An Aqueous Gel Fixed Combination of Clindamycin Phosphate 1.2% and Benzoyl Peroxide 3.75% for the Once-Daily Treatment of Moderate to Severe Acne Vulgaris

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ABSTRACT

Objective: To evaluate efficacy, safety, and tolerability of a fixed combination clindamycin phosphate 1.2% and benzoyl peroxide 3.75% (clindamycin-BP 3.75%) aqueous gel in moderate to severe acne vulgaris.

Methods: A total of 498 patients, 12-40 years of age, were randomized to receive clindamycin-BP 3.75% or vehicle in a double-blind, controlled 12-week, 2-arm study evaluating safety and efficacy using inflammatory and noninflammatory lesion counts, Evaluator Global Severity Scores (EGSS) and subject self-assessment (SSA). In addition, patients completed a patient satisfaction survey (PSS), acne-specific QoL questionnaire, and assessed their facial skin for shininess/oiliness.

Results: Clindamycin-BP 3.75% demonstrated statistical superiority to vehicle in reducing both inflammatory and noninflammatory lesions and acne severity. Clindamycin-BP 3.75% showed greater efficacy relative to vehicle in assessments of skin oiliness, SSA and PSS. No substantive differences were seen in cutaneous tolerability among treatment groups and no patients discontinued treatment with Clindamycin-BP 3.75% because of adverse events.

Limitations: Data from controlled studies may differ from clinical practice. It is not possible to determine the contributions from the individual active ingredients.

Conclusions: Clindamycin-BP 3.75% provides statistically significant greater efficacy than vehicle with a favorable safety and tolerability profile.


INTRODUCTION

Combination therapy for acne, simultaneously targeting multiple pathogenic factors is now commonplace, and many studies have shown that the combination of clindamycin 1% with benzoyl peroxide (BP) 5% is superior to each individual active ingredient. As a result, fixed combination products of clindamycin 1% and BP 5% have seen extensive use for the treatment of acne vulgaris. Although these products are very effective, dryness and irritation from the BP component are still limiting side effects in some patients.

Consequently, a fixed-dose, once-daily combination product containing clindamycin phosphate 1.2% (equivalent to 1% clindamycin) and a low concentration (2.5%) of BP (clindamycin-BP 2.5%) was developed to effectively treat both the inflammatory and non-inflammatory lesions of acne vulgaris, while minimizing the potential for skin irritation.

Clindamycin-BP 2.5% is an alcohol-free aqueous gel with a humectant and solubilizing properties that may enhance both delivery and bioavailability of the micronized BP and clindamycin phosphate into the pilosebaceous unit. A combination of lower BP concentration and this formulation provided a fixed combination product shown to be effective and well tolerated in moderate to severe acne.

A post-hoc analysis showed greater efficacy in moderate acne patients compared to severe patients. It was postulated that BP concentrations might be increased using the same formulation to provide greater effectiveness in those moderately severe acne patients, without significantly impacting safety and tolerability. This article reports the findings of a well-controlled trial of this higher BP strength formulation.

METHODS

Study Design
The study received approval before patient enrollment from the appropriate institutional review board for each center. It was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices (GCP) and in compliance with local regulatory requirements. All patients provided written informed consent before entering the study.

This was a multicenter, randomized, double-blind, vehicle-controlled, parallel group study in 498 patients with moderate to...
severe acne vulgaris who met specific inclusion/exclusion criteria as described below. Before randomization, patients were stratified by severity of acne vulgaris (Evaluator Global Severity Score [EGSS], ranging from 0 [clear] to 5 [very severe]). They were dichotomized into a moderate acne group (EGSS of 3) and severe acne group (EGSS of 4).

Patient treatments were randomized using permuted blocks within strata to ensure not only an appropriate distribution of patients across treatment groups, but also a relatively equal balance of patients by acne severity within treatment groups. Following the established stratification scheme, eligible patients were randomized (1:1) into one of 2 treatment groups: clindamycin-BP 3.75% gel or vehicle. All patients applied study medication to the face once daily for 12 weeks.

**Study Population**

Eligible subjects included male and female patients of any race and ethnicity aged 12-40 years, with moderate to severe acne (a score of 3 or 4 on the EGSS), who presented with 20 to 40 inflammatory lesions (papules, pustules, and nodules), 20 to 100 non-inflammatory lesions (open and closed comedones), and two nodules or less. Women of childbearing potential were required to have a negative urine pregnancy test result and to agree to use an effective form of contraception for the duration of the study. A washout period of up to 1 month was required for patients who used previous prescription and over-the-counter acne treatments. Specifically, the following mandatory washout periods and restrictions applied to these topical (face) and systemic treatments: topical astringents and abrasives (1 week); topical antiacne products, including soaps containing antimicrobials, and known comedogenic products (2 weeks); topical retinoids, retinol, and systemic acne treatments (4 weeks); and systemic retinoids (6 months).

Approximately 500 patients (250 in each study group) were planned for enrollment.

**Efficacy Evaluation**

Efficacy evaluations of the face comprised inflammatory, non-inflammatory, and total lesion counts and an EGSS at screening, baseline, and during treatment (weeks 4, 8, and 12) performed by the investigator. Primary efficacy endpoints included absolute change from baseline to week 12 in mean inflammatory and non-inflammatory lesion counts, and the proportion of patients who achieved at least a 2-grade reduction from baseline to week 12 in the EGSS. Secondary efficacy endpoints included mean percent change from baseline to week 12 in inflammatory and non-inflammatory lesion counts and the proportion of patients who achieved at least a 2-grade reduction from baseline and were also considered ‘clear’ or ‘almost clear’ at that same visit (ie, had an EGSS of 0 or 1 at the specified visit) was conducted.

Additional analyses evaluated efficacy results using a subject self-assessment (SSA) where severity and degree of improvement were evaluated relative to baseline on a scale ranging from 1 (clear) to 7 (worse) from week 2, a patient satisfaction score (PSS) ranging from 1-10 (where 10 was the most satisfied), a completed acne-specific quality of life (Acne-QoL) questionnaire (Merck & Co, Inc. Whitehouse, NJ), and an assessment of both shininess/visibility of the skin on patient’s face (using a 4-point scale) and degree of bothersomeness (using a 5-point scale). These analyses included the frequency and percent distributions for the oily/shiny skin assessments at baseline and week 12, frequency and percent distributions for the SSA at baseline and weeks 2, 4, 8, and 12, descriptive statistics, frequency and percent distributions for the PSS at baseline and week 12, and descriptive statistics for the Acne-QoL questionnaire at baseline and week 12.

**Safety Evaluation**

The investigator assessed cutaneous safety and tolerability evaluations at each study visit. Cutaneous safety evaluations included erythema and scaling, and tolerability evaluations included itching, burning, and stinging; each evaluated on a scale from 0 (none) to 3 (severe) at each visit (Table 1). The investigator assessed erythema and scaling at the time of the study visit. Itching, burning, and stinging were solicited from the patient and recorded as an average of the patient’s symptoms during the period since the previous visit.

Safety was also evaluated through reported adverse events (AEs), which were summarized by treatment group, severity, and relationship to study medication.

**Statistical Analysis**

The intent-to-treat (ITT) population comprised all patients randomized and provided with study drug. The safety population comprised all randomized patients who were presumed to have used the study medication at least once and who provided at least one post baseline evaluation. The per-protocol (PP) population included all patients who completed the 12-week evaluation without major study protocol violations.

The primary method of handling missing efficacy data in the ITT analysis set was based on estimation using the Markov Chain Monte Carlo multiple imputation method. In the PP analysis set, missing values were imputed as baseline carried forward. No imputations were made for missing safety data.

The investigator assessments (EGSS, lesion counts) were conducted independently of the SSA. In patients who discontinued treatment before week 12 or missed visits between baseline and final evaluation, the last observation was carried forward for all efficacy end points excluding SSA.
 Statistical significance was based on 2-tailed tests of the null hypothesis resulting in P values of 0.05 or less.

All AEs occurring during the study were recorded and classified on the basis of medical dictionary for drug regulatory activities terminology for the safety population. Treatment group comparisons were made by tabulating the frequency of patients with one or more AEs during the study. The Fish-

er exact test was used to compare the proportion of patients in each treatment group who reported any AE at a significance level of 0.05.

**RESULTS**

**Baseline Characteristics**

A total of 498 patients were enrolled across 28 investigative sites across the United States, randomly assigned to clindamycin-BP 3.75% (N=253) or vehicle (N=245) and included in the ITT analysis. Overall, 447 patients (89.8%) completed the study, including 234 patients (92.5%) in the clindamycin-BP 3.75% group and 213 patients (86.9%) on vehicle (Figure 1). The most common reasons for study discontinuation were 'lost to follow-up' or patient withdrawal (self, or by parent/guardian).

Demographic data (Table 2) was not statistically different across the two treatment groups, apart from age. The mean age (standard deviation) across both treatment groups was 18.7 (5.82) years. Patients in the clindamycin-BP 3.75% group were younger (mean [SD]= 18.2[5.6] years) compared to those treated with vehicle (19.3 [6.0] years, P= 0.020). Patients were approximately balanced by sex (51.4% male and 48.6% female), and predominantly Caucasian (83.9%).

There were no significant differences between treatment groups in regard to baseline lesion counts, or EGSs. At baseline, the mean number (SD) of inflammatory and non-inflammatory lesions was 27.0 (6.04) and 37.8 (17.87).
**TABLE 2.**

<table>
<thead>
<tr>
<th>Patient Demographics and Baseline Characteristics (ITT population)</th>
<th>Clindamycin-BP 3.75% (N=253)</th>
<th>Vehicle (N=245)</th>
<th>Total (N=498)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>18.2 (5.6) (P=0.020)</td>
<td>19.3 (6.0)</td>
<td>18.7 (5.82)</td>
</tr>
<tr>
<td>Median</td>
<td>16.0</td>
<td>17.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Range</td>
<td>12-40</td>
<td>12-39</td>
<td>12-40</td>
</tr>
<tr>
<td><strong>Sex, N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>130 (51.4)</td>
<td>126 (51.4)</td>
<td>256 (51.4)</td>
</tr>
<tr>
<td>Female</td>
<td>123 (48.6)</td>
<td>119 (48.6)</td>
<td>242 (48.6)</td>
</tr>
<tr>
<td><strong>Ethnicity, N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>64 (25.3)</td>
<td>72 (29.4)</td>
<td>136 (27.3)</td>
</tr>
<tr>
<td>Non-Hispanic/Latino</td>
<td>189 (74.7)</td>
<td>173 (70.6)</td>
<td>362 (72.7)</td>
</tr>
<tr>
<td><strong>Race, N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>208 (82.2)</td>
<td>210 (85.7)</td>
<td>418 (83.9)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>33 (13.0)</td>
<td>24 (9.8)</td>
<td>57 (11.4)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (4.8)</td>
<td>11 (4.5)</td>
<td>23 (4.7)</td>
</tr>
<tr>
<td><strong>Evaluator’s Global Severity Score, N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0=Clear</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>1=Almost Clear</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>2=Mild</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>3=Moderate</td>
<td>212 (83.8)</td>
<td>200 (81.6)</td>
<td>412 (82.7)</td>
</tr>
<tr>
<td>4=Severe</td>
<td>41 (16.2)</td>
<td>45 (18.4)</td>
<td>86 (17.3)</td>
</tr>
<tr>
<td>5=Very Severe</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Lesion Counts (mean [SD])</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory</td>
<td>27.2 (5.99)</td>
<td>26.7 (6.09)</td>
<td>27.0 (6.04)</td>
</tr>
<tr>
<td>Non-inflammatory</td>
<td>38.3 (18.63)</td>
<td>37.2 (17.07)</td>
<td>37.8 (17.87)</td>
</tr>
</tbody>
</table>

Although 83% of the patients were classified as having moderate acne, almost one in 5 patients (17%) had severe acne (an EGSS of 4) at baseline.

**Efficacy**

**Lesion Counts**

Clindamycin-BP 3.75% was statistically superior to vehicle in terms of both inflammatory and non-inflammatory lesion reduction. Mean percent change from baseline to week 12 in inflammatory lesion counts was 60.6% vs 31.4% with vehicle (P<0.001), and in non-inflammatory lesion counts 51.6% vs 27.4% with vehicle (P<0.001). Median percent change from baseline to week 12 in inflammatory and non-inflammatory lesion counts was 88.4% and 57.9% vs 35.5% and 32.5% with vehicle respectively (both P<0.001) (Figure 2).

**Investigator Assessment (EGSS)**

Treatment success was defined as at least a 2-grade improvement in global severity by EGSS. At week 12, 34.3% of patients achieved treatment success with clindamycin-BP 3.75%, compared to 15.6% with vehicle (P<0.001) (Figure 3). In addition by week 12, 25.9% of patients were also ‘clear’ or ‘almost clear’ (an EGSS of 0 or 1) with clindamycin-BP 3.75% compared to only 12.2% with vehicle (P<.001).
FIGURE 3. Investigator Assessment: percent of patients considered treatment success on dichotomized Evaluator Global Severity Score (EGSS) scale. Treatment success defined as at least a 2-grade improvement in severity over baseline (ITT population).

Subject Self-Assessment (SSA)
At week 12, 34.9% of clindamycin-BP 3.75% patients reported an SSA of 'clear' or 'almost clear' compared with 17.4% of patients on vehicle (Figure 4). A total of 66.8% of patients had clear/almost clear or 'marked improvement' in their acne at week 12, compared to 41.3% with vehicle. Over 96% of patients noted some improvement in their acne following 12 weeks clindamycin-BP 3.75% treatment; only 3.8% of patients reported their acne as unchanged or worsened compared to 19.3% of patients treated with vehicle.

Additional Efficacy Assessments: Oiliness, Patient Satisfaction, and Quality of Life
At baseline, the percent of patients reporting facial skin oiliness as 'none' or 'mild' during the previous week was similar in both clindamycin-BP 3.75% and vehicle groups (62.1% and 56.7%, respectively). At week 12, the percent of patients reporting skin oiliness as none or mild had increased to 84.7% and 72.3% with clindamycin-BP 3.75% and vehicle respectively, with a corresponding decrease in those patients reporting 'moderate' or 'severe' symptoms. Among patients reporting some degree of oiliness in the past week, almost 45% of patients treated with clindamycin-BP 3.75% reported having been 'not bothered at all' compared to 29.1% with vehicle. At week 12, 81.8% of patients treated with clindamycin-BP 3.75% who reported having oily skin were not bothered or 'only a little bothered' compared to 69.0% on vehicle.

At baseline, patients in both treatment groups also had similar mean PSS scores with their prior facial acne treatment (4.8 and 4.4, respectively). By week 12, the mean PSS score for patients treated with clindamycin-BP 3.75% had increased to 7.5 (a 56% increase) compared to 6.2 with vehicle.

There were no meaningful differences in improvement between treatment groups based on the mean Acne-QoL assessments in each of the 4 evaluated domains, although mean scores were numerically higher with clindamycin-BP 3.75%. The increase in mean scores from baseline to week 12 with clindamycin-BP 3.75% were 7.6 (self-perception), 5.5 (role-emotional), 4.7 (role-social) and 6.5 (acne symptoms), compared to 5.9, 4.5, 3.7, and 4.3, respectively with vehicle.

Subgroup Analyses
The subgroup analyses also confirmed that clindamycin-BP 3.75% was effective among patients regardless of age, race, or ethnicity; the results suggested a somewhat greater effect in female subjects than in male subjects and among subjects with severe acne relative to subjects with moderate acne.

Safety
A similar percent of patients in each treatment group (22.2% and 24.2%, clindamycin-BP 3.75% and vehicle respectively) reported TEAEs that were mostly mild or moderate (97.1% and 94.4%, respectively) and not related to study drug (94.1% and 90.1%, respectively). A summary of the TEAEs occurring at a frequency of ≥1% is shown in Table 3. The most common TEAE was nasopharyngitis and none of the TEAEs listed were significantly different between clindamycin-BP 3.75% and vehicle. There were 4 treatment-related TEAEs with clindamycin-BP 3.75% (burning sensation, contact dermatitis, pruritus and rash) and 7 with vehicle (cystic acne, contact dermatitis, facial pain, hypersensitivity, lip swelling, pruritus, and swelling face). No subject in the clindamycin-BP 3.75% group discontinued due to TEAE.

Cutaneous Tolerability Assessment
In the clindamycin-BP 3.75% treatment group more than 80% of patients had no erythema, more than 88% no scaling, more than 87% no itching, at least 95% no burning, and more than 95% no stinging at any post-baseline study visit. Cutaneous tolerability was similar to that seen with vehicle where more than 71% of patients had no erythema, more than 86% no scaling,
TABLE 3.

<table>
<thead>
<tr>
<th>Preferred adverse event term, n (%)</th>
<th>Clindamycin-BP 3.75% (N=243)</th>
<th>Vehicle (N=236)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal discomfort</td>
<td>0 (0.0)</td>
<td>3 (1.3)</td>
<td>0.119</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (1.2)</td>
<td>5 (2.1)</td>
<td>0.498</td>
</tr>
<tr>
<td>Influenza</td>
<td>5 (2.1)</td>
<td>5 (2.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>18 (7.4)</td>
<td>12 (5.1)</td>
<td>0.348</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (1.2)</td>
<td>2 (0.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>7 (2.9)</td>
<td>1 (0.4)</td>
<td>0.068</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2 (0.8)</td>
<td>3 (1.3)</td>
<td>0.682</td>
</tr>
</tbody>
</table>

Note: Treatment-emergent adverse events are those with an onset after the first application of study medication.

more than 78% no itching, at least 94% no burning, and more than 93% no stinging at any post-baseline study visit.

At week 12, mean erythema scores were the same in both treatment groups. Mean scaling, burning and stinging scores were slightly lower with vehicle and itching scores higher.

DISCUSSION

Clindamycin-BP 3.75% is a new fixed combination product for the treatment of moderate to severe acne vulgaris. This study demonstrated that the group treated with clindamycin-BP 3.75% showed superior results compared to vehicle, with both co-primary and co-secondary efficacy outcomes, including measures of inflammatory and non-inflammatory lesion reduction, treatment success, patient satisfaction, and reduction in facial skin oiliness. Clindamycin-BP 3.75% was also rated as generally safe and well tolerated when applied once daily for 12 weeks. Treatment related AEs occurred in less than 2% of patients (1.6% compared to 3.0% with vehicle). Local signs and symptoms of erythema, scaling, itching, burning, or stinging were not seen in the majority of patients across both treatment groups and when present were generally mild.

The rationale behind development of fixed combinations with lower BP concentrations stemmed from the potential for BP to cause concentration dependent skin irritation and dryness, shown to be both bothersome in many patients and to impact successful acne treatment. In addition, it was well known that surfactants, preservatives, and high levels of organic solvents used in some fixed combinations with BP or for solubilizing retinoids are potential irritants. As a result, formulation development focused on novel drug delivery strategies coupled with employing lower concentrations of potentially irritating active ingredients. Resulting fixed combinations of retinoids or clindamycin with BP 2.5% became common, replacing the older BP 5% combinations. A meta-analysis comparing fixed combination products containing clindamycin and either BP 5% or BP 2.5% concluded that their efficacy was comparable, with perhaps more favorable results seen with clindamycin-BP 2.5% in non-inflammatory lesions. Intuitively, tolerability with a lower concentration of BP would be expected to be better, but this was not compared.

Data from controlled studies may differ from clinical practice, and there remains skepticism whether comparable efficacy can be achieved with fixed combinations containing lower concentrations of active ingredients, especially in the moderately severe acne patients. Thus, it was hypothesized that higher concentrations of BP might be used with these unique formulations to provide greater efficacy without compromising safety and tolerability. Median percent inflammatory and non-inflammatory lesion reductions of 68.4% and 57.9% were seen in our study with clindamycin-BP 3.75%. In addition, we observed that 22 (55.1%) of patients rated with severe acne at baseline achieved a 'clear'/almost clear' rating at week 12, which is at least a 3- to 4-grade improvement in EGS scores. Our data is consistent with other reports and suggests that topical therapy may be more valuable than often assumed in patients with severe acne, and a post-hoc analysis of these data in this cohort may provide additional insights.

Excessive and recurring oiliness are common in acne sufferers, with a number believing that excess oil causes breakouts, and many seeking an oil-free benefit from their acne treatment. However, while patients report that the lack of facial oiliness and shine is significant, there is limited clinical data designed to characterize the effect of individual acne treatments on oiliness and shine. Clindamycin-BP 3.75% was shown to be very effective in reducing skin oiliness.

Generalizability of these data may be limited from using carefully selected patients and controlled methods. In addition, while many studies have shown that combination of clindamycin and BP is superior to each individual active ingredient, it is not possible to determine the contributions from the individual active ingredients in our study.
CONCLUSION

The results of this vehicle-controlled study suggest that a fixed combination of clindamycin-BP 3.75% aqueous gel may be an effective, safe, and well-tolerated topical treatment of patients with moderate to severe inflammatory and non-inflammatory acne vulgaris.

ACKNOWLEDGEMENTS

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DISCLOSURES

Drs. Pariser, Rich, and Cook-Bolden were all principle investigators in the clinical study. Drs Pariser, Rich and Cook-Bolden were all advisers to Valeant Pharmaceuticals North America LLC and Andrew Korotzer is an employee of Valeant Pharmaceuticals North America LLC.

REFERENCES