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A 6-month maintenance therapy with adapalene-benzoyl peroxide gel prevents relapse and continuously improves efficacy among patients with severe acne vulgaris: results of a randomized controlled trial

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Conflicts of interest
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Summary

Background Acne vulgaris is a chronic and frequently recurring disease. A fixed-dose adapalene-benzoyl peroxide (adapalene-BPO) gel is an efficacious and safe acne treatment.

Objectives To assess the long-term effect of adapalene-BPO on relapse prevention among patients with severe acne after successful initial treatments.

Methods This is a multicentre, double-blind, randomized and controlled study. In total, 243 subjects who had severe acne vulgaris and at least 50% global improvement after a previous 12-week treatment were randomized into the present study to receive adapalene-BPO gel or its vehicle once daily for 24 weeks.

Results At week 24, compared with vehicle, adapalene-BPO resulted in significantly higher lesion maintenance success rate (defined as having at least 50% improvement in lesion counts achieved in initial treatment) for all types of lesions (total lesions: 78·9% vs. 45·8%; inflammatory lesions: 78·0% vs. 48·3%; noninflammatory lesions: 78·0% vs. 43·3%; all $P < 0·001$). Significantly more subjects with adapalene-BPO than with vehicle had the same or better Investigator's Global Assessment score at week 24 than at baseline (70·7% vs. 34·2%; $P < 0·001$). The time when 25% of subjects relapsed was 175 days with adapalene-BPO and 56 days with vehicle (17 weeks earlier; $P < 0·0001$). Adapalene-BPO led to further decrease of lesion counts during the study and 45·7% of subjects were 'clear' or 'almost clear' at week 24. It was also safe and well tolerated in the study.

Conclusions Adapalene-BPO not only prevents the occurrence of relapse among patients with severe acne, but also continues to reduce disease symptoms during 6 months.

Acne vulgaris is defined as a chronic disease, because of its long duration, pattern of recurrence or relapse, and psychological and social impacts on patients' quality of life.[1,2] Duration of acne varies from 3 months to 5–40 years; for 80% of patients the disease does not spontaneously regress until they are in their thirties.[1] Consequently, long-term management is often necessary for patients with acne to prevent relapses and to maintain the improvement achieved in short-term therapy.[3,4] The maintenance therapy is particularly important among patients with more severe acne, as recent studies suggested that relapse occurred more frequently among patients with severe acne than among patients with a more moderate disease.[5,6]

To help address the multiple aetiological factors of acne,[3,7] combination therapy utilizing agents with complementary mechanisms is in standard use as part of therapeutic strategy.[8] A fixed-dose combination gel with adapalene 0·1% and benzoyl peroxide 2·5% (adapalene-BPO) is an efficacious and safe treatment of moderate acne, as demonstrated in several randomized and double-blind clinical studies of 12 weeks,[9–12] and appears to be especially efficacious among patients with a high number of acne lesions before treatment.[13] Its combination with doxycycline 100 mg daily provided significant benefit compared with doxycycline alone in a 12-week treatment of severe acne.[14] Adapalene-BPO can be also used as a long-term therapy, because neither adapalene nor BPO generates antibiotic resistance.[4,15] Adapalene provides long-lasting benefit by controlling microcomedo formation.[16–19] Moreover, a 12-month continuous-use study supports the safe and efficacious use of adapalene-BPO for the long-term management of patients with mild and moderate acne.[20]

The objective of the present study was to compare the effect of a 6-month maintenance therapy with adapalene-BPO or its vehicle among patients with severe acne who had shown at least 50% global improvement after a 12-week treatment from a previous study.[14]

Materials and methods

Study design

This randomized, double-blind and vehicle-controlled study was a follow-up of a previous 12-week study in which subjects with severe acne vulgaris [defined as having an Investigator's Global Assessment (IGA) of 4] were randomized to receive doxycycline 100 mg daily and adapalene-BPO (Epiduo™; Galderma LP, Fort Worth, TX, U.S.A.) or its vehicle.[14] The subjects who showed at least 50% global improvement with either therapy at the end of the previous study were eligible to be enrolled into the present study and were re-randomized 1 : 1 to receive either adapalene-BPO or its gel vehicle once daily in the evening for 24 weeks. Randomization was on an ongoing basis and was achieved using a central telephone/web system to assure that the subjects who received adapalene-BPO and doxycycline or vehicle and doxycycline in the previous study would be evenly distributed between the adapalene-BPO group and the vehicle group in the present study. The use of a sun protection factor 15 daily facial moisturizer and a gentle skin cleanser was encouraged: moisturizer for symptomatic relief and outdoor activities, and cleanser prior to applying study medication. Women were excluded if they were pregnant, nursing or planning a pregnancy, as were men with facial hair that would interfere with the assessments. Efficacy and safety evaluations were performed at baseline and at weeks 4, 8, 12, 16, 20 and 24. Subjects were free to withdraw from the study at any time and for any reason. Subjects not completing the entire study were to be fully evaluated when possible.

This study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and Good Clinical Practices and in compliance with local regulatory requirements. The study was reviewed and approved by institutional review boards. All patients (and parents/guardians if applicable) provided their written informed consent prior to entering the study.

Efficacy and safety assessments

Inflammatory and noninflammatory lesion counts as well as IGA were assessed at each study visit. The percentage change from baseline in lesion counts and IGA success rate (percentage of subjects rated 'clear' or 'almost clear') were analysed for each visit. To analyse the relapse of acne at each visit, the lesion maintenance success rates (percentage of subjects having at least 50% of improvement in lesion counts obtained in previous therapy) for each type of lesion and the IGA maintenance success rate (percentage of subjects with the same or better IGA score compared with baseline) were analysed. The definition of lesion maintenance was adapted from an assessment developed by the National Psoriasis Foundation to evaluate the duration of effect for psoriasis treatments[21,22] and a similar method has been utilized in previous acne maintenance studies.[16,17] Correspondingly, relapse was defined as having < 50% of improvement in lesion counts obtained in the previous therapy, or having an IGA score worse than that at baseline. The time to relapse in terms of total lesions was also analysed and defined as the duration between baseline and the first visit when relapse occurs. *Propionibacterium acnes* counts were assessed using ultraviolet photography at five selected sites at weeks 12 and 24. Postinflammatory hyperpigmentation (PIH) was assessed on the subjects of phototype IV–VI on a five-point scale from 0 (none) to 4 (severe). At the last visit, subjects completed a seven-item satisfaction questionnaire.

Safety was assessed through evaluations of local cutaneous tolerability and adverse events (AEs). At each visit, the investigator rated local cutaneous tolerability (erythema, scaling, dryness and stinging/burning) on a scale ranging from 0 (none) to 3 (severe) and assessed the AEs. Mean scores at each postbaseline visit and mean worst score postbaseline were recorded.

Statistical analyses

All randomized subjects [intent-to-treat (ITT) population] were included in the analyses (ITT-observed population). For maintenance variables, in order to limit the bias, any missing data were considered as failure, except when values of both previous and following visits were success (ITT-worst case population). Centres with a low recruitment rate were combined into analysis centres (by geographical areas) to allow an appropriate stratification of statistical analyses.

All variables except the time to relapse were analysed by using the Cochran–Mantel–Haenszel statistic, stratified by analysis centres and previous treatments (from the previous

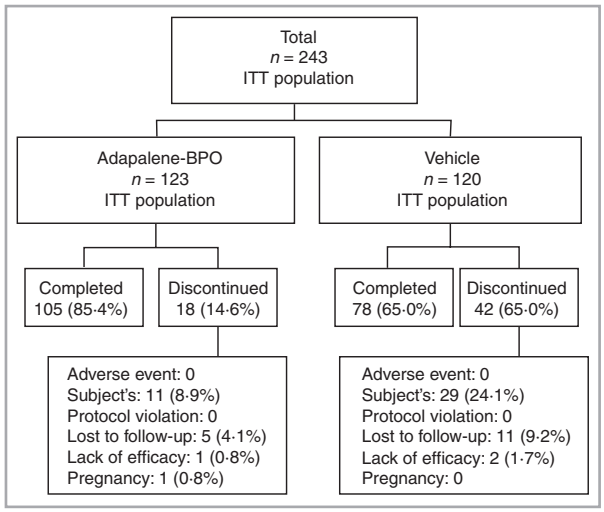

Fig 1. Subject disposition. ITT, intent-to-treat; BPO, benzoyl peroxide.

12-week study), after ridit transformation with row mean difference statistics, testing the hypothesis of equality. The time to relapse was analysed using survival analysis (Kaplan–Meier). Tests were two sided, with significance declared at the level of 0·05. AEs and local tolerability were summarized descriptively.

Results

Subject disposition and baseline characteristics

Two hundred and forty-three subjects were randomized and included in the ITT population, with 123 receiving adapalene-BPO and 120 receiving vehicle (Fig. 1). Overall, 75·3% of subjects completed the study. Subject disposition was similar between the treatment groups, except that more subjects discontinued in the vehicle group (35·0%) compared with adapalene-BPO group (14·6%). Most subjects who discontinued were either lost to follow-up or discontinued at their own request.

The demographic and baseline disease characteristics were comparable between the treatment groups (Table 1). The mean duration of acne was more than 5 years. Both groups had a similar number of inflammatory, noninflammatory and total lesion counts, while more subjects in the vehicle group than in the adapalene-BPO group had 'clear' or 'almost clear' IGA evaluations (37·5% vs. 26·8%) after the previous 12-week treatment with doxycycline and adapalene-BPO or its vehicle.[14]

Efficacy evaluation

After 24 weeks of treatment, subjects receiving adapalene-BPO had a significantly superior lesion maintenance success rate relative to subjects receiving vehicle for each lesion type (total lesions: 78·9% vs. 45·8%; inflammatory lesions: 78·0% vs. 48·3%; noninflammatory lesions: 78·0% vs. 43·3%; all $P < 0·001$; Table 2). Significant differences were observed in favour of adapalene-BPO vs. vehicle as early as week 4 for total ($P < 0·05$) and noninflammatory lesions ($P < 0·01$), and week 8 for inflammatory lesions ($P < 0·01$). The time when 25% of subjects relapsed was 175 days with adapalene-BPO and 56 days with vehicle (17 weeks or 119 days earlier; $P < 0·0001$). For IGA maintenance success rate, 70·7% of subjects in the adapalene-BPO group remained stable or

Table 1 Baseline demographic and disease characteristics (intent-to-treat)

	Adapalene-BPO (n = 123)	Vehicle (n = 120)	Total (n = 243)
Gender, n (%)			
Male	65 (52·8)	67 (55·8)	132 (54·3)
Female	58 (47·2)	53 (44·2)	111 (45·7)
Age (years), mean ± SD (range)	19·1 ± 5·89 (12–38)	18·2 ± 5·23 (12–35)	18·6 ± 5·58 (12–38)
Fitzpatrick phototype, n (%)			
I	3 (2·5)	3 (2·5)	6 (2·5)
II	27 (22·1)	43 (35·8)	70 (28·9)
III	57 (46·7)	49 (40·8)	106 (43·8)
IV	25 (20·5)	19 (15·8)	44 (18·2)
V	5 (4·1)	3 (2·5)	8 (3·3)
VI	5 (4·1)	3 (2·5)	8 (3·3)
Duration of acne (years), mean ± SD	5·92 ± 4·36	5·27 ± 4·05	5·60 ± 4·21
IGA, n (%)			
0: clear	1 (0·8)	–	1 (0·4)
1: almost clear	32 (26·0)	45 (37·5)	77 (31·7)
2: mild	62 (50·4)	56 (46·7)	118 (48·6)
3: moderate	28 (22·8)	19 (15·8)	47 (19·3)
Inflammatory lesion counts, mean ± SD (range)	10·9 ± 7·8 (0–36)	10·6 ± 9·2 (0–50)	10·8 ± 8·5 (0–50)
Noninflammatory lesion counts, mean ± SD (range)	25·3 ± 18·2 (0–89)	23·5 ± 21·7 (0–138)	24·4 ± 20·0 (0–138)
Total lesion counts, mean ± SD (range)	36·2 ± 22·0 (0–104)	34·1 ± 26·1 (2–158)	35·2 ± 24·1 (0–158)

IGA, Investigator's Global Assessment; BPO, benzoyl peroxide.

Table 2 Maintenance success rates for total, inflammatory and noninflammatory lesions and Investigator's Global Assessment (IGA) (intent-to-treat–worst case). For lesion counts, maintenance success rate was defined as percentage of subjects having at least 50% of improvement obtained in prior therapy. For IGA, maintenance success rate was defined as percentage of subjects having the same or better IGA score compared with baseline

	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Total lesions						
Adapalene-BPO	95·1	87·8	86·2	84·6	82·1	78·9
Vehicle	86·7	72·5	63·3	57·5	50·0	45·8
P-value	< 0·05	< 0·005	< 0·001	< 0·001	< 0·001	< 0·001
Inflammatory lesions						
Adapalene-BPO	92·7	87·0	82·1	82·1	75·6	78·0
Vehicle	85·0	71·7	61·7	60·0	51·7	48·3
P-value	NS	< 0·005	< 0·001	< 0·001	< 0·001	< 0·001
Noninflammatory lesions						
Adapalene-BPO	93·5	90·2	83·7	82·1	79·7	78·0
Vehicle	83·3	73·3	60·0	50·8	45·0	43·3
P-value	< 0·01	< 0·001	< 0·001	< 0·001	< 0·001	< 0·001
IGA						
Adapalene-BPO	83·7	82·1	76·4	74·0	69·9	70·7
Vehicle	69·2	55·8	48·3	40·8	35·8	34·2
P-value	< 0·01	< 0·001	< 0·001	< 0·001	< 0·001	< 0·001

BPO, benzoyl peroxide; NS, not significant.

improved at week 24, vs. 34·2% in the vehicle group ($P < 0·001$).

In terms of percentage change from baseline, subjects receiving adapalene-BPO experienced a further decrease of lesion counts during the present study (−26·0%, −21·2% and −31·0% for total, inflammatory and noninflammatory lesions, respectively), whereas subjects receiving vehicle experienced an increase in lesion counts from baseline (+46·3%, +28·6% and +45·0% for total, inflammatory and noninflammatory lesions, respectively; all $P < 0·01$; Fig. 2). Similarly, IGA success rate (percentage of subjects rated 'clear' or 'almost clear') increased from 26·8% to 45·7% after 6 months of maintenance therapy with adapalene-BPO, whereas it decreased for the vehicle group from 37·5% to 25·6% during the same period ($P < 0·01$, Fig. 3).

Consistent results were observed for other efficacy assessments. *Propionibacterium acnes* counts remained stable with no rebound for subjects with adapalene-BPO, whereas the level increased with vehicle (percentage change from baseline of −3·8% vs. +136·0%). PIH was reduced among subjects in the adapalene-BPO group but was increased in the vehicle group (percentage change from baseline of −13·2% vs. +28·1%; $P = 0·02$). The effect on facial lesions after 12 weeks of adapalene-BPO plus doxycycline treatment (baseline of present study) and after 24 weeks of adapalene-BPO maintenance treatment is illustrated in Figure 4.

The subject assessment results mirrored the efficacy evaluations by the investigators. Overall, significantly more subjects were 'very satisfied' or 'satisfied' with the treatment of adapalene-BPO compared with vehicle (84·1% vs. 54·9%; $P < 0·001$), and would consider using the treatment again (88·4% vs. 61·4%; $P < 0·001$).

Safety evaluation

During the 6-month study period, treatment-related AEs were rare and occurred only in 4·1% of subjects in the adapalene-BPO group (five subjects) and 0·8% of subjects in the vehicle group (one subject). Almost all related AEs were dermatological in nature, with none being severe or serious. No AE led to study discontinuation.

Overall, the mean tolerability scores at each visit and the postbaseline mean worst score were low for both groups and never exceeded 0·6 (1 was defined as 'mild'). Subjects in the adapalene-BPO group experienced slightly more irritation than subjects in the vehicle group. However, the majority of subjects did not worsen after baseline for each of the assessed signs and symptoms (erythema 76·7%, scaling 70·8%, dryness 73·3% and stinging/burning 78·3% with adapalene-BPO vs. 83·5%, 92·2%, 88·7% and 92·2% with vehicle).

Consistent with the safety evaluation by investigators, the majority of subjects from both groups was 'not bothered at all' by the treatment side-effects (74·3% with adapalene-BPO and 72·3% with vehicle; $P = 0·787$).

Discussion

Acne is a chronic and frequently relapsing condition which necessitates long-term treatment. Controlling relapse is difficult even after successful treatments.[13,14] For example, while oral isotretinoin remains an efficacious treatment for severe nodulocystic acne or acne that failed antibiotic treatments, studies showed that 21–52% of patients on isotretinoin relapsed, most within the first 2 years.[5,6,23] Maintenance therapy after a successful initial treatment may be useful to prevent lesions from

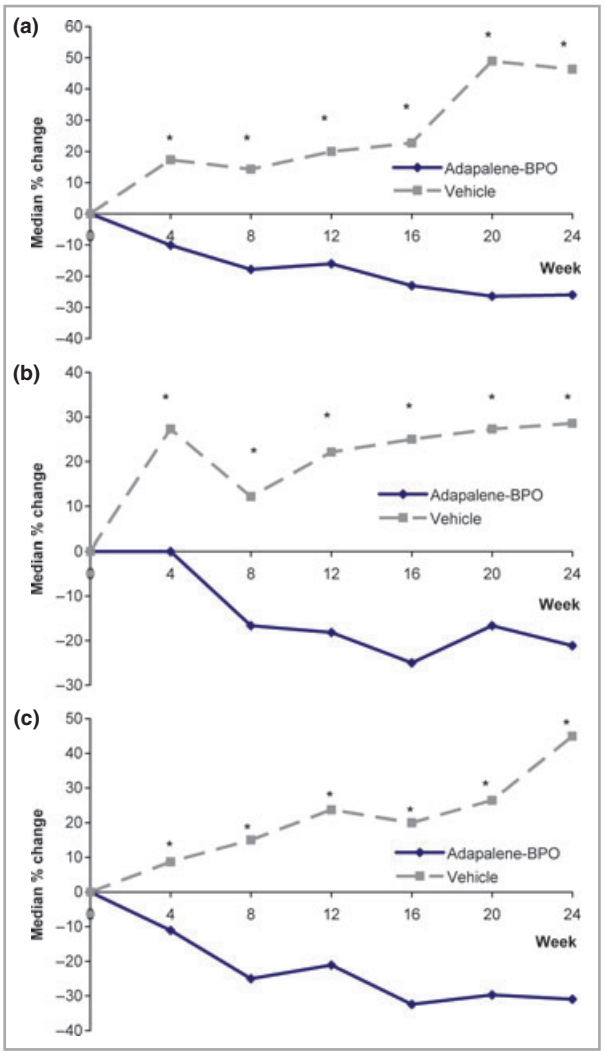

Fig 2. Median percentage change from baseline in total, inflammatory and noninflammatory lesions (intent-to-treat–observed population). (a) Total lesions †P < 0·001; (b) inflammatory lesions *P < 0·05; (c) noninflammatory lesions #P ≤ 0·001.

returning by suppressing the development of microcomedones and by continuously targeting *P. acnes* colonization.[8,24] Maintenance therapy may be especially beneficial to patients with more severe acne, as relapse generally occurs more frequently in patients with more severe disease presentations.[5,6]

Definitions of relapse vary considerably in the literature and there is no widely accepted formal definition. The design of this study set a high threshold for achieving success by using a parallel control group, 'worst case' statistical methodology and subject questionnaire, as well as by re-randomizing subjects after the previous 12-week study.[25] In the absence of a formally accepted methodology, the approach used in this study (having at least 100% of previous improvement in terms of IGA or at least 50% of previous improvement in terms of lesion counts) is practical, objective, and easily transferable to a clinical setting. Previously available data on acne maintenance therapy were limited to studies of 12 or 16 weeks.[16–19] Although the durations of those studies were long enough to depict between-group differences, studies of longer duration may more accurately determine the efficacy of a maintenance treatment.[2] The present study represents the first 6-month, randomized and controlled maintenance trial with a topical acne treatment.

In this study, adapalene-BPO was demonstrated to be significantly more efficacious than its vehicle in maintaining the improvement from previous therapy. Furthermore, the treatment with adapalene-BPO continuously decreased lesion counts and increased treatment success during 6 months. Differences between the adapalene-BPO and vehicle groups in maintenance success rates based on IGA or on total and noninflammatory lesion counts were apparent at the first study visit (week 4), indicating that relapse may occur as soon as active therapy is discontinued. The early effect of adapalene-BPO was sustained until the end of the study for all efficacy assessments, demonstrating improved results over vehicle in *P. acnes* counts as well as subject satisfaction. In addition, an improvement in PIH was observed in the adapalene-BPO

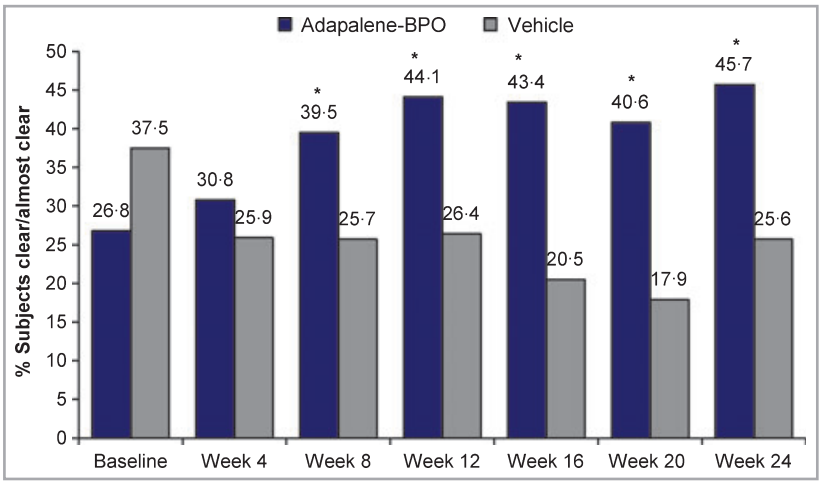

Fig 3. Success rates (percentage of subjects rated 'clear' or 'almost clear'; intent-to-treat–observed population). BPO, benzoyl peroxide. *P < 0·05.

Fig 4. Photographs of a subject at (a) baseline of the previous study,[14] (b) after 12 weeks of adapalene-benzoyl peroxide (adapalene-BPO) + doxycycline treatment (baseline of the present study), and (c) after 24 weeks of adapalene-BPO maintenance treatment.

group among darker-skinned patients compared with a worsening in the vehicle group. Such finding might be of particular interest for subjects with darker skin colour and prone to PIH.

Two general concerns for prescribing long-term maintenance therapy are the possibility of AEs and the potential for *P. acnes* resistance. Adapalene-BPO gel was safe and well tolerated during the study, with few treatment-related AEs reported. As expected, adapalene-BPO local tolerability scores were higher than those for vehicle, but nevertheless remained below 1 (mild) for the entire study and never exceeded 0·6. Consistent with the safety data, a similar percentage of subjects in both groups was not bothered at all by the treatment side-effects. These results are also consistent with previous studies showing that adapalene can be added to other therapies without significantly increasing skin irritation.[10–12,26,27] Neither retinoid nor BPO creates selective pressure for bacterial resistance. Therefore, the combination is suitable for long-term usage and may be expected to decrease the incidence of bacterial resistance due to antibiotics usage.[8,28,29] Consistently, this study showed no apparent rebound of *P. acnes* by ultraviolet photography in the adapalene-BPO group after 6 months of daily treatment.

Overall, the results of this study demonstrated a clear clinical benefit for continued usage of adapalene-BPO as a maintenance therapy for patients with severe acne who responded to initial therapy. Long-term treatment with adapalene-BPO is safe and well tolerated, prevents relapse, continues to reduce acne lesions and further increases treatment success.

What's already known about this topic?

- Long-term management of patients with acne is essential to prevent relapse and to maintain the improvement achieved in short-term therapy. However, very few acne treatments are suitable for prolonged usage.
- The fixed-dose adapalene and benzoyl peroxide (adapalene-BPO) combination gel is an efficacious and safe acne treatment.

What does this study add?

- Among patients with severe acne, adapalene-BPO provided significant advantages compared with vehicle in preventing relapse and continuously improving disease symptoms for 6 months.

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