ADAPALENE-BENZOYL PEROXIDE, A NEW ONCE DAILY FIXED-DOSE COMBINATION FOR THE TREATMENT OF ACNE VULGARIS: A RANDOMIZED, BILATERAL (SPLIT-FACE), DOSE-ASSESSMENT STUDY OF CUTANEOUS TOLERABILITY IN HEALTHY SUBJECTS

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INTRODUCTION

Combination therapy is an effective approach to simultaneously target multiple pathogenic factors of acne.[1-3] International guidelines recommend the use of topical retinoids and benzoyl peroxide (BPO) for acne treatment.[3] These drugs are often prescribed as a free combination without any safety concern associated with antibiotic use. Recently, a unique, once-daily, fixed-dose combination gel with adapalene 0.1% and BPO 2.5% (Epiduo™, Galderma) has been developed. Pre-clinical studies showed that a formulation containing adapalene and BPO has an overall pre-clinical profile similar to the individual agents. Moreover, unlike tretinoin, adapalene is stable when combined to BPO in presence or absence of light.[4]

METHODS

Study design and objectives

- 3-week, randomized, controlled, investigator-blind, single-center, split-face study.
- Comparison of the cutaneous tolerability of 2 adapalene-BPO fixed-dose combinations with various concentrations of BPO monotherapy.

Subject selection

- Healthy subjects
- At least 18 years of age
- Skin phototype I to III

Treatments

- Subjects were randomized in 4 parallel groups in order to compare 2 adapalene BPO combinations (adapalene-BPO 2.5% and adapalene-BPO 5%) with 3 concentrations of BPO (2.5%, 5% and 10%) applied as monotherapy.
- Each group compared two treatments, a combination and a monotherapy (Table 1).
- Test products were applied once-daily for 3 weeks.
- 2 treatments were randomized to be applied to the left or to the right half-face.

Tolerability/safety assessments

- Local Cutaneous tolerability parameters: Erythema, dryness, scaling, stinging/burning and pruritus on a scale from 0 (no reaction) to 3 (severe).
- Adverse events (AEs) reported by the patients or observed by the investigator.

Table 1 COMPARISON GROUPS

Study Group	Adapalene-BPO Combination	BPO Monotherapy	Subjects (n)
1	adapalene 0.1% - BPO 2.5%	BPO 2.5%	15
2	adapalene 0.1% - BPO 2.5%	BPO 5%	16
3	adapalene 0.1% - BPO 5%	BPO 5%	15
4	adapalene 0.1% - BPO 5%	BPO 10%	14

RESULTS

Subject disposition and demographics (Table 2)

- Out of 60 healthy subjects enrolled, 50 (83%) completed the study.
- 7 subjects discontinued prematurely because of an adverse event: 2 irritant dermatitis with the combination product with 2.5% BPO, 4 irritant dermatitis with the combination product with 5% BPO and 1 irritant dermatitis due to reactions with BPO 5% alone.
- 3 subjects discontinued prematurely for a reason unrelated to the study (subject's request).

Tolerability/Safety assessments (Tables 3 and 4)

- The overall cutaneous tolerability profile of the combination with 2.5% BPO was better than that of the combination with 5% BPO and similar to that of BPO 2.5% or 5% alone.
- The combination with 5% BPO induced significantly more irritation than BPO 5% or 10% alone.

Table 3 TOTAL SUM SCORE (TSS) OF THE SIGNS/SYMPTOMS OF IRRITATION AVERAGED OVER ALL POST-BASELINE VISITS

	TSS (mean±SEM)	Least square mean of difference (estimate ±SEM)	P-value
Combination with BPO 2.5% vs. BPO 2.5% (n=15)			
- Combination with BPO 2.5%	1.05 ± 0.29		
- BPO 2.5%	0.45 ± 0.17	0.60±0.35	0.088
Combination with BPO 2.5% vs. BPO 5% (n=16)			
- Combination with BPO 2.5%	1.68 ± 0.34		
- BPO 5%	1.03 ± 0.33	0.64±0.34	0.061
Combination with BP 5% vs. BPO 5% (n=15)			
- Combination with BPO 5%	2.12 ± 0.29		
- BPO 5%	0.72 ± 0.22	1.40±0.36	<0.001
Combination with BPO 5% vs. BPO 10% (n=14)			
- Combination with BPO 5%	2.62 ± 0.41		
- BPO 10%	1.33 ± 0.28	1.29±0.36	0.001

Table 4 MEAN WORST SCORE DIFFERENCE FOR THE SIGNS/SYMPTOMS OF IRRITATION

	Worst Score Difference (Combination minus BPO alone) Mean ± STD	P-value
Combination with BPO 2.5% vs. BPO 2.5%		
Burning	0.53±0.92	0.072
Desquamation	0.33±0.90	0.281
Dryness	0.27±0.59	0.219
Erythema	0.13±0.64	0.750
Pruritus	0.40±0.83	0.156
Combination with BPO 2.5% vs. BPO 5%		
Burning	0.44±1.36	0.219
Desquamation	0.75±1.00	0.016
Dryness	0.50±0.73	0.035
Erythema	0.25±1.29	0.469
Pruritus	0.19±0.66	0.500
Combination with BPO 5% vs. BPO 5%		
Burning	1.07±1.07	0.004
Desquamation	1.07±0.73	<0.001
Dryness	0.93±0.83	0.002
Erythema	0.50±0.76	0.063
Pruritus	0.14±0.66	0.750
Combination with BPO 5% vs. BPO 10%		
Burning	0.79±0.89	0.008
Desquamation	0.64±0.63	0.008
Dryness	0.50±0.52	0.016
Erythema	0.50±0.65	0.031
Pruritus	0.43±0.85	0.250

Table 2 SUBJECT DISPOSITION AND DEMOGRAPHICS

		Combination with BPO 2.5% vs. BPO 2.5%	Combination with BPO 2.5% vs. BPO 5%	Combination with BPO 5% vs. BPO 5%	Combination with BPO 5% vs. BPO 10%	All
Enrolled	n (%)	15 (25)	16 (26.7)	15 (25)	14 (23.3)	60 (100)
Discontinued	n (%)	0	3 (18.8)	4 (26.6)	3 (21.4)	10 (16.7)
Adverse event	n (%)	0	3 (18.8)	2 (13.3)	2 (14.3)	7 (11.7)
Subject request	n (%)	0	0	2 (13.3)	1 (7.1)	3 (5.0)
Completed	n (%)	15 (100)	13 (81.3)	11 (73.3)	11 (78.6)	50 (83.3)
Age	Mean	46	40	34	37	39
	Min	22	19	20	20	19
	Max	66	64	51	53	66
Gender						
Male	n (%)	7 (46.7)	2 (12.5)	2 (13.3)	4 (28.6)	15 (25.0)
Female	n (%)	8 (53.3)	14 (87.5)	13 (86.7)	10 (71.4)	45 (75.0)
Race						
Caucasian	n (%)	14 (93.3)	16 (100.0)	15 (100.0)	14 (100.0)	59 (98.3)
Black	n (%)	0	0	0	0	0
Other	n (%)	1 (6.7)	0	0	0	1 (1.7)
Phototype						
I	n (%)	0	1 (6.3)	0	0	1 (1.7)
II	n (%)	0	4 (25.0)	1 (6.7)	2 (14.3)	7 (11.7)
III	n (%)	15 (100.0)	11 (68.8)	14 (93.3)	12 (85.7)	52 (86.7)

CONCLUSIONS

The new fixed-dose combination of adapalene 0.1% and BPO 2.5% provided the best overall cutaneous tolerability profile relative to BPO monotherapy.

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