LONG-TERM EFFICACY AND SAFETY OF BENZOYL PEROXIDE CREAM, 5%, PREPARED WITH MICROENCAPSULATION IN PAPULOPUSTULAR ROSACEA: RESULTS FROM AN EXTENSION OF TWO PHASE 3, VEHICLE-CONTROLLED TRIALS

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INTRODUCTION

- In a new microencapsulated formulation (E-BPO Cream, 5%), the drug is entrapped in silica microcapsules. This extends drug delivery time to improve efficacy and potently reduces the potential for skin irritation.[1]
- The efficacy, safety, and tolerability of E-BPO Cream, 5% were evaluated in two identical randomized, double-blind, phase 3 trials which demonstrated significant superiority of this encapsulated BPO over vehicle for percentage of patients achieving success (clear or almost clear) on the Investigators Global Assessment (IGA) and reducing the number of lesions.2
- E-BPO Cream, 5% was also well tolerated with adverse events (AEs) and cutaneous safety and tolerability was comparable to that for vehicle. [2]
- This report summarizes results from the 40-week extension of the two phase 3 trials E-BPO Cream, 5%. The primary objective was evaluation of safety.

METHODS

2x trials / phase 3 / 52 weeks

Patients

- Patients met the following criteria when entering the phase 3 trials:
  - Males and females ≥18 years of age with moderate-to-severe rosacea with a baseline IGA score of 3 (moderate severity) or 4 (severe) on a severity scale of 0-4.
  - ≥15 and ≤70 total inflammatory lesions and ≤2 nodules (defined as a papule or pustule >5 mm in diameter).

Study Design and Treatment

- All patients were assigned to treatment with E-BPO Cream, 5%:
  - If a patient was assessed as clear (IGA = 0) or almost clear (IGA = 1), he or she was instructed not to apply E-BPO Cream, 5% and it was not dispensed.
  - If a patient was assessed as mild, moderate, or severe (IGA = 2-4), E-BPO Cream, 5% was dispensed, and the patient was instructed to apply the product daily.
- Patients were followed for up to 40 additional weeks in the extension and for up to a total of 52 weeks, including the time in the phase 3 trial.

ASSESSMENTS

Safety and Tolerability

- Any adverse events (AEs) including local and systemic events.
- Investigators' cutaneous safety assessment rating (dryness and scaling) and patients' local tolerability assessments rating (itching and burning/stinging) on scales ranging from 0 (none) to 3 (severe).
- Physical examinations and recording of vital signs.

Additional Assessments

- At each extension visit (baseline and weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40/end of study), patients were assessed using a 5-point IGA scale of rosacea severity.
- Relapse was defined as the number of treatment-free days until the first retreatment and was calculated for each patient. Retreatment was initiated at the time of relapse.
- Erythema and telangiectasia (each score on a scale of 0-3).
- Rosacea Quality of Life Questionnaire.

RESULTS

Patients

- A total of 547 patients were enrolled, including 363 previously treated with E-BPO Cream, 5% and 184 previously treated with vehicle. The percentage of patients who completed the study was 85.7% according to an ad-hoc analysis, which included those discontinued early due to the sponsor's decision to terminate the study as completers. Patient characteristics are summarized in **Table 1**.

IGA Success

- IGA success was defined as achievement of clear or almost clear at the week 40 visit.
- At this evaluation, 67.2% of patients achieved success. This was the case for 67.6% of the patients who received E-BPO Cream, 5% in the double-blind studies and 66.5% of those who received vehicle (**Figure 1**).

Retreatment

- A mean of 1.4 retreatments was reported for all patients in the extension. The median number of treatment-free days was 58 (95% CI = 57.0-64.0).
- For patients with a score of 0 at the beginning of the extension (n=48), the mean time to first retreatment was 125.1 days (SD = 99.3, median = 112.5 days) and the mean number of retreatments was 1.15. The respective values for patients with a score of 1 (n=122) were 92.6 days (SD = 75.2, median = 61.5 days) and 1.66 (SD = 1.16) ($p<0.05$ for both comparisons) (**Figure 3**).

Erythema and Telangiectasia

- Facial erythema generally improved during the course of the study. There was an increase from baseline to week 40 in the percentage of patients with no or mild erythema (10.1% to 76.2%). The proportion of patients with mild or no telangiectasia at baseline was 58.2% and this increased to 80.1% by week 40.

Rosacea Quality of Life Questionnaire

- The results of the RosaQoL questionnaire showed mean decreases (improvements) from baseline to week 40/end of treatment for the total score (0.7), symptom subscale score (0.7), functional subscale score (0.4), and emotional subscale score (0.8).

Safety and Tolerability

- For each of the cutaneous safety and tolerability parameters, there were small increases in the percentages of patients with no or mild signs/symptoms over 52 weeks (**Figure 4**).
- 185 patients (34.6%) reported at least one treatment-related AE (TEAE) (**Table 2**). Most TEAEs were mild or moderate in severity and were not considered to be related to study treatment.
- No deaths were reported in the study.
- 10 patients (1.9%) experienced serious AEs, none of which were considered to be related to study treatment.

Table 1. Baseline demographic and clinical characteristics

	Vehicle Phase 3 Trials (n=172)	E-BPO Cream, 5% in Phase 3 Trials (n=363)	All Patients (n=535)
Age (years)			
Mean (SD)	52.0 (12.75)	51.3 (13.88)	51.5 (13.52)
Median	53.0 (22-81)	52.0 (19-81)	53.0 (19-81)
Sex			
Male	52 (30.2%)	101 (27.8%)	153 (28.6%)
Female	120 (69.8%)	262 (72.2%)	382 (71.4%)
Ethnicity			
Hispanic or Latino	53 (30.8%)	102 (28.1%)	155 (29.0%)
Not Hispanic or Latino	119 (69.2%)	261 (71.9%)	380 (71.0%)
Not Reported/Unknown	0	0	0
Race			
American Indian or Alaska Native	1 (0.6%)	0	1 (0.2%)
Asian	9 (5.2%)	27 (7.4%)	36 (6.7%)
Black or African American	0	1 (0.3%)	1 (0.2%)
Native Hawaiian or Other Pacific Islander	1 (0.6%)	1 (0.3%)	2 (0.4%)
White	161 (93.6%)	331 (91.2%)	492 (92.0%)
Multiple/Other	0	3 (0.8%)	3 (0.6%)
Inflammatory Lesion Count			
Mean (SD)	27.6 (12.83)	28.8 (13.24)	28.4 (13.11)
Median	23.0 (15-70)	24.0 (15-70)	24.0 (15-70)
IGA			
3 - Moderate	157 (91.3%)	320 (88.2%)	477 (89.2%)
4 - Severe	15 (8.7%)	43 (11.8%)	58 (10.8%)

Figure 1. Percentage of patients achieving of IGA success at 40 weeks

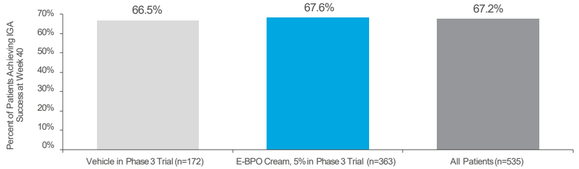

Figure 2. Time to first retreatment

A Kaplan-Meier analysis of time to first retreatment is shown in **Figure 2**.

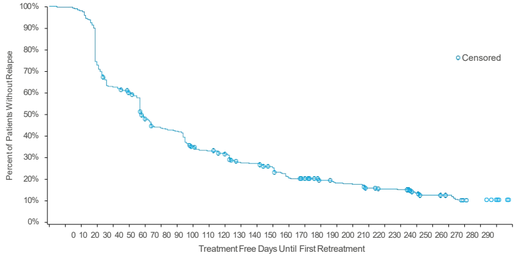

Figure 3. Time to retreatment and number of retreatments for all patients and for patients treated with E-BPO Cream, 5% during the phase 3 trials and who had an IGA score of 0 (clear) or 1 (almost clear) at the end of 12-week double-blind treatment

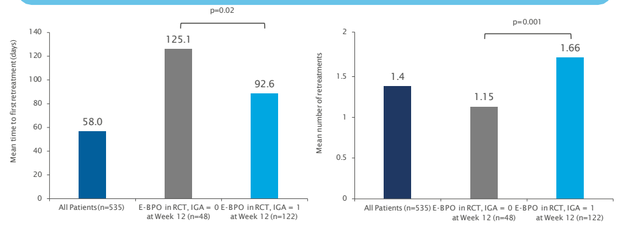

Figure 4. Percentages of patients reporting mild/no and no: A. Dryness. B. Scaling. C. Itching. D. Burning/stinging at each evaluation (open symbols denote results limited to patients who received E-BPO Cream, 5% during the phase 3 trials)

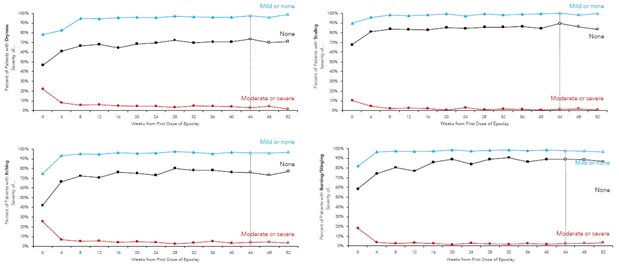

Table 2. Adverse events

	E-BPO Cream, 5% (n=535)
Any TEAE	185 (34.6%)
Any serious TEAE	10 (1.9%)
Death	0
Discontinued E-BPO Cream, 5% due to a TEAE	5 (0.9%)
Discontinued from the study due to a TEAE	4 (0.7%)
Maximum severity of TEAE	
Severe	8 (1.5%)
Moderate	81 (15.1%)
Mild	96 (17.9%)
Relationship to study drug	
Related	17 (3.2%)
Not Related	168 (31.4%)
TEAEs reported for >2% of patients	
Nasopharyngitis	29 (5.4%)
Upper respiratory tract infection	12 (2.2%)

CONCLUSIONS

The results from this long-term extension of two phase 3 randomized controlled trials demonstrated progressive clinical improvement as reflected by percentage of patients achieving IGA success and reduction in erythema as well as good cutaneous safety and tolerability with E-BPO Cream, 5% applied for up to 52 weeks in patients with rosacea.

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