

Adapalene/Benzoyl Peroxide Gel 0.3%/2.5%: Effective Acne Therapy Regardless of Age or Gender

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ABSTRACT

Background: Acne vulgaris affects a diverse group of people, and there is an increasingly wide variety of acne treatments. Because of the many options, clinicians have a better ability to individualize treatment; however, achieving optimal results relies on understanding how various agents perform in specific population segments. Fixed-combination adapalene plus benzoyl peroxide (A/BPO) is a first-line recommended acne therapy and is available in two adapalene concentrations (0.1% and 0.3%) combined with BPO 2.5%. This analysis investigated whether gender and age have an impact on either the efficacy or safety of topical A/BPO 0.3%.

Methods: A post-hoc subanalysis was performed on data from a multicenter, randomized, double-blind, parallelgroup, 12-week study of A/BPO gel 0.3%/2.5% or vehicle gel in subjects ≥ 12 years old with moderate to severe acne vulgaris (Investigator global assessment [IGA] of 3 or 4). Efficacy measurements included achievement of an IGA of clear (0) or almost clear (1), and change in lesion counts from baseline to week 12. Safety measures included adverse events and cutaneous tolerability. The intent to treat (ITT) and safety populations were analyzed.

Results: The A/BPO gel 0.3%/2.5% treatment group included 217 subjects. Among the subjects, 111 were 12-17 years old and 106 were ≥ 18 years old; 104 were male and 113 were female. A/BPO 0.3%/2.5% was safe, tolerable, and significantly superior to vehicle in success rates (IGA 0 or 1) and reduction of inflammatory/noninflammatory lesions ($P \leq 0.05$) across both age groups and genders.

Conclusions: A/BPO 0.3%/2.5% treatment achieved success and was equally effective and safe in younger vs older subjects and in males vs females. These results support the use of A/BPO 0.3%/2.5% in all subjects 12 and older.

Clinicaltrials.gov registry: (NCT01880320)

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INTRODUCTION

Acne vulgaris is the most frequently diagnosed dermatologic condition in the US among those between 5 and 44 years of age.[1,2] With a large number of topical agents available to treat acne, it is becoming increasingly important to understand how various population segments may respond to acne therapies. Clinicians today have the opportunity to individualize treatment; however, achieving optimal results requires knowledge of how various agents perform in specific population segments.

Acne is slightly more common and generally more severe in adolescent males but is becoming increasingly common among adult females.[3,4] Reports have indicated that as many as 54% of adult females may have acne.[4-7] Certain concerns are heightened among adult women with acne, including an often increased psychosocial burden of the disease and the potential for pregnancy.[8,9] Adult female acne has traditionally been perceived as different from adolescent acne in clinical presentation, treatment response, and therapeutic concerns.[7,8] Some women appear to respond more slowly to acne therapy, and hormonal and genetic factors may play a more prominent role in this setting compared with adolescent acne.[10] However, a recent study that observed acne in 374 females over the age of 25 found that approximately 90% had acne that was similar in presentation to typical adolescent acne, suggesting that these women may respond well to the same acne therapies as their adolescent counterparts.[7]

Gender differences among acne subjects may be most prominent in adolescent subjects. Males with acne are at higher risk for truncal acne and scarring.[11] In addition, acne can be more severe in males than in females during late adolescence.[12] Males may be less likely to adhere to acne therapy, particularly if the regimen is complicated.[13,14] They may also have lifestyle factors that could potentially reduce adherence to acne therapy by contributing to forgetting to apply medication or being too busy, such as participating in sports.[13] Recommendations for treatment of adolescents (males or females) suggest a simple treatment regimen that is convenient for the patient's daily routine.[15]

Adapalene, a retinoid, and benzoyl peroxide (BPO) have complementary and synergistic mechanisms of action that are

effective against both inflammatory and noninflammatory lesions.[16] BPO is a potent oxidative antibacterial agent with anti-inflammatory and keratolytic/comedolytic activity that does not promote antibiotic resistance.[17,18] Adapalene has comedolytic and anti-inflammatory activity, and has been shown to reduce the formation of microcomedones.[4]The fixed combination of A/BPO is available with two adapalene concentrations (0.1% and 0.3%) combined with BPO 2.5%.

A multicenter, randomized, double-blind, vehicle-controlled study assessed the safety and efficacy of A/BPO 0.3%/2.5% gel applied once daily for 12 weeks for the treatment of acne vulgaris. At baseline, 50% of subjects were graded as "moderate" (investigator's global assessment [IGA] Grade 3) and 50% were graded as "severe" (IGA Grade 4). Subjects ranged in age from 12 to 57 years, and an approximately equal number of males and females were enrolled. Treatment success (defined as the percent of subjects who were rated "clear" or "almost clear" at Week 12, with at least a two grade improvement in IGA) was significantly greater in the A/BPO 0.3%/2.5% group compared to vehicle (33.7% vs 11.0%) in the intent to treat (ITT) population. Mean absolute change from baseline at Week 12 in both inflammatory and noninflammatory lesion counts was also significantly greater for the A/BPO 0.3%/2.5% group than for the vehicle group. The A/BPO 0.3%/2.5% group experienced an average reduction in inflammatory lesions of 27.8 (vs 13.2 for vehicle) and an average reduction in noninflammatory lesions of 40.5 (vs 19.7 for vehicle).

Adapalene has been shown to have a concentration-dependent effect, both in vitro and in clinical studies,[19] and A/BPO 0.3%/2.5% is stronger than A/BPO 0.1%/2.5%, with improved efficacy shown in moderate to severe acne.[16,18] In a population with severe inflammatory acne (n=252), A/BPO 0.3% was shown to be statistically significantly superior to vehicle in achieving success (IGA rating of clear (0) or almost clear (1), indicating at least 3 grades of improvement) vs vehicle (31.9% vs 11.8%, *P*=0.029). In comparison, success of A/BPO 0.1% was not significantly superior to vehicle (*P*=0.443), despite similar sample sizes.[20]

This report details the results of a subanalysis of the well-controlled, randomized pivotal clinical trial[16] of topical A/BPO 0.3%/2.5% in two groups of patients with moderate to severe acne: males vs females and 12-17 vs ≥ 18 years.

METHODS

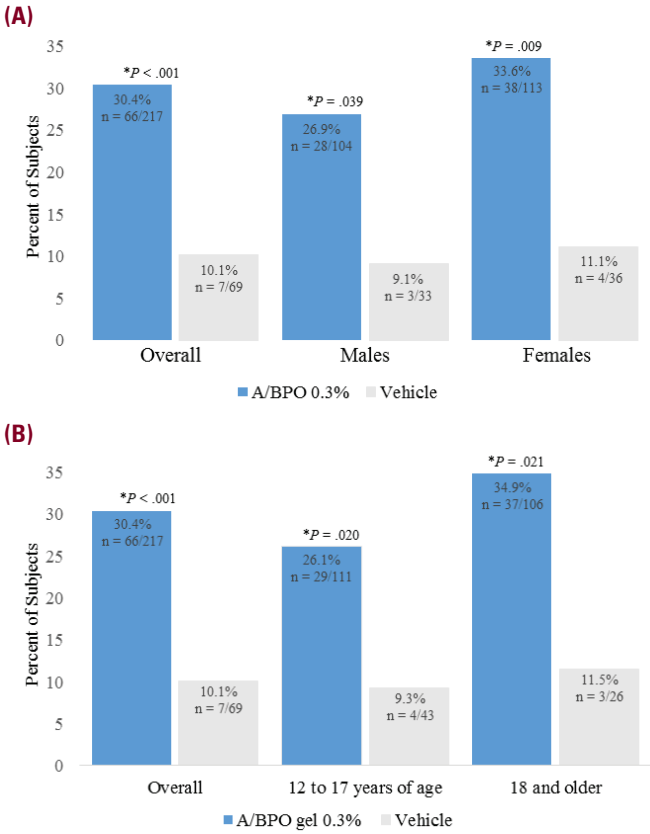
Study Design

Data were analyzed from a multicenter (31 sites, US and Canada), randomized, double-blind, parallel-group, 12-week, controlled study of A/BPO gel 0.3%/2.5% vs vehicle gel in subjects with moderate and severe acne vulgaris. Overall results from the study were published by Stein Gold et al in 2016.[16]The objective of this sub-group analysis was to compare the efficacy and safety of A/BPO gel 0.3%/2.5% and vehicle gel in males vs females and in subjects 12-17 years vs ≥ 18 years. A group of subjects treated with A/BPO 0.1%/2.5% was included and served as a benchmark for tolerability – the study was not designed or powered to show superiority between active groups thus results presented here focus on comparison of A/BPO gel 0.3%/2.5% vs vehicle. This study was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with good clinical practices and local regulatory requirements, and was approved by an institutional review board. All subjects provided written informed consent before entering the study.

Subjects

Subjects were aged 12 years or older and had an IGA (5-point scale, 0 - 4) of moderate (IGA 3) to severe (IGA 4). Inclusion criteria were: 20 to 100 inflammatory lesions, 30 to 150 noninflammatory lesions, and no more than 2 acne nodules on the face. Exclusion criteria included acne conglobate, acne fulminans, nodulocystic acne, or acne requiring systemic treatment. Women of childbearing potential were required to agree to use

FIGURE 1. Similar success (IGA Score of 0 or 1) rates with A/BPO 0.3%: (A) by gender and (B) by age. LOCF used to impute missing data.



a highly effective contraceptive method for the duration of the clinical trial; women were excluded from the study if they were using hormonal contraceptives for less than three months prior to the baseline or for any length of time solely for the control of acne. Acceptable contraceptive methods included bilateral tubal ligation, vasectomized partner, combined oral (estrogens and progesterone), or hormonal intrauterine device with a stable dose at least 3 months prior to baseline. To achieve equal distribution of baseline acne severity in the treatment arms, subjects were stratified by IGA score prior to randomization into treatment arms. Randomization was planned with a 3:1 ratio for active:vehicle.

Treatments

The study treatments were A/BPO gel 0.3%/2.5% or its vehicle. All subjects received a moisturizer and gentle cleanser, along with instructions for product dosing and application (oral and written). Subjects applied the assigned study treatment to the entire face (1 pea-sized amount to the forehead, chin, and each cheek) once in the evening after washing. If the once daily treatment regimen was altered to every other day, the investigator had to attempt to return the subject to once daily treatment within 2 weeks. Subjects were also instructed to apply a thin film to affected areas of the trunk, if applicable. Additionally, subjects were requested to use the moisturizer (up to 3 times daily) and the gentle cleanser throughout the study.

Efficacy Measurements

The co-primary endpoints were success rate, defined as the percentage of subjects with an IGA of clear (0) or almost clear (1) and at least a two-grade improvement at week 12, and the change in inflammatory and noninflammatory lesion counts from baseline to week 12.

Safety Measurements

The incidence of adverse events (AE) was analyzed for all subjects throughout the study. Cutaneous tolerability, measured as erythema, scaling, dryness, and stinging/burning were assessed on a 4-point scale (0–3) at each study visit.

Statistical Analysis

The intent to treat (ITT, all randomized subjects) population was used for efficacy analyses and the safety population (ITT subjects who applied the study drug at least once) was used for cutaneous tolerability and safety analyses. Success rates were analyzed using Cochran-Mantel-Haenszel (CMH) tests and Analysis of Variance with baseline IGA and lesion counts as covariates. The last observation carried forward (LOCF) method was used for success rates and lesion counts.

RESULTS

Demographics and Clinical Characteristics

The following populations are described in Table 1: females and males, and age groups 12 - 17 and ≥ 18 years. There was a similar

FIGURE 2. Mean change from baseline in lesions after 12 weeks of treatment with adapalene and benzoyl peroxide (A/BPO) gel 0.3%/2.5% or vehicle, by gender.

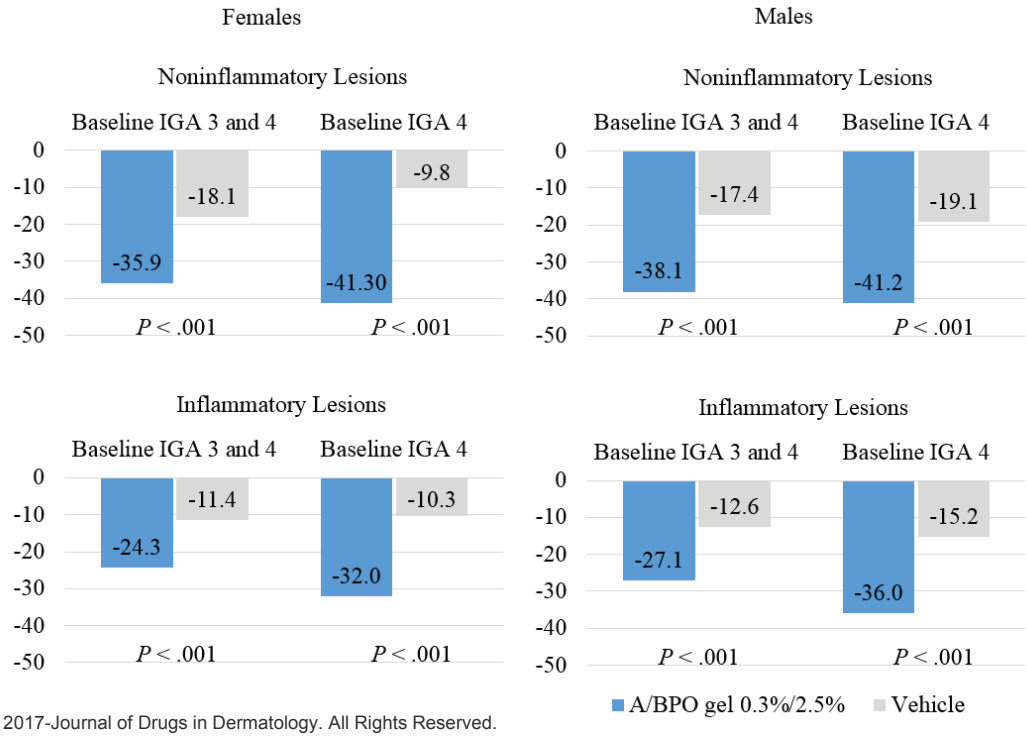


FIGURE 3A. Percent change noninflammatory lesions by gender. Means (LOCF) at each time point. *P<0.005, **P<0.001.

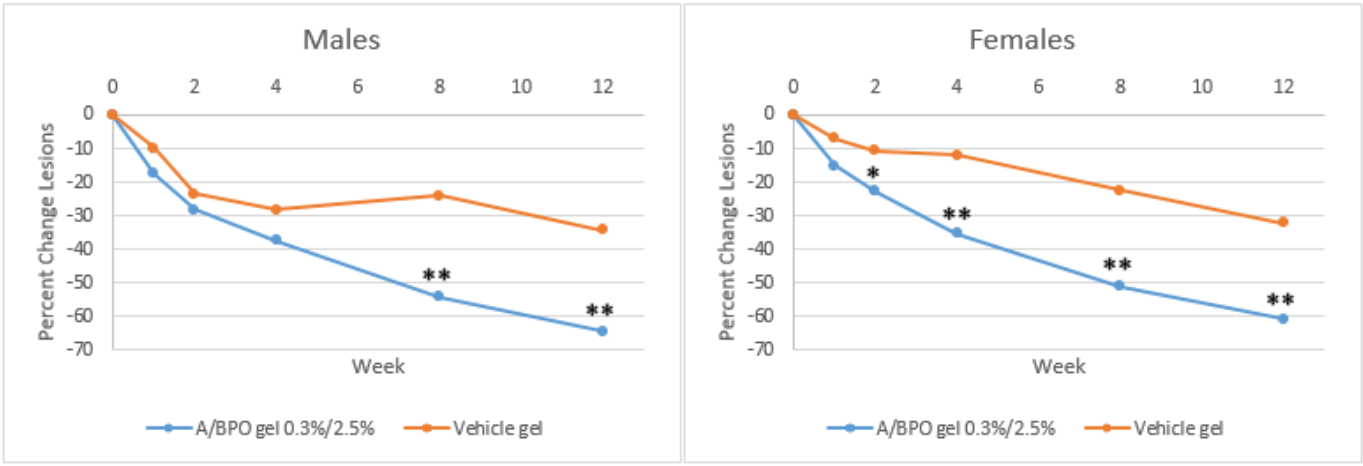
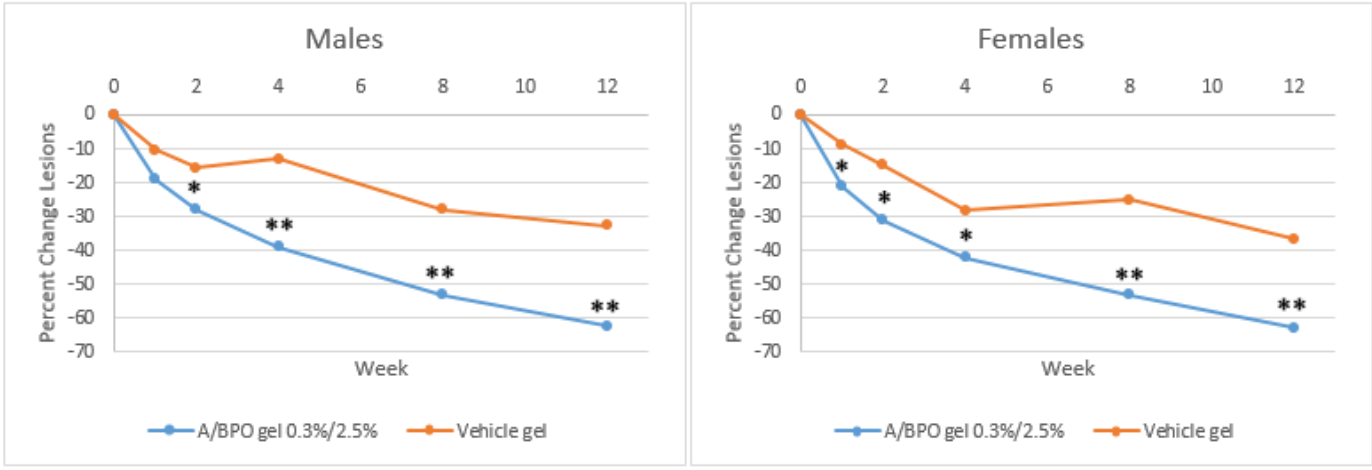


FIGURE 3B. Percent change inflammatory lesions by gender. Means (LOCF) at each time point. *P<0.005, **P<0.001.



ratio of females to males in each treatment group, and there was a higher percentage of subjects aged 12 - 17 years in the vehicle group. Total baseline lesion counts were high, averaging 98.5±39.0 in the A/BPO gel 0.3%/2.5% group and 97.6±36.6 in the vehicle group. Baseline inflammatory and noninflammatory lesion counts were comparable across groups (Table 1).

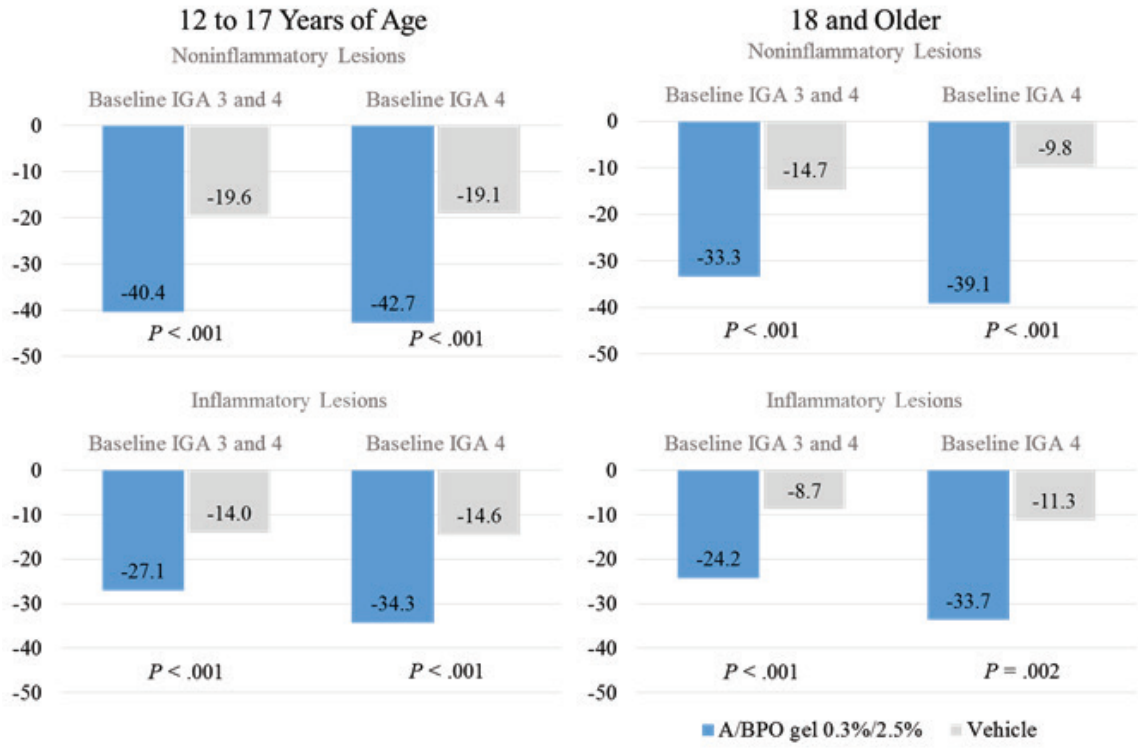
Efficacy by Gender

Success rates were significantly superior with A/BPO gel 0.3%/2.5% compared to vehicle at week 12 in both males (P=0.039) and females (P=0.009; Figure 1). As shown in Figure 2, there were comparable lesion count reductions at week 12 in acne lesions among both males and females, with statistically significantly superior reductions in all cases (P<0.001) compared with vehicle. As shown, the improvements were greatest among those with the most severe acne (IGA 4) at baseline. Males in the A/BPO gel 0.3%/2.5% group experienced a mean -64.5% change in noninflammatory lesions (vs -33.3% change for the vehicle group; P<0.001; Figure 3A) and females experienced a mean -60.8%% change (vs -32.4% change in the vehicle group, P<0.001; Figure 3A) at week 12 (LOCF). For inflammatory lesions, males in the A/BPO gel 0.3%/2.5% group experienced a mean -62.6% change (vs -32.8% change for the vehicle group, P<0.001; Figure 3B) and females experienced a mean -62.9%% change (vs -36.7% change in the vehicle group, P<0.001; Figure 3B) at week 12 (LOCF).

Efficacy by Age

Figure 4 presents the lesion reduction stratified by age (12-17 vs ≥18 years). Both age groups exhibited significant reductions from baseline in mean noninflammatory and inflammatory lesions when A/BPO gel 0.3%/2.5% treatment was compared with vehicle at week 12. Again, A/BPO gel 0.3%/2.5% treatment showed greater efficacy in subjects with more severe acne (IGA 4) at baseline. Subjects age 12–17 years old in the A/BPO gel 0.3%/2.5% group experienced a mean -62.7%

FIGURE 4. Mean change from baseline in lesions after 12 weeks of treatment with adapalene and benzoyl peroxide (A/BPO) gel 0.3%/2.5% or vehicle, by age.



change in noninflammatory lesions (vs -32.4% for the vehicle group, *P*<0.001; Figure 5A) and subjects over age 18 experienced a mean -62.4% change (vs -34.8% for the vehicle group, *P*<0.001; Figure 5A). For inflammatory lesions, subjects age 12 – 17 years old in the A/BPO gel 0.3%/2.5% group experienced a mean -61.8% change (vs -39.9% for the vehicle group, *P*<0.001; Figure 5B) and subjects over age 18 experienced a mean -63.8% change (vs -26.5% for the vehicle group, *P*<0.001; Figure 5B).

Safety and Tolerability

A/BPO gel 0.3%/2.5% was safe and well tolerated in all groups, with no significant differences based on gender or age. Adverse events in this study were generally mild to moderate in severity, and most were unrelated to the study drug. Only 9.7% of A/BPO gel 0.3%/2.5% treated subjects had to adopt the modified every-other-day application. The most common adverse events occurring in ≥1% of subjects in the A/BPO gel 0.3% group included nasopharyngitis (n=14), gastroenteritis (n=3), skin irritation (n=9), eczema (n=3), and headache (n=3). Figure 6 presents mean tolerability scores for A/BPO 0.3% vs vehicle stratified by gender; in both genders, tolerability scores were highest at the week 1 assessment and diminished for the remainder of the study. By week 12, A/BPO gel 0.3%/2.5% tolerability scores were similar to or below baseline tolerability scores, and similar to or below week 12 vehicle scores.

DISCUSSION

The results of this study support the use of A/BPO 0.3%/2.5% as a first line and foundational acne therapy in subjects 12 and older, including both genders, adolescents, and adults. While acne has traditionally been seen as predominantly a disease of teenagers, the changing demographics of the disease are highlighting the need for acne treatments shown to be effective and safe in population sub-groups. This is perhaps particularly important in severe inflammatory acne, a patient population that comprised 50% of the subjects in the study.[16] As shown in Table 1, the subjects in this study had a relatively high number of baseline lesions (98.5 total lesions in the A/BPO 0.3% group vs 65.5 - 79 total lesions in recent studies of other topical acne drugs).[16,21,22]

Gender can influence the experience of acne, and this should be considered when designing a treatment regimen. Differences in the impact of acne on the quality of life of women and men have been reported.[9,23,24] A 2011 study of 211 subjects compared women and men and found that women reported a lower quality of life regardless of acne severity at the first clinical visit; further, women with moderate acne were more likely to receive aggressive acne therapy.[23] Hassan et al reported women with acne had a more negative self-consciousness about appearance (*P*=0.001) and lower self-concept than men (*P*=0.004).[9] In addition, the individual's subjective rating of severity of their

FIGURE 5A. Percent change noninflammatory lesions by age. Means (LOCF) at each time point. *P<0.005, **P<0.001.

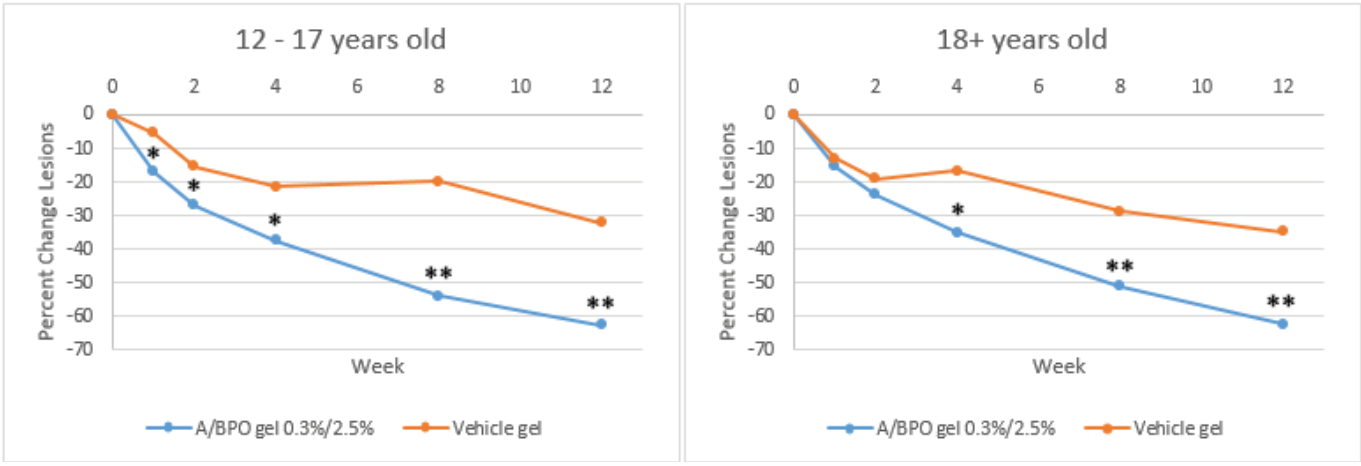
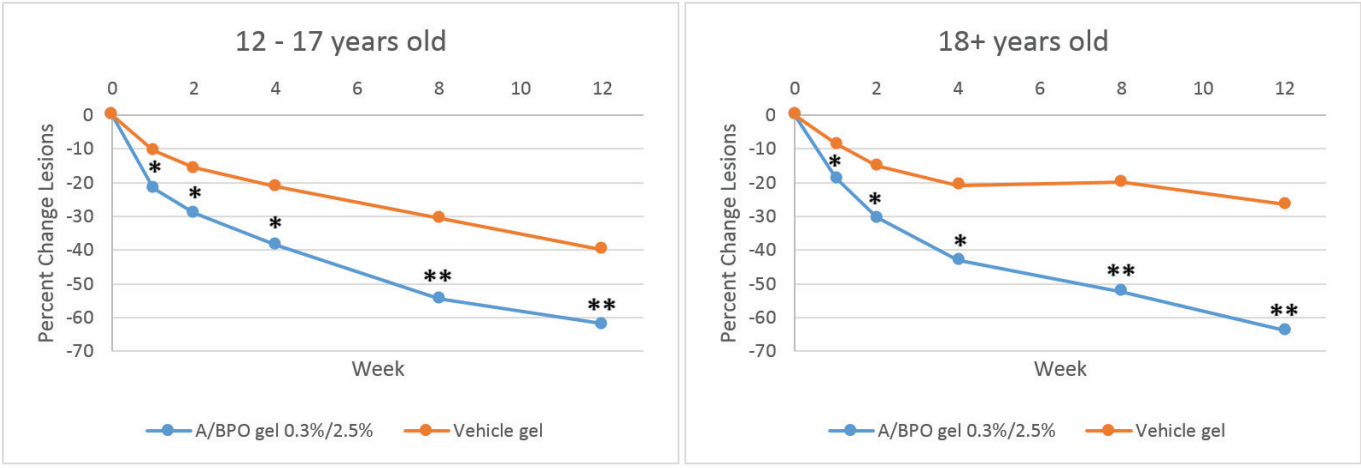


FIGURE 5B. Percent change inflammatory lesions by age. Means (LOCF) at each time point. *P<0.005, **P<0.001.



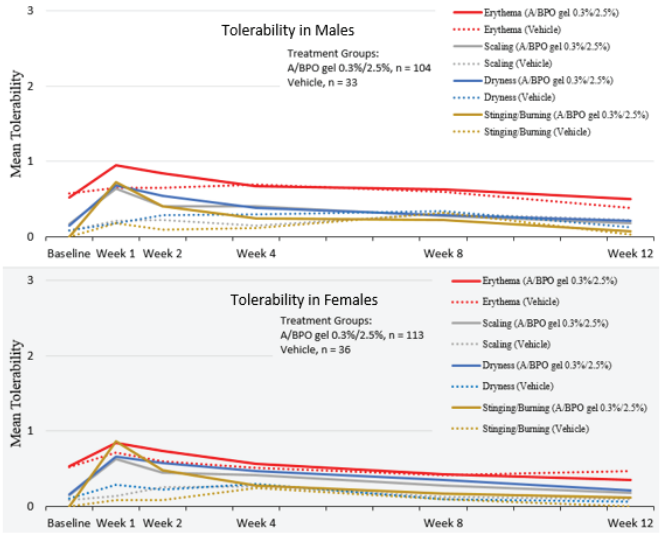
facial acne was significantly associated with increased social self-consciousness in women, but not in men.[9] This agrees with a finding by Motley et al that the patients perception of acne severity is most likely to predict psychosocial distress.[24]

Age may also have an impact on patients' responses and attitudes toward acne therapy. It is commonly understood that most adolescents will experience acne at some point, with the prevalence and severity of the disease each slightly higher in adolescent boys.[5] Adult acne has become an increasingly important topic, especially among the growing number of adult females who suffer from the condition.[10] There is a lag between perception of acne as an adolescent disease and the reality that a not unsubstantial proportion of adults have acne, which can present a challenge for older patients.[25] Hassan et al reported that patients ≥ 20 years had significantly more appearance-related distress compared with adolescents (P<0.05).[9]

Regardless of age or gender, adherence is an important factor in the success of acne therapy. Tuchayi et al reported that there were multiple factors associated with non-adherence to acne lifestyle issues such as not being able to follow complex regimens, busy lifestyle, forgetfulness and inconvenience as well as clinical issues such as lack of results, side effects, and psychiatric comorbidity.[26] Meta-analysis of 14 clinical studies involving more than 2,300 subjects showed that A/BPO achieved clinically meaningful results in reduction of acne lesions by 4 weeks and was well tolerated by the majority of subjects.[27] Because A/BPO addresses some of the factors that contribute to nonadherence (simple regimen, low potential for side effects, and convenience), it is well suited for treatment of both males and females and individuals of varying ages.

There are preliminary data that early treatment of acne with adapalene 0.3% reduces the potential risk for scarring, particularly in

FIGURE 6. Mean tolerability scores for A/BPO gel 0.3%/2.5% vs vehicle stratified by gender.



severe acne, which may be an additional important reason for using A/BPO 0.3% early in treatment. A phase II open-label pilot study of adapalene 0.3% and vehicle on the appearance of new scars showed that 24 weeks treatment with adapalene resulted in a 1 - 2 grade improvement of global scar grade in 56% of patients.[28] A follow-up split-face study of A/BPO gel 0.3%/2.5% in subjects with moderate acne and facial atrophic scars showed that A/BPO gel 0.3%/2.5% stabilized total scar count at 6 months. In contrast, scars continued to form on the vehicle treated side, and by month 6 the difference in scar count change between A/BPO 0.3%/2.5% and vehicle was statistically significant ($P = 0.036$).[29] At the molecular level, adapalene down-regulates expression of toll-like receptor 2 (TLR2), beta defensing 4, and interleukin 18, and has been shown to increase CD1d expression, reducing overall inflammation.[30-32] In scarring, adapalene treatment was associated with enhanced collagen synthesis (collagen-3 and procollagen-1).[28]

We have previously reported that the efficacy and safety of A/BPO 0.1%/2.5% in adult females was comparable to that observed in adolescent females.[33] This analysis shows that the higher concentration A/BPO 0.3% is a good option for patients with moderate to severe acne (with a greater number of baseline inflammatory and noninflammatory lesions than is generally seen in acne trials) of both genders and across the age spectrum. A/BPO gel 0.3%/2.5% was safe and well tolerated in all population sub-groups, with tolerability that was comparable to vehicle at week 12. Although the original study was not designed to compare A/BPO gel 0.3%/2.5% vs A/BPO gel 0.1%/2.5%, a treatment arm with A/BPO 0.1%/2.5% was included to provide a tolerability benchmark. As Stein Gold et al reported, the local tolerability profile of A/BPO gel 0.3%/2.5% in this study was similar to that of A/BPO gel 0.1%/2.5%.[16] With both concentrations, scores for tolerability signs/symptoms such as erythema, dryness, and stinging/burning were worst in the first week but were primarily mild to moderate in intensity and diminished with continued therapy.[16] In addition to a favorable tolerability profile, this study demonstrates that A/BPO 0.3%/2.5% is efficacious in moderate to severe acne, males and females, and both children (ages 12 – 17 years old) and adults. This makes A/BPO 0.3%/2.5% an ideal foundational topical therapy for a wide range of acne vulgaris patients.

TABLE 1.

Demographics and Disposition by Age, Gender, and Severity (ITT)		
n (%)	A/BPO gel 0.3%/2.5%	Vehicle
Overall	217	69
Age		
12 to 17 Years	111 (51.2)	43 (62.3)
18 Years and Older	106 (48.8)	26 (37.7)
Gender		
Males	104 (47.9)	33 (47.8)
Females	113 (52.1)	36 (52.2)
Severity		
IGA 3 (Moderate)	111 (51.2)	35 (50.7)
IGA 4 (Severe)	106 (48.8)	34 (49.3)
Baseline Lesion Counts: Inflammatory (Mean ± SD)		
Age 12-17 years	42.1 ± 18.9	39.0 ± 16.7
18 Years and Older	36.1 ± 17.8	32.2 ± 15.4
Males	41.1 ± 19.0	39.4 ± 17.9
Females	37.4 ± 18.1	33.8 ± 14.8
Baseline Lesion Counts: Noninflammatory (Mean ± SD)		
Age 12-17 years	63.7 ± 27.3	67.1 ± 29.9
18 Years and Older	53.9 ± 25.7	50.1 ± 21.9
Males	58.6 ± 25.8	59.9 ± 28.3
Females	59.2 ± 28.0	61.4 ± 28.6

IGA, investigator global assessment; 0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe.
ITT, intent to treat group. A/BPO, adapalene and benzoyl peroxide.
Source: US18240

DISCLOSURES

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