An overview of adapalene and benzoyl peroxide once-daily topical gel as a therapeutic option for acne

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Abstract

Introduction: Acne vulgaris is the most common skin condition worldwide, and it is associated with substantial psychological comorbidity. Topical therapies—including retinoids, antibiotics, and benzoyl peroxide—are the cornerstones of treatment for patients with acne. The main barriers to care in the treatment of acne are poor adherence to therapy and lack of tolerability.

Areas covered: Herein, the authors review the safety and efficacy of adapalene/benzoyl peroxide combination gel (0.1%/2.5% and 0.3%/2.5%), as well as its specific mechanisms of action that target acne vulgaris. The authors also offer an expert opinion on the use of adapalene/benzoyl peroxide gel compared with other topical therapies.
Expert opinion: Adapalene/benzoyl peroxide gel is safe and highly effective in the treatment of acne vulgaris. Its efficacy, tolerability, and ease-of-use are superior to other topical acne therapies, and its use does not contribute to antibiotic resistance. However, the cost of adapalene/benzoyl peroxide gel and lack of available generics may prohibit its use.

Keywords
acne vulgaris, adapalene, benzoyl peroxide, combination therapy, retinoids, topical
1. Introduction

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit which almost universally afflicts adolescents between the ages of 15 and 17 [1]. In 15-20% of these cases, the acne is moderate to severe [1]. Although acne is associated with adolescence and the onset of puberty, it commonly persists into adulthood; 64% of adults aged 20-29 and 43% of adults aged 30-39 report some degree of continued acne [2]. At any given time, acne affects 40 to 50 million people in the United States alone [3].

Acne pathogenesis is multifactorial and includes:

1) Activation of the innate immune system,
2) production of excessive sebum,
3) colonization of the pilosebaceous canal with *Cutibacterium acnes* with subsequent release of inflammatory mediators, and
4) abnormal desquamation of keratinocytes in the follicular canal [4].

The formation of a microcomedone represents the initial stage of acne pathogenesis [4]. In a microcomedone, the follicular canal is occluded with sloughed keratinocytes and sebum, which creates a hospitable environment for the proliferation of *C. acnes* [4].

Acne treatment depends on acne type, severity, anatomic location, and patient preference. First-line therapy for mild acne includes topical application of benzoyl peroxide, retinoids, or a combination of the two [5]. A topical antibiotic—typically erythromycin or clindamycin—may also be added as part of combination therapy [5]. For moderate acne, topical therapies may be supplemented with oral antibiotics [5]. For severe and recalcitrant disease, patients may require oral isotretinoin [5]. Topical therapies are a component of all acne treatment regimens except for the most severe cases, in which oral isotretinoin is used as monotherapy. Despite the disease’s high prevalence, there is no universal grading tool used in clinical assessment [5]. Therefore, a
successful response to treatment is often subjectively determined by clinician assessment and patient satisfaction with treatment outcome.

Unmet medical needs among patients with acne vulgaris primarily concern its impact on mental health and poor adherence to therapy. Acne is associated with substantial psychological comorbidity; acne increases the risk for anxiety, depression, and suicidal ideation [6]. Left untreated, it may lead to scarring and social impairment. Among patients with acne, females report worse scores on the Dermatology Life Quality Index than males [7].

Poor adherence to treatment is a significant barrier to achieving a satisfactory response. Adherence to topical therapies is notoriously poor compared with oral therapies, and adherence declines as the complexity of therapy increases [8, 9]. In patients randomized to use a topical combination therapy once daily versus using its two separate subcomponents once daily, median adherence in the combination group was 88% versus 61% in the subcomponents group [9]. Unsurprisingly, poor adherence results in poor clinical response.

2. Adapalene and benzoyl peroxide

2.1 Overview of the market
There is a plethora of over-the-counter and prescription acne therapies available, which reflects acne’s multi-factorial nature. Common classes of medications include antibiotics, retinoids, and hormonal agents [5]. Though each of these classes may be used as monotherapy, combination therapy is recommended for better efficacy. Among the most common topical treatments for acne are tretinoin, erythromycin, clindamycin, and benzoyl peroxide [5]. Tretinoin is the most commonly prescribed retinoid worldwide and is available as a cream, gel, and in microsphere formulations [10, 11]. It is highly efficacious but also highly irritating. Topical erythromycin and
clindamycin, although still widely used, should not be used as monotherapy due to increasing rates of antibiotic resistance [12].

2.2 Adapalene
Adapalene is a synthetic third-generation retinoid which received FDA-approval in 1996 for the treatment of acne in patients 12 and older [13]. Like other retinoids, it modulates DNA transcription and has comedolytic and anti-inflammatory properties. Adapalene is available in cream, gel, and lotion vehicles, in which it exists as a suspension of lipophilic microcrystals ranging from 3 to 10 µm in diameter [14]. This particle size allows adapalene to preferentially penetrate pilosebaceous canals, the target site in acne vulgaris [14].

2.3 Benzoyl peroxide
Benzoyl peroxide has been used since the early 1900s for its antimicrobial properties and is on the World Health Organization’s list of essential medicines [15, 16]. It is available in numerous vehicles and is often used in topical combination therapy for acne vulgaris. Benzoyl peroxide is most frequently combined with erythromycin, clindamycin, or adapalene, where it is used to suppress and—when combined with antibiotics—prevent the emergence of antibiotic-resistant strains of *Cutibacterium acnes* [12, 17].

2.4 An adapalene and benzoyl peroxide combination product
Adapalene is unique among retinoids in that it can be combined with benzoyl peroxide and remain chemically stable [18]. Benzoyl peroxide is a strong oxidizing agent, and adapalene’s aromatic structure is highly stable against light and oxidation, especially compared with tretinoin’s polyenic structure [19]. Fixed-dose adapalene/benzoyl peroxide (A/BPO) combination
gel is available in two formulations, 0.1%/2.5% (Epiduo®, Tactupump®, Tactuo®) and 0.3%/2.5% (Epiduo Forte®, Tactupump Forte®).

A/BPO (0.1%/2.5%) combination gel is indicated for the treatment of acne vulgaris in patients 9 years of age and older [20]; A/BPO (0.3%/2.5%) is indicated for patients 12 years and older [21]. A thin film of gel should be applied to affected areas of the face and/or trunk once daily after washing, using a pea-sized amount for each area of the face and avoiding the eyes, lips, and mucous membranes [20, 21].

3. Chemistry

Adapalene is a napthoic acid derivative in the retinoid family; in its pure form, it exists as a white to off-white powder [22]. Its empirical formula is C_{28}H_{28}O_{3}, and it has a molecular weight of 412.52 g/mol (see drug summary box) [23]. Adapalene’s IUPAC name is 6-[3-(1-adamantyl)-4-methoxyphenyl]naphthalene-2-carboxylic acid [24].

Benzoyl peroxide is formed by two benzoyl groups joined by a peroxide link. Its molecular formula is C_{14}H_{10}O_{4}, and it has a molecular weight of 242.23 g/mol (see drug summary box) [23]. Benzoyl peroxide’s IUPAC name is benzoyl benzenecarboperoxoate [25].

4. Pharmacodynamics

Retinoids modulate DNA transcription through the binding of retinoid acid receptors (RAR) and retinoid X receptors (RXR) [11]. These receptors each have three isotypes—\( \alpha \), \( \beta \), and \( \gamma \)—and retinoids differ in their ability to bind the isotypes [11]. The third-generation retinoids, adapalene and tazarotene, are selective agonists for RAR\( \beta \) and RAR\( \gamma \) [11]. RARs dimerize upon binding a retinoid ligand, and the receptor-ligand complex binds to regulatory elements in retinoic acid
response elements (RARE) [11]. This leads to multiple downstream effects responsible for adapalene’s mechanism of action.

Adapalene acts upon three of the four main pathogenic factors in acne:

1. Adapalene inhibits sebum production and leads to sebaceous gland atrophy [11, 26].
2. Adapalene normalizes keratinocyte differentiation, which loosens comedones and prevents obstruction of the follicular canal [11].
3. Adapalene decreases the expression of toll-like receptor 2 (TLR2) and activator protein-1 (AP-1) [4]. Toll-like receptors are part of the innate immune system, and TLR2 recognizes *C. acnes* and is responsible for propagating an inflammatory response to the bacteria [4]. AP-1 induces synthesis of matrix metalloproteinases, which break down collagen and contribute to scarring [11].

Benzoyl peroxide acts upon the fourth pathogenic factor in acne by exerting bactericidal effects against *C. acnes*. Benzoyl peroxide is lipophilic and penetrates pilosebaceous units well [12]. Following topical application, benzoyl peroxide is absorbed by the skin and converted to benzoic acid [17]. Benzoic acid is then metabolized by cutaneous cysteine, which releases free-radical oxygen species that lyse cell walls and destroy bacteria [4, 17]. In fixed-dose combination therapy, adapalene and benzoyl peroxide work synergistically [27].

5. Pharmacokinetics and metabolism

Absorption of adapalene is low—about 30 ng/g of a topically-applied dose [24]. Systemic adapalene is metabolized hepatically, undergoing o-methylation, hydroxylation, and conjugation before being excreted in bile [28]. Its elimination half-life is approximately 15 hours [21]. In 24 subjects with acne vulgaris treated with 2g of A/BPO (0.1%/2.5%) gel daily for 30 days, two
subjects had plasma adapalene concentrations above the limit of quantification (0.1 ng/mL) after four weeks of treatment [20]. The highest adapalene C\text{max} was 0.21 ng/mL [20]. In 26 subjects treated with an average of 2.3g of A/BPO (0.3%/2.5%) gel daily for four weeks, 16 subjects had plasma adapalene concentrations above the limit of quantification at the end of the study period [21]. The highest and mean adapalene C\text{max} were 0.35 ng/mL and 0.16 ± 0.08 ng/mL, respectively [21].

The skin converts benzoyl peroxide to benzoic acid, of which approximately 5% is absorbed systemically before being excreted renally [17]. Transepidermal delivery is concentration-dependent, and renal excretion of benzoic acid is so rapid that hepatic metabolism does not occur [29].

6. Clinical efficacy
Two major phase III studies have been conducted to assess the safety and efficacy of A/BPO gel (Table 1). Additional studies have evaluated the effects of A/BPO gel on atrophic acne scarring, and a pooled analysis has examined the synergistic efficacy of A/BPO combination therapy.

6.1 A 12-week, multi-center, randomized, double-blind, parallel-group, vehicle-controlled phase III clinical trial assessing the safety and efficacy of A/BPO (0.1%/2.5%) gel in subjects aged 12 to 64 with acne vulgaris (NCT00421993; 2006) [30]
A total of 1670 subjects with moderate acne vulgaris were randomized to one of four groups: A/BPO (0.1%/2.5%), 0.1% adapalene monotherapy, 2.5% benzoyl peroxide monotherapy, or vehicle gel. All groups were comparable in size and demographic composition, and subjects were instructed to apply the study medication once daily in the evening. Primary outcome measures included an Investigator’s Global Assessment (IGA) score of 0 (clear) or 1 (almost
clear) on a scale of 0-4, changes in inflammatory lesion counts, and changes in noninflammatory lesion counts at week 12.

In the intent-to-treat (ITT) population, 37.9% of subjects in the A/BPO group achieved an IGA score of 0 or 1 at week 12, compared with 21.8%, 26.7%, and 17.9% in the adapalene, benzoyl peroxide, and vehicle groups, respectively. Median reduction in inflammatory lesion counts at week 12 were 18 (A/BPO), 15 (adapalene), 16 (benzoyl peroxide), and 12 (vehicle). Median reduction in noninflammatory lesion counts at week 12 were 28, 24, 23, and 18, respectively.

6.2 A 12-week, multi-center, randomized, double-blind, parallel-group vehicle- and comparator-controlled phase III clinical trial assessing the safety and efficacy of A/BPO (0.3%/2.5%) gel in subjects aged 12 to 64 with acne vulgaris (NCT01880320; 2013) [31]

A total of 503 subjects with moderate to severe acne vulgaris were randomized 3:3:1 to receive A/BPO (0.3%/2.5%), A/BPO (0.1%/2.5%), or vehicle gel. Subjects were instructed to apply the study medication once daily, and the primary outcome measures were identical to the previously described study. Additional analyses were performed for subjects with a baseline IGA of 4 (severe).

In the ITT population, 33.7%, 27.3%, and 11.0% of subjects achieved an IGA of 0 or 1 in the A/BPO (0.3%/2.5%), A/BPO (0.1%/2.5%), and vehicle groups, respectively. Least squares mean reduction in inflammatory lesion counts were 27.04, 26.72, and 14.40, and least squares mean reduction in noninflammatory lesion counts were 40.18, 39.00, and 18.47, respectively. In the additional analyses of subjects with a baseline IGA of 4, A/BPO (0.3%/2.5%) and A/BPO (0.1%/2.5%) were each compared with vehicle. Statistical significance for success rate, defined
as an IGA of 0 or 1, was achieved by the higher dose A/BPO (p=0.029) but not by the lower
dose A/BPO (p=0.443) [32].

6.3 A 6-month, multi-center, randomized, investigator-blinded, vehicle-controlled, split-
face study evaluating the effect of A/BPO (0.1%/2.5%) gel in adults with atrophic acne
scars and primary acne lesions (NCT01688531; 2012) [33]
A total of 38 adult subjects with moderate facial acne vulgaris and a minimum of 10 atrophic
acne scars were instructed to apply A/BPO (0.1%/2.5%) and vehicle gel on each half-face daily
for 6 months. Outcome measures included acne lesion counts, atrophic acne scar counts, and
global assessment of acne scarring (Scar Global Assessment; SGA) at month 6.

In the per-protocol (PP) population (n=31), the mean number of total acne lesions
decreased from 24.1 to 8.5 at month 6 with A/BPO (a 65% reduction); mean total acne lesions
decreased from 25.0 to 16.1 with vehicle (a 36% reduction; p < 0.001). The mean number of
atrophic scars increased with both A/BPO (11.1 to 11.6 scars, a 4.5% increase) and vehicle (10.9
to 13.6 scars, a 24.8% increase; p = 0.0361). The percentage of subjects who achieved a rating of
“almost clear” on SGA at month 6 increased from 9.7% to 45.2% with A/BPO compared with
9.7% to 6.5% with vehicle (p = 0.0032).

6.4 A 6-month, multi-center, randomized, investigator-blinded, vehicle-controlled, split-
face study evaluating the effect of A/BPO (0.3%/2.5%) gel in adults with atrophic acne
scars and primary acne lesions (NCT02735421; 2016) [34]
A total of 67 adult subjects with moderate facial acne vulgaris and a minimum of 10 atrophic
acne scars were instructed to apply A/BPO (0.3%/2.5%) and vehicle gel on each half-face daily
for 6 months. Outcome measures were comparable to the prior study of A/BPO (0.1%/2.5%) on atrophic acne scarring.

In the per-protocol (PP) population (n=51), the percentage reduction in total acne lesions was 73.3% in the A/BPO group compared with 50.9% in the vehicle group (p < 0.005). Percentage change in total atrophic scar count was a 15.5% reduction in the A/BPO group compared with a 14.4% increase in the vehicle group (p < 0.0001). The percentage of subjects who achieved a rating of “clear” or “almost clear” on SGA at month 6 was 32.9% in the A/BPO group versus 16.4% in the vehicle group (a 16.5% difference; p < 0.01).

6.5 A pooled analysis comparing efficacy of A/BPO (0.1%/2.5%), 0.1% adapalene monotherapy, 2.5% benzoyl peroxide monotherapy, and vehicle gel [27]

A total of 3855 subjects from three double-blind, randomized, controlled trials were included in the ITT population. Subjects were instructed to use either A/BPO (0.1%/2.5%), 0.1% adapalene monotherapy, 2.5% benzoyl peroxide monotherapy, or vehicle gel once daily. Demographics were comparable across treatment groups, which were approximately equivalent in size. Primary outcomes included percent change in total acne lesion counts and percentage of subjects achieving an IGA score of 0 (clear) or 1 (almost clear) at weeks 1, 2, 4, and 8; these data were used to calculate the contribution of A/BPO synergy.

A/BPO gel demonstrated greatest synergy early in the course of treatment; synergy accounted for 48.7%, 44.4%, 20.0%, and 9.5% of efficacy in reducing total lesion counts at weeks 1, 2, 4, and 8, respectively. Additionally, synergy accounted for 128.6%, 13.2%, 41.7%, and 22.2% of efficacy in achieving an IGA score of 0 or 1 at weeks 1, 2, 4, and 8.

7. Safety and tolerability
Few studies have examined the tolerability of combination A/BPO gel. However, the combination product has low rates of adverse effects and is generally accepted as easily tolerated. As monotherapy, adapalene is considered the most tolerable retinoid, and 0.1% adapalene gel has equal efficacy and greater tolerability than 0.025% tretinoin gel [35]. In studies of benzoyl peroxide monotherapy, concentrations of 2.5%, 5%, and 10% showed equal efficacy but a dose-dependent risk of adverse reactions [36].

The most common side effects of combination A/BPO gel are local skin irritation, dryness, erythema, contact dermatitis, and a stinging or burning sensation [21]. Local skin irritation occurred in 4% of study participants in clinical trials of A/BPO (0.3%/2.5%) gel [21]; all other side effects occurred at rates of 1% or less [21]. Less common adverse events identified in post-marketing surveillance of A/BPO (0.3%/2.5%) gel include irritant contact dermatitis, facial edema, pruritus, and rash [37].

The safety and efficacy of A/BPO gel have not been established in pregnant women or nursing mothers [20, 21]. A/BPO is pregnancy Category C [21]; retinoids are teratogenic and contraindicated in pregnancy. However, in animal reproduction studies, topical adapalene administered at 19.5 times the maximum recommended human dose did not exhibit fetotoxicity [21]. Safety and efficacy have also not been established in patients under the age of 9 for the 0.1%/2.5% formulation, under the age of 12 for the 0.3%/2.5% formulation, or over the age of 64 for either formulation.

8. Conclusion

A/BPO gel represents a unique combination therapy that targets the four major factors in acne pathogenesis. It has an excellent safety and tolerability profile, and its physicochemical properties allow it to target the pilosebaceous unit selectively. In clinical trials, fixed-dose
combination therapy demonstrated superior efficacy compared with either adapalene or benzoyl peroxide monotherapy.

9. Expert opinion
A/BPO gel offers several advantages over other available therapies. First, adapalene is far less irritating than other retinoids, and its combination with 2.5% benzoyl peroxide suggests drug design with an emphasis on tolerability. There is a human tendency towards the belief that if some is good, more must be better—hence the availability of 5% and 10% (“maximum strength”) formulations of benzoyl peroxide. However, more is not always better in medicine, and the decision to use 2.5% benzoyl peroxide minimizes the risk of adverse effects without compromising efficacy [36]. In contrast, the higher concentration of adapalene in A/BPO (0.3%/2.5%) offers better efficacy than A/BPO (0.1%/2.5%) but at the cost of increased risk of side effects.

Second, in addition to being minimally irritating, A/BPO combination gel is convenient and simplifies application compared with therapies that require the use of more than one product. This translates to improved treatment adherence. Poor adherence is a major barrier to treatment success; approximately 40% of patients prescribed topical therapy do not use their medication as prescribed [38]. In addition to simplifying treatment, physicians may wish to further enhance adherence by offering supplemental educational materials to patients or instituting a daily electronic reminder system, methods which have improved adherence to topical acne therapies in clinical trials [39, 40].

Finally, adapalene and benzoyl peroxide work synergistically to reduce and prevent acne lesions without any risk for antibiotic resistance. Antibiotic resistance has increased drastically in recent years; based on studies of dermatology patients with acne vulgaris, 49-73% of C. acnes
isolates are now resistant to erythromycin [41, 42]. Benzoyl peroxide is equally effective against erythromycin-sensitive and erythromycin-resistant strains of *C. acnes*, and its use inhibits the development of resistant bacteria [43].

Topical combination therapy is a cornerstone of treatment at all levels of acne severity [5]. Based on current treatment guidelines, A/BPO combination gel is likely to remain a first-line therapy for treatment of mild to moderate acne vulgaris. Its higher dose formulation, A/BPO (0.3%/2.5%), may become part of a first-line regimen for severe acne. A/BPO (0.3%/2.5%) prescribed concurrently with oral doxycycline or limecycline may be particularly effective for patients with severe acne who wish to avoid oral isotretinoin [44, 45]. Overall, physicians are likely to prescribe A/BPO combination gel with several caveats.

First, A/BPO gel may be costly. When cost is a consideration, physicians may choose to prescribe more affordable but less efficacious therapies, such as retinoid or benzoyl peroxide monotherapy. Patients may also elect to purchase adapalene and benzoyl peroxide separately as over-the-counter preparations. Next, patients may not like a leave-on therapy. Leave-on benzoyl peroxide products can bleach clothing and bedding, and patients who use acne medications at night may prefer to use a product that will not potentially damage their sheets. Finally, some patients may not like the gel vehicle. Few data are available on vehicle preference in acne vulgaris, but vehicle characteristics influence adherence to therapy [46].

Further data on the safety and efficacy of A/BPO gel are needed in special populations. No human studies have been performed evaluating the safety of A/BPO gel in pregnant or nursing women; A/BPO gel use in pregnancy should be reserved for patients in whom the potential benefit justifies potential risks. Further studies are also needed to establish the safety and efficacy of A/BPO gel in adults aged 65 and older. Although adults in this age group were
eligible to participate in both phase III trials described previously, no participants in this age
group were recruited.

Overall, A/BPO combination gel is likely to remain a first-line therapy for patients with
acne vulgaris, especially in cases where cost is not an issue. The development of cost-effective
generics as well as the development of newer retinoids—such as the fourth-generation retinoid
trifarotene—may ultimately increase the accessibility and use of A/BPO gel.

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Declaration of Interest

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Almirall, Leo Pharma, Mylan, Merck & Co, Pierre Fabre, Promius, Foamix, Forte, TwoXar,
Arena Pharmaceuticals Ltd, Menlo, Ortho Pharmaceutical, Mayne Pharma, Sienna
Biopharmaceuticals, Avva, Alcimed, and Qurient. He is founder and majority owner of
www.DrScore.com and founder and part owner of Causa Research. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

**Reviewer Disclosures:**

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.
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<table>
<thead>
<tr>
<th>Drug name</th>
<th>Adapalene and benzoyl peroxide (once daily)</th>
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<tbody>
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<td>Launched</td>
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<tr>
<td>Indication</td>
<td>Acne Vulgaris</td>
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<tr>
<td>Pharmacology description</td>
<td>Retinoic acid beta receptor agonist</td>
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<td>Protein synthesis inhibitor</td>
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<td>Microbial collagenase inhibitor</td>
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<tr>
<td>Pivotal trial(s)</td>
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Table 1. Comparison of Phase III Clinical Trials of Adapalene/Benzoyl Peroxide (0.1%/2.5%) Gel and Adapalene/Benzoyl Peroxide (0.3%/2.5%) Gel for Acne Vulgaris

<table>
<thead>
<tr>
<th>Study design</th>
<th>A/BPO, 0.1%/2.5%</th>
<th>A/BPO, 0.3%/2.5%</th>
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</thead>
<tbody>
<tr>
<td>12-week, multi-center, randomized (1:1:1:1), double-blind, parallel-group, vehicle-controlled clinical trial</td>
<td>12-week, multi-center, randomized (3:3:1), double-blind, parallel-group, comparator- and vehicle-controlled clinical trial</td>
<td></td>
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<tr>
<td>Participants</td>
<td>1670 subjects aged 12 years and older with moderate acne vulgaris involving the face</td>
<td>503 subjects aged 12 years and older with moderate to severe acne vulgaris involving the face</td>
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<tr>
<td>Treatment arms</td>
<td>A/BPO (0.1%/2.5%) gel, Adapalene (0.1%) gel, Benzoyl peroxide (2.5%) gel, Vehicle gel</td>
<td>A/BPO (0.3%/2.5%) gel, A/BPO (0.1%/2.5%) gel, Vehicle gel</td>
</tr>
<tr>
<td>Incidence of application site AEs</td>
<td>A/BPO (0.1%/2.5%): dry skin (21.48%) Adapalene (0.1%): dry skin (14.35%) Benzoyl peroxide (2.5%): dry skin (8.43%) Vehicle gel: dry skin (5.26%)</td>
<td>A/BPO (0.3%/2.5%): skin irritation (4.15%), allergic dermatitis (0.46%), eczema (1.38%), rash (0.46%), urticaria (0.46%) A/BPO (0.1%/2.5%): skin irritation (0.46%), allergic dermatitis (1.38%) Vehicle gel: rash (1.45%), urticaria (1.45%)</td>
</tr>
</tbody>
</table>

Pharmacotherapy Adapalene
Pharmacotherapy: Benzoyl Peroxide