CRITICAL EVALUATION OF BENZOYL PEROXIDE IN ROSACEA: OLD CHALLENGES AND NEW CLINICAL OPPORTUNITIES WITH ENCAPSULATED BENZOYL PEROXIDE

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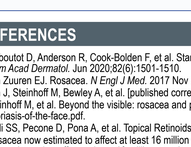
INTRODUCTION

- Rosacea affects at least 10% of fair skinned individuals and not uncommon in Black, Asian, and Hispanic populations[1,7,8]
- Over 16 million people in the United States have rosacea[2]
- Triggers for rosacea are wide-ranging and can include skin care products, cold and/or hot weather, spicy foods, and emotional stress[1]
- Rosacea is characterized as an inflammatory disorder of the facial skin that primarily affects the cheeks, nose, chin, forehead, and eyes[1]
- Rosacea signs present as facial erythema, flushing, papules, pustules, phymas, and telangiectasias[1,7]
- The disease is frequently characterized by remissions and exacerbations[1]

Drug Microencapsulation Background

Benefits of Microencapsulation

- Creates a silicon dioxide (silica) microcapsule shell between the BPO and the skin[5]
- Helps control the release rate of the drug to improve tolerability[6]
- Can preserve the advantages of BPO while minimizing limitations[6]



Encapsulation Process[4]

Silica is added in 5–100 repetitive cycles to build up a silica shell around the BPO

Table 1. Baseline Characteristics of Subjects

	Study 1		Study 2	
Characteristic	**E-BPO n=243**	**Vehicle n=118**	**E-BPO n=250**	**Vehicle n=122**
IGA: Moderate	210 (86.4%)	104 (88.1%)	227 (90.8%)	112 (91.8%)
IGA: Severe	33 (13.6%)	14 (11.9%)	23 (9.2%)	10 (8.2%)
Mean lesion count (SD)	25.7 (11.07)	26.3 (12.45)	29.8 (14.00)	27.5 (13.04)
Median lesion count (range)	22.0 (15–69)	21.0 (15–70)	25.0 (15–70)	22.5 (15–70)
Mean age (years)	52.8	52.4	49.5	51.5
Male	60 (24.7%)	35 (29.7%)	69 (27.6%)	35 (28.7%)
Female	183 (75.3%)	83 (70.3%)	181 (72.4%)	87 (71.3%)

Table 2. Investigator Global Assessment (IGA) Scale

Grade	Description
0 – Clear	Skin clear of inflammatory papules or pustules
1 – Almost Clear	Very few small papules or pustules and very mild dull erythema are present
2 – Mild	Few small papules or pustules and mild dull or light pink erythema are present
3 – Moderate	Several to many small or larger papules or pustules and moderate light to bright red erythema are present
4 – Severe	Numerous small and/or larger papules or pustules and severe erythema that is bright red to deep red are present

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Abbreviations: E-BPO = encapsulated benzoyl peroxide; IGA = investigator global assessment; ITT = intent-to-treat; SD = standard deviation; TEAE = treatment-emergent adverse event

METHODS

Co-primary Endpoints

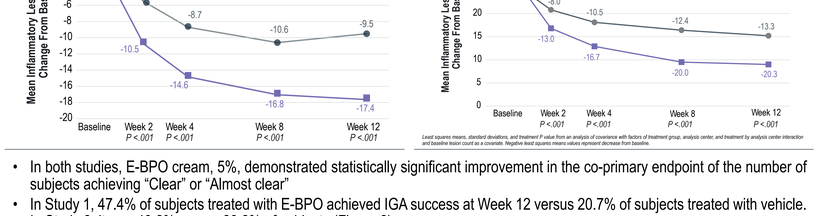
- Proportion of subjects with the primary measure of success, "Clear" (0) or "Almost clear" (1), in the Investigator Global Assessment (IGA) relative to baseline at Week 12
  - The IGA scale ranged from "Clear" (0) to "Severe" (4) and included the number of papules/pustules and erythema severity
- Absolute mean change in inflammatory lesion counts from baseline to Week 12

Secondary Endpoints

- Percentage change in inflammatory lesion count from baseline to Week 12
- Absolute change in inflammatory lesion count from baseline to Week 8

Study Design of the Two Pivotal Phase 3 Trials for E-BPO Cream, 5% (Figure 1)

Figure 1. Two Phase 3, Double-blind, Randomized, Vehicle-controlled Studies



Co-primary Endpoint

Figure 2. IGA Success at Week 12

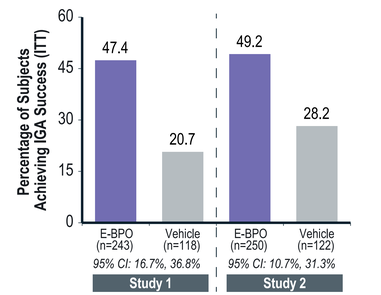


Figure 3. Mean Inflammatory Lesion Count Change From Baseline to Week 12

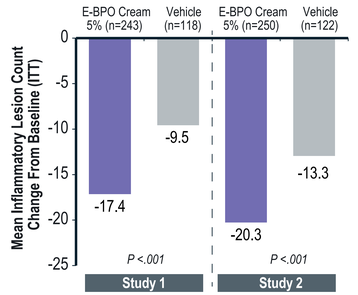


Figure 4. Mean Inflammatory Lesion Count Change From Baseline

Least squares means, standard deviations, and treatment P value from an analysis of covariance with factors of treatment group, analysis center, and treatment by analysis center interaction and baseline lesion count as a covariate. Negative least squares means values represent decrease from baseline.

- In both studies, E-BPO cream, 5%, demonstrated statistically significant improvement in the co-primary endpoint of the number of subjects achieving "Clear" or "Almost clear"
- In Study 1, 47.4% of subjects treated with E-BPO achieved IGA success at Week 12 versus 20.7% of subjects treated with vehicle. In Study 2, it was 49.2% versus 28.2% of subjects (Figure 2)
- In both studies, E-BPO demonstrated a significant reduction in inflammatory lesion counts from baseline to Week 12 versus vehicle (Figure 3)

RESULTS

- A reduction in mean inflammatory count was seen as early as Week 2 in both studies and was maintained for the entirety of each 12-week study (Figure 4)
- Most subjects experienced adverse reactions that were mild or moderate in severity (Table 3)
- The serious adverse event reported in the treatment arm was determined by the investigators to not be related to study drug
- TEAEs are combined from Study 1 and Study 2

Figure 5. IGA Success With E-BPO — Study 1 Subject 101021

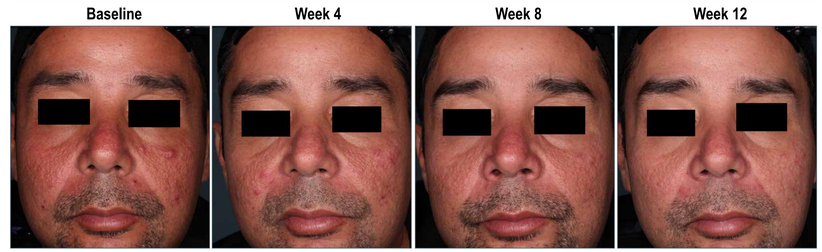


Figure 6. IGA Failure With E-BPO — Study 1 Subject 106017

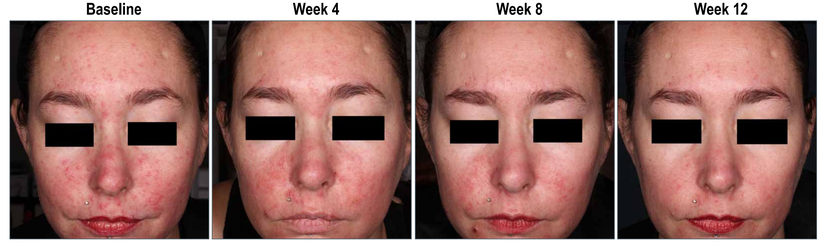


Table 3. Treatment-Emergent Adverse Events (Safety Population)

	E-BPO (n=488)	Vehicle (n=234)
Subjects reporting any TEAE	99 (20.3%)	39 (16.7%)
Serious TEAE	1 (0.2%)	1 (0.4%)
Discontinued study drug	11 (2.3%)	3 (1.3%)
Discontinued study	9 (1.8%)	2 (0.9%)
Related AEs occurring in >1% of subjects treated with E-BPO		
Application site pain	11 (2%)	2 (1%)
Application site erythema	11 (2%)	2 (1%)
Application site pruritis	6 (1%)	1 (<1%)
Application site edema*	4 (1%)	0 (0%)

**Application site edema includes application site swelling and application site edema.*

SUMMARY

- Both Phase 3 studies met the co-primary endpoints of IGA success "Clear" (0) or "Almost clear" (1) (*P* <.02) and a significant reduction in the absolute mean change in inflammatory lesion counts (*P* <.001) versus vehicle at 12 weeks
- E-BPO cream, 5%, had a well-tolerated safety profile similar to vehicle in both studies
- A reduction in mean inflammatory count was seen as early as Week 2 in both studies and was maintained for the entirety of each 12-week study

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