The combination of either CLNP-BPO5 or CLNP-BPO2.5 gel in the mornings with TZ cream 0.1% in the evenings was shown to be generally well-tolerated with similar efficacy profiles. Both adjuvant therapies differed only in the concentration of BPO (5% BPO in the CLNP-BPO5/TZ group vs 2.5% BPO in the CLNP-BPO2.5/TZ group) and in their delivery agents (glycerin and dimethicone in CLNP-BPO5/TZ and propylene glycol in CLNP-BPO2.5/TZ). The glycerin and dimethicone in the CLNP-BPO5 gel may increase the moisturization potential compared with CLNP-BPO2.5.[11] However, the propylene glycol in the CLNP-BPO2.5 gel may act as a humectant and a solubilizer of BPO, optimizing the penetration of ingredients.[12]

Both treatment regimens generally were well-tolerated with mean levels of erythema, dryness, and peeling (investigator rated), and burning/stinging, itching, and oiliness (participant rated) consistently less than mild at all end points. Increases in tolerability parameters were observed in both groups but returned to baseline values over the course of the study. At week 4, there was a significant difference between CLNP-BPO5/TZ and CLNP-BPO2.5/TZ in the burning/stinging participant assessment ($P<.05$). However, by week 8, the levels of burning/stinging returned to less than trace for both groups. No other clinically or statistically significant differences in investigator or participant tolerability assessments were observed between groups.

Both treatments were effective up to 12 weeks in reducing the number of inflammatory, noninflammatory, and total lesions. No significant differences between treatment groups were observed for any of the efficacy parameters at any time point. In both groups, reductions in lesion counts were achieved by week 2. The mean reduction in total lesion counts from baseline to week 12 was the same in both groups (approximately 68%). After 12 weeks, the mean reduction from baseline in ISGA scores was similar for both groups (−1.45 for CLNP-BPO5/TZ vs −1.50 for CLNP-BPO2.5/TZ). At week 12, the proportion of participants with a minimum 2-grade improvement in ISGA scores was lower in the CLNP-BPO5/TZ group (35%) compared with the CLNP-BPO2.5/TZ group (50%).

Quality of life as determined by the Skindex-29 global index scores were not significantly different between the 2 groups. Participant satisfaction was equally high in both groups. The treatment-emergent AEs were similar in both groups and were not related to the treatments. Only 1 participant receiving CLNP-BPO5/TZ experienced 2 treatment-related AEs.

CONCLUSION

Our study shows that CLNP-BPO5 or CLNP-BPO2.5 fixed-dose gels in combination with TZ cream 0.1% are well-tolerated and effective therapies for moderate

to severe facial acne when applied once daily for up to 12 weeks.

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