ENCAPSULATED BENZOYL PEROXIDE (E-BPO): A NOVEL FORMULATION OF BPO FOR LONG-TERM MANAGEMENT OF ROSACEA

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INTRODUCTION

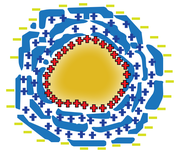
Key Points
- BPO is a potent oxidizing agent
- The utility of BPO in rosacea has been limited due to limited data on efficacy and adverse skin tolerability
- A new formulation incorporating microencapsulation technology is tolerable over long-term use

BPO has had a complex history in rosacea
- Limited data in previous studies, especially with monotherapy
- Effective when used in combination with clindamycin or erythromycin[1,2]
- While proven effective, unencapsulated BPO causes local skin irritation, including stinging, burning, and itching after application[3]
- Demonstrated to be effective in killing *Demodex folliculorum*[4]

Drug Microencapsulation Background

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

Figure 1. Encapsulation



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

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Abbreviations: E-BPO=encapsulated benzoyl peroxide; ICH=International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; IGA=investigator global assessment; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.

METHODS

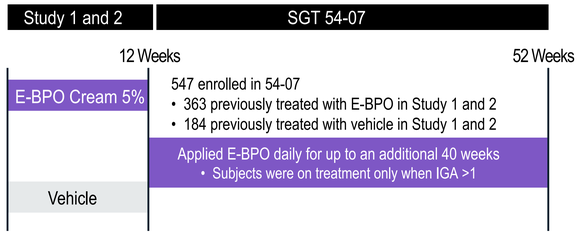
Study Objective:
- Two 12-week phase 3 trials of microencapsulated benzoyl peroxide cream, 5% (E-BPO) previously demonstrated significant efficacy, rapid onset of action as early as week 2, and good safety and tolerability at week 12
- This 52-week study observed the nature, severity, and frequency of adverse events and the cutaneous safety and local tolerability of E-BPO when applied once daily (Figure 1)

Safety endpoints:
- The frequency of both local and systemic adverse events
- Investigator cutaneous safety assessment (dryness and scaling) and local tolerability assessment (itching and burning/stinging) at baseline and all postbaseline study visits

Termination:
- The study was terminated early per protocol when a minimum number of patients were followed for a minimum time to adequately assess long-term safety as specified in the ICH E1A guidance.

Figure 2. Study Design

A Multicenter, Open-label, Long-term Safety Study of E-BPO to Evaluate the Safety of E-BPO in Patients With Papulopustular Rosacea



All Enrolled Subjects, N=547, 59% (N=323) completed the study, and 41% (N=224) did not complete. See Table 3.

Table 1. Baseline Demographic and Clinical Characteristics

	Vehicle in 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 (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%)
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%)

RESULTS

Subjects
- 547 adult subjects were enrolled in the 40-week extension of the two 12-week, double-blind, vehicle-controlled phase 3 trials (Table 1).
- Subjects were ≥18 years old with an Investigator Global Assessment [IGA] of 3 or 4, ≥15 inflammatory lesions, and ≤2 nodules
- The Safety population included 535 of the 547 enrolled subjects (97.8%). All analyses were performed using the Safety population
- 363 subjects enrolled in the extension were previously treated with E-BPO and 184 were previously treated with vehicle during the phase 3 trials.
- All subjects were assigned to treatment with E-BPO. Subjects were followed for up to 40 weeks in the extension (for a total of up to 52 weeks).

Safety Summary of Treatment-Emergent Adverse Events
- Most TEAEs were mild or moderate in severity and were not considered to be related to study treatment (Table 2).

Table 2. Patient Adverse Event Summary

	E-BPO (n=535)
Any TEAE	185 (34.6%)
Any serious TEAE	10 (1.9%)
Discontinued E-BPO because of a TEAE	5 (0.9%)
Discontinued from the study because of 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%)

*Note: Treatment-emergent adverse events are those events with an onset after the first application of E-BPO Cream 5%. Related defined as "definitely," "probably," or "possible." Not related defined as "unlikely" or "not related."

Table 3. Summary of Subject Completion/Discontinuation

Study terminated by sponsor	146 (26.7%)
Withdrawal by subject	48 (8.8%)
Lost to follow-up	21 (3.8%)
Adverse event	**4 (0.7%)**
Protocol violation	2 (0.4%)
Pregnancy	1 (0.2%)
Physician decision	1 (0.2%)
Other	1 (0.2%)
Worsening of condition	**0**
Lack of efficacy	**0**

Summary: Tolerability, Safety Population, Baseline to Week 52
- E-BPO remained well-tolerated over the course of 52 weeks
- For each of the cutaneous safety and tolerability parameters, the percentage of subjects with no signs/symptoms increased from week 4 to week 52 (range 60.8% to 90.6%)
- Reports of severe cutaneous safety and/or tolerability evaluations included 2 subjects with dryness, 1 subject with itching, and 1 subject with burning/stinging at week 40
- There were no severe cutaneous safety evaluations at week 52
- Facial erythema generally improved during the study (n=535), with a total percentage increase for subjects with none and mild erythema at week 52 and a total percentage decrease for subject with moderate and severe erythema (Figure 3)

Figure 3. Erythema at Postbaseline Visits, Safety Population

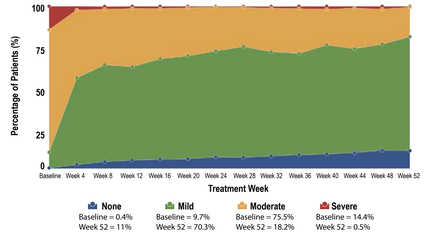
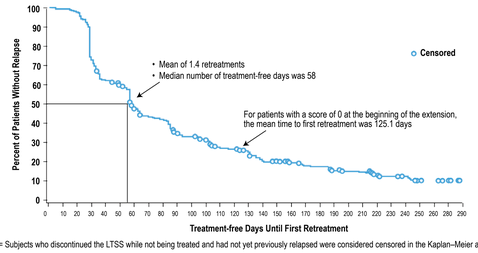


Figure 4. Kaplan–Meier Analysis of Time to First Retreatment

E-BPO Provided a Sustained Effect in Rosacea Patients for Over 1 Year (52 Weeks)



Censored = Subjects who discontinued the LTSS while not being treated and had not yet previously relapsed were considered censored in the Kaplan–Meier analysis.

SUMMARY

- The cutaneous safety and local tolerability assessments demonstrated that E-BPO, when applied once daily for up to 52 weeks, was generally safe and well-tolerated
- The evaluations of IGA score and facial erythema showed improved clinical outcomes after 4 weeks and for up to 52 weeks of treatment with E-BPO

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