

# THE PHARMACOLOGIC SCIENCE OF A NOVEL BENZOYL PEROXIDE FORMULATION AND THE IMPLICATIONS FOR CLINICAL EFFECTS

John Erienne, MD  
Essex Testing Clinic,  
Verona, New Jersey

Daniel L Prince, PhD  
Gibraltar Laboratories,  
Fairfield, New Jersey

Jose Ramirez, PhD  
JR Chemical,  
Milford, Connecticut

David Wilson, MD  
Education and Research  
Foundation,  
Lynchburg, Virginia

Joshua Zeichner, MD  
Mount Sinai Medical Center,  
Department of Dermatology,  
New York, New York

## INTRODUCTION

The proliferation of *Propionibacterium acnes* can be a major factor in the development of acne vulgaris.<sup>1</sup> Benzoyl peroxide (BPO) has a bactericidal effect on *P. acnes* and is commonly used in the topical treatment of acne. It has a key advantage over antibiotics as it is not associated with the development of bacterial resistance.<sup>1</sup>

BPO molecules are poorly soluble and aggregate together to form crystalline clusters. Currently available formulations of BPO are generally emulsions of these clusters, in which most of the BPO is trapped in the cluster interior and is not entirely available to interact with *P. acnes*. In addition, although the anaerobic environment of the follicles is particularly conducive to the proliferation of *P. acnes*, the size of the clusters can prevent them from reaching these areas. The diameter of an average hair follicle on the surface of the skin is approximately 50  $\mu\text{m}$  and an evaluation of BPO clusters in a sample of three commercially available BPO formulations revealed their diameters to be 5-50  $\mu\text{m}$ , 10-100  $\mu\text{m}$ , and 50-100  $\mu\text{m}$ , respectively.<sup>2</sup> Thus, a significant proportion of the BPO may be unable to penetrate the follicles. Furthermore, BPO formulations are generally oil in water emulsions, which do not readily flow into follicles—further hindering the ability of BPO to reach follicular *P. acnes*. Together, these four factors—poor solubility, clustering, size of the clusters, and vehicle—have been estimated to result in the delivery of only 0.03% to 1% of the available BPO molecules to the follicles.<sup>3</sup>

In the past, attempts to enhance the solubility of BPO using different solvents have been hindered by stability problems.<sup>4</sup> However, a novel, liquefied, proprietary formulation (OMP, Inc.) has now been developed that offers superior BPO solubility and stability. The novel formulation contains liquefied BPO molecules in a homogeneous solution; as a result, the BPO molecules penetrate the follicles easily. Furthermore, because the vehicle is anhydrous, the formulation has lower surface tension than commercially available formulations—which should further facilitate follicular penetration.

This novel formulation has been designed to enhance both the bioavailability and penetration of BPO, and therefore, has the potential to enhance clinical efficacy. A series of investigations are described that evaluate its penetration into the skin, and its bactericidal activity on the surface of the stratum corneum and within follicles. Results from pilot clinical studies are also presented.

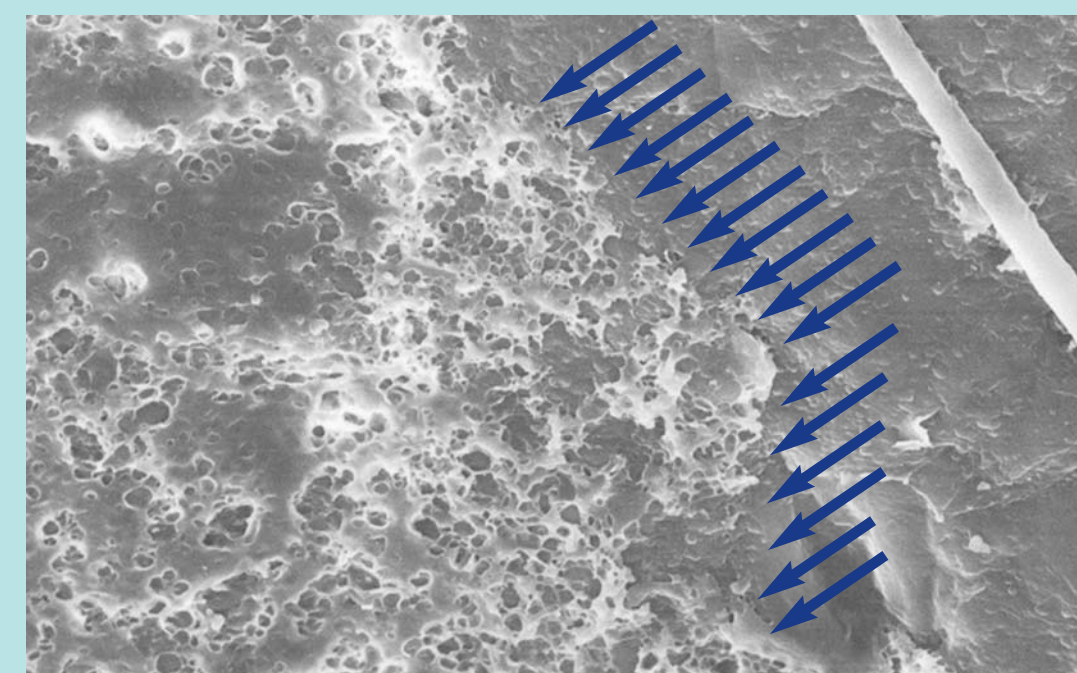
## METHODS & RESULTS

### Studies assessing skin penetration

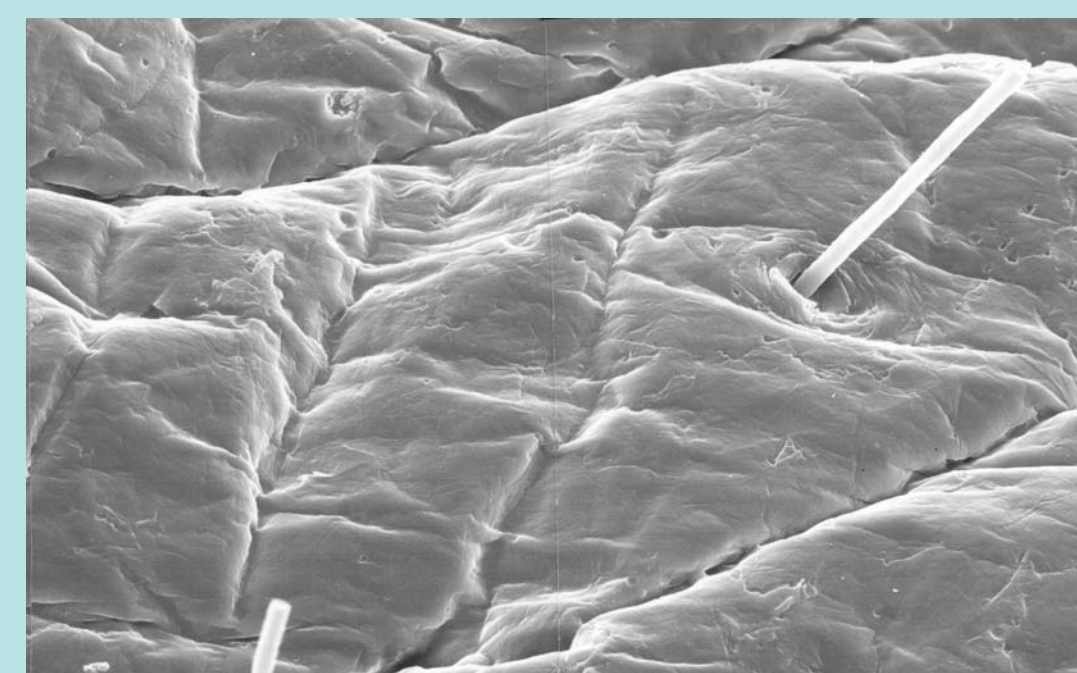
**Methods:** After cleansing of the skin, equal aliquots of the novel BPO formulation and a generic BPO formulation were applied to the face of a healthy volunteer—one formulation on the left side of the face and one formulation on the right side of the face. After 30 minutes, a replica of the skin surface was created with a silicone elastomer, and scanning electron microscopy was used to compare the appearance of the skin on both sides of the face. The evaluator was blinded to which side of the face received which products and to the anticipated effects of the products on the skin.

**Results:** Following the application of the generic BPO formulation, the electron microscopy images reveal a significant volume of residual material on the surface of intact squamous cells (Figure 1). In contrast, following the application of the novel BPO formulation, no visible residue is evident on the skin's surface,

**FIGURE 1** Generic 5% BPO formulation remains mostly on the skin's surface. (Magnification x 300)



**FIGURE 2** The novel liquefied 5% BPO formulation appears to have penetrated the skin. (Magnification x 300)

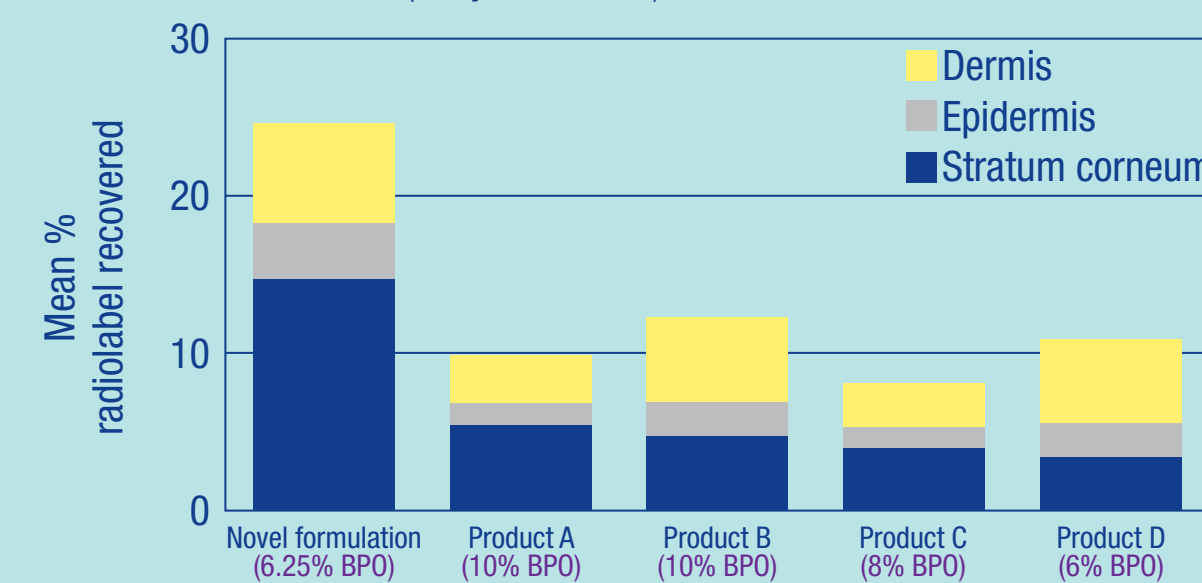


which suggests complete absorption into the skin and follicular ostia (Figure 2). Thus, it appears that the novel formulation was able to penetrate the skin and follicles more readily than the generic formulation.

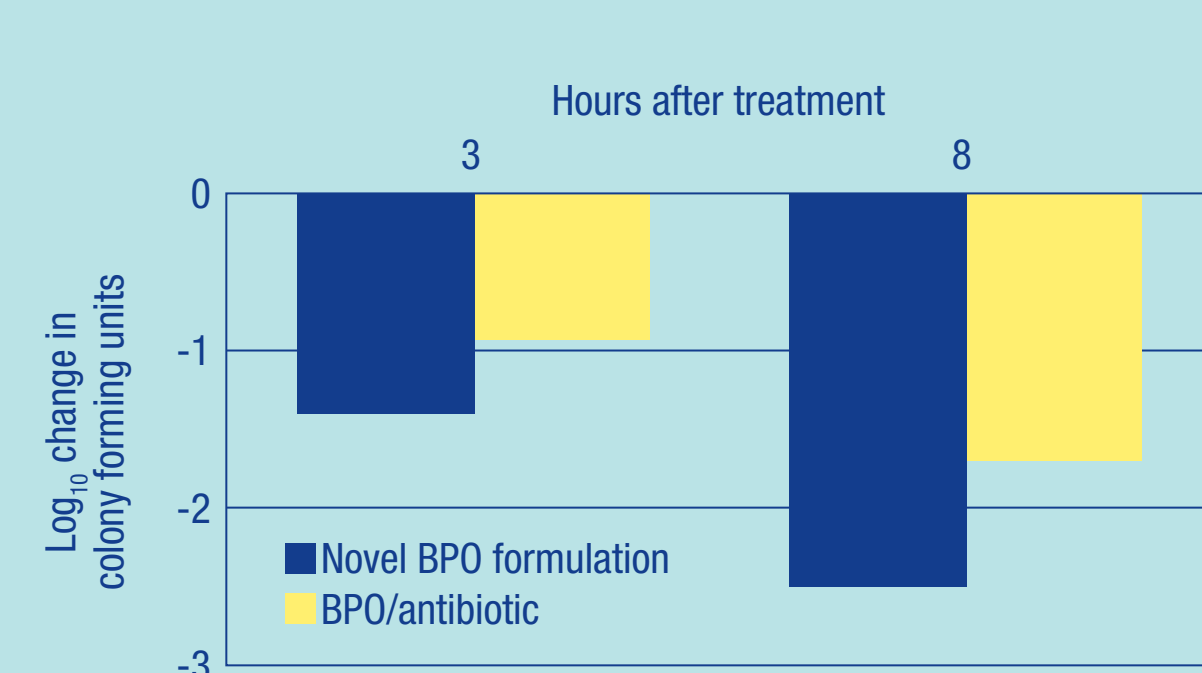
**Methods (study OMP-05-03):** The *in vitro* penetration of the novel BPO formulation was compared with that of four commercially available branded BPO formulations in intact human cadaver skin. First, <sup>14</sup>C benzoyl peroxide was used to spike each of the test BPO formulations—the novel formulation containing 6.25% BPO, two commercial 10% BPO formulations (products A and B), a commercial 8% BPO formulation (product C), and a commercial 6% BPO formulation (product D). Next, skin samples were positioned in Franz cell diffusion chambers. For each sample, the stratum corneum was wiped with wet gauze and allowed to dry for 2 minutes and then 15 mg of a spiked test formulation was applied with a rubber spatula and allowed to dry for an additional 2 minutes. After 8 hours, the stratum corneum was wiped twice to remove the test formulation from the surface and separated from the epidermis by repeated tape-stripping. Then, the epidermis and dermis were separated using microwaves and the proportion of radioactivity in the stratum corneum, epidermis, and dermis was assessed.

**Results:** A greater degree of BPO penetration into the stratum corneum, epidermis, and dermis was detected with the novel BPO formulation (6.25% BPO) than with the other BPO formulations (6%, 8%, 10% BPO) (Figure 3), including those with higher concentrations of BPO. The penetration profile suggests that the BPO from the novel formulation may be more bioavailable to the follicle due to its extensive presence in the stratum corneum and epidermis.

**FIGURE 3** A greater proportion of <sup>14</sup>C BPO is recovered in the stratum corneum, epidermis, and dermis with the novel BPO formulation than with four other commercially available branded formulations. The novel BPO formulation therefore shows greater penetration into these layers of the skin than the other formulations (study OMP-05-03).



**FIGURE 4** The log reduction in colony forming units of follicular *P. acnes* from the forehead was greater with the novel BPO formulation than the BPO/antibiotic product (study NOA 004).



### Study assessing intrafollicular bactericidal activity

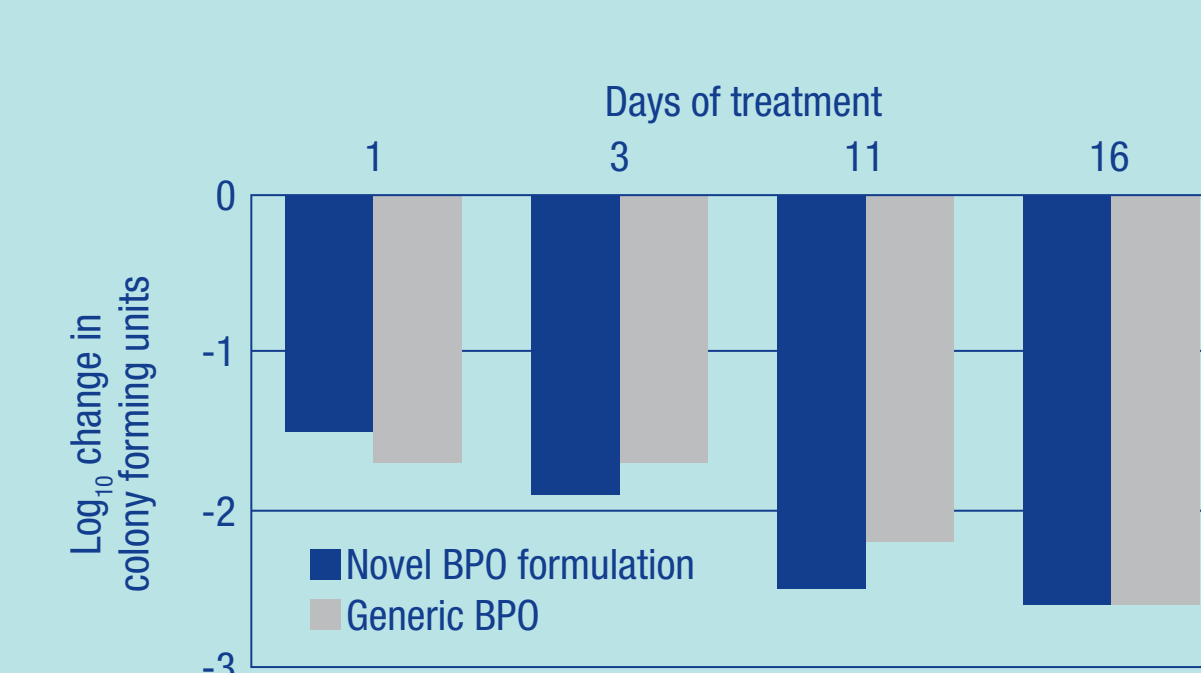
**Methods (study NOA 004):** A split-face randomized study was conducted to compare the intrafollicular bactericidal activity of the novel formulation with a prescription generic BPO and BPO/antibiotic combination product. All products contained 5% BPO. A total of 24 healthy volunteers were divided into two treatment cohorts (N = 12 each), who refrained from washing their face after 10pm on the evening before the study start. In the morning, a technician applied 0.2 mL of the novel formulation to one side of the face of each subject and 0.2 mL of either the generic BPO or the BPO/antibiotic product to the other side. The density of *P. acnes* in the follicles was assessed (before treatment at the baseline visit, and at 3 hours and 8 hours post-treatment) by extracting follicular plugs with cyanoacrylate glue, plating them onto agar, and incubating them anaerobically for 7 days.

**Results:** The novel BPO formulation resulted in a greater reduction in colony forming units of *P. acnes* at 8 hours compared with the generic BPO (1.9 versus 1.7 log<sub>10</sub> reduction, respectively). The reductions were also greater for the novel BPO formulation compared to the BPO/antibiotic product (2.5 versus 1.7 log<sub>10</sub> reduction, respectively) (Figure 4).

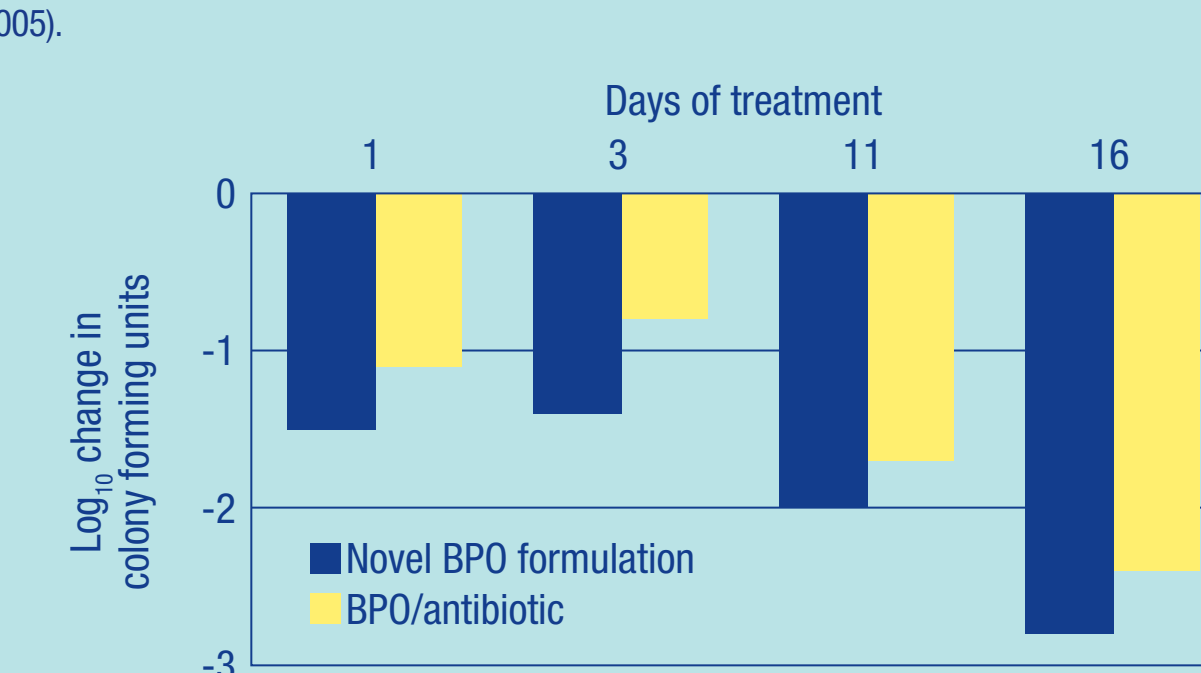
### Study assessing skin surface bactericidal activity

**Methods (study NOA 005):** A follow-on split-face randomized study was performed to compare the bactericidal activity of the same three 5% BPO formulations on the surface of facial skin. In this study, a total of 24 healthy volunteers who were divided into two treatment cohorts (N = 12), refrained from washing their face after 10pm on the evening before the study start.

**FIGURE 5** Overall, the log reduction in colony forming units of *P. acnes* from surface scrubs of the cheek was greater with the novel BPO formulation than with the generic BPO (study NOA 005).



**FIGURE 6** The log reduction in colony forming units of *P. acnes* from surface scrubs of the cheek was greater with the novel BPO formulation than the BPO/antibiotic product (study NOA 005).



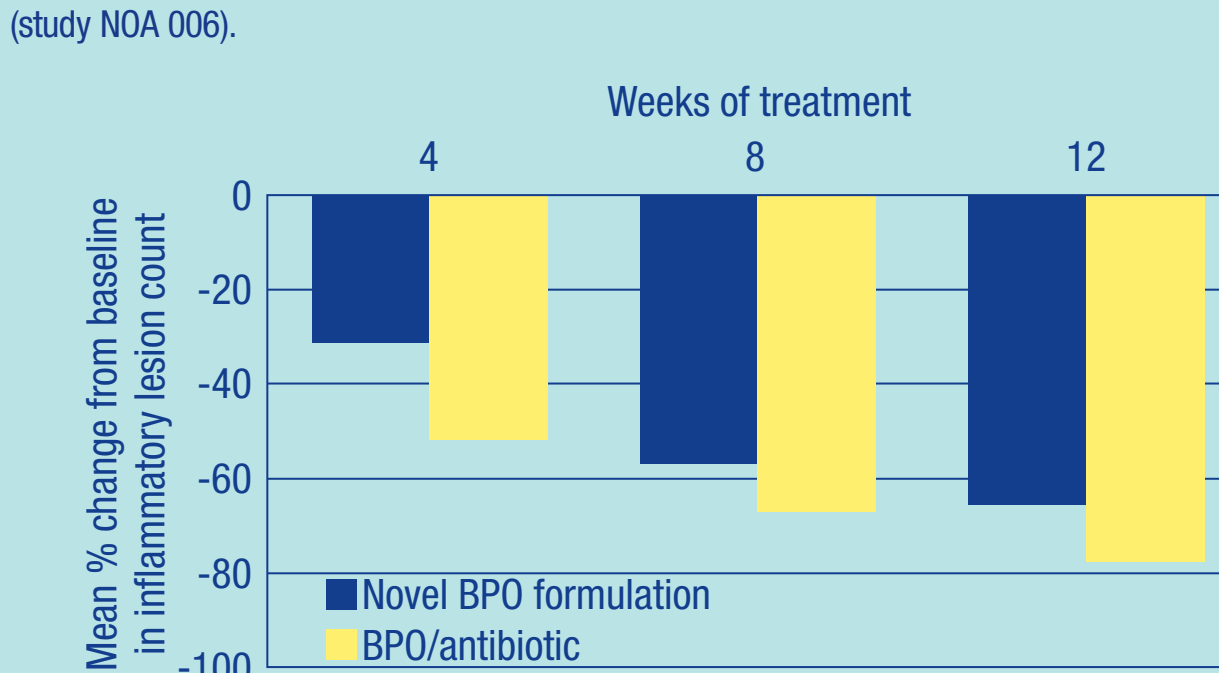
In the morning, a technician applied 0.2 mL of the novel formulation to one side of the face of each subject and 0.2 mL of either the prescription generic BPO or the BPO/antibiotic product to the other side once daily for 16 days. The cheeks and forehead were mapped at the beginning of the study so that the site of each surface scrub was pre-determined. Bacteriologic scrubs of the cheeks and forehead were sampled at baseline and at Days 1, 3, 11, and 16 and assessed for the density of *P. acnes*.

**Results:** The novel BPO formulation resulted in a greater reduction in colony forming units of *P. acnes* at day 16 than the BPO/antibiotic prescription product. On the cheek, the log<sub>10</sub> reductions were 2.6 with the novel formulation compared with 2.6 with the generic BPO (Figure 5), and 2.8 with the novel formulation compared with 2.4 for the BPO/antibiotic product (Figure 6). On the forehead, the log<sub>10</sub> reductions were 3.8 with the novel formulation compared with 2.5 for the generic BPO and 3.0 with the novel formulation compared with 2.9 for the BPO/antibiotic product. Importantly, the initial dramatic reduction in *P. acnes* was not only sustained but enhanced with additional treatment through day 16.

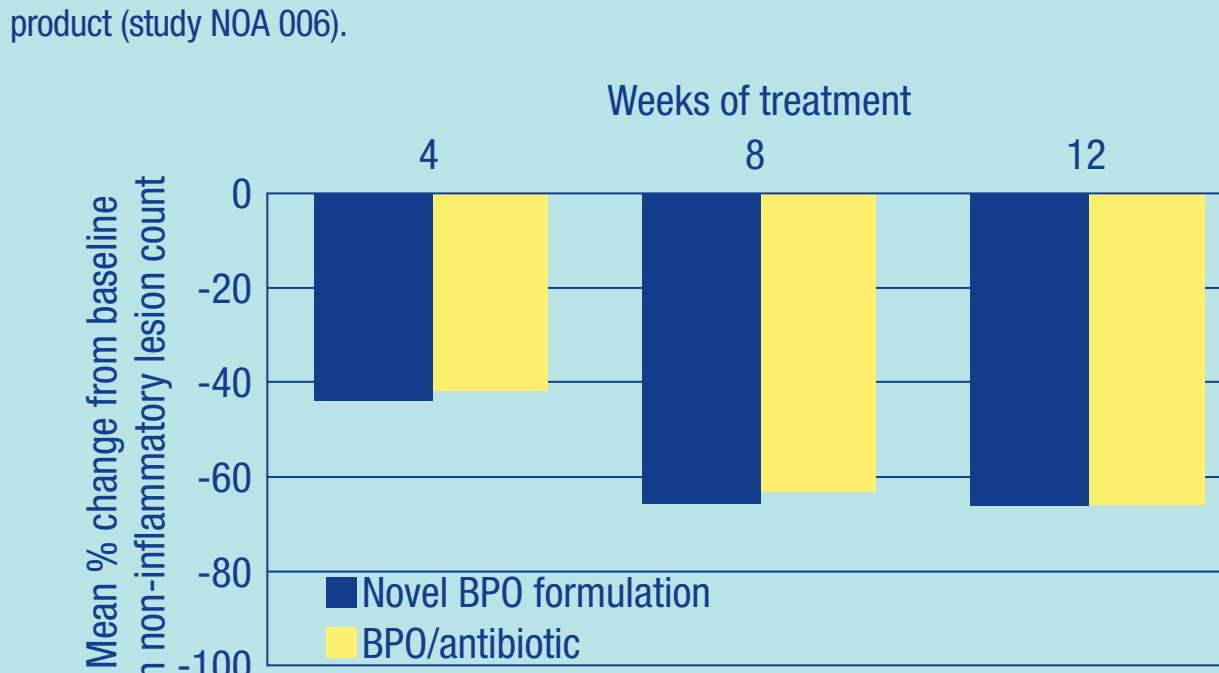
### Pilot clinical study

**Methods (study NOA 006):** A randomized pilot study was conducted in 38 subjects with facial acne vulgaris to compare the clinical efficacy of the novel 5% BPO formulation with that of a prescription 5% BPO/antibiotic combination product after twice-daily applications for 12 weeks.

**FIGURE 7** In the pilot clinical study, the inflammatory lesion count was reduced by at least 65% after 12 weeks of treatment with either the novel BPO formulation or the BPO/antibiotic product (study NOA 006).



**FIGURE 8** In the pilot clinical study, the non-inflammatory lesion count was reduced by at least 65% after 12 weeks of treatment with either the novel BPO formulation or the BPO/antibiotic product (study NOA 006).



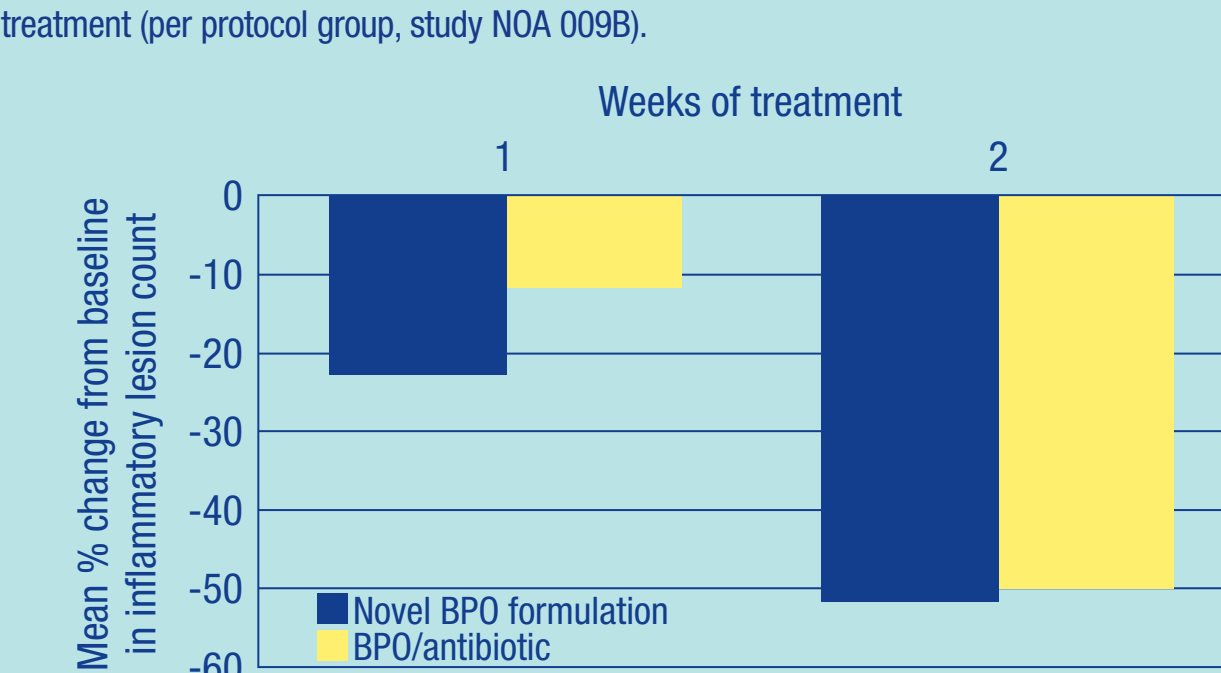
**Results:** Among the 20 subjects who completed the study (per protocol population), the mean inflammatory lesion count at baseline was 22 in the group assigned to the novel formulation (n = 8) and 14 in the group assigned to the BPO/antibiotic (n = 12). The mean non-inflammatory count was 32 in the novel formulation group and 36 in the BPO/antibiotic group. Use of either formulation resulted in at least 65% reductions in inflammatory and non-inflammatory lesion counts at week 12 (Figures 7 and 8). The results demonstrate that the novel BPO formulation can provide efficacy comparable to a two-product combination including both BPO and an antibiotic.

### Follow-on clinical study

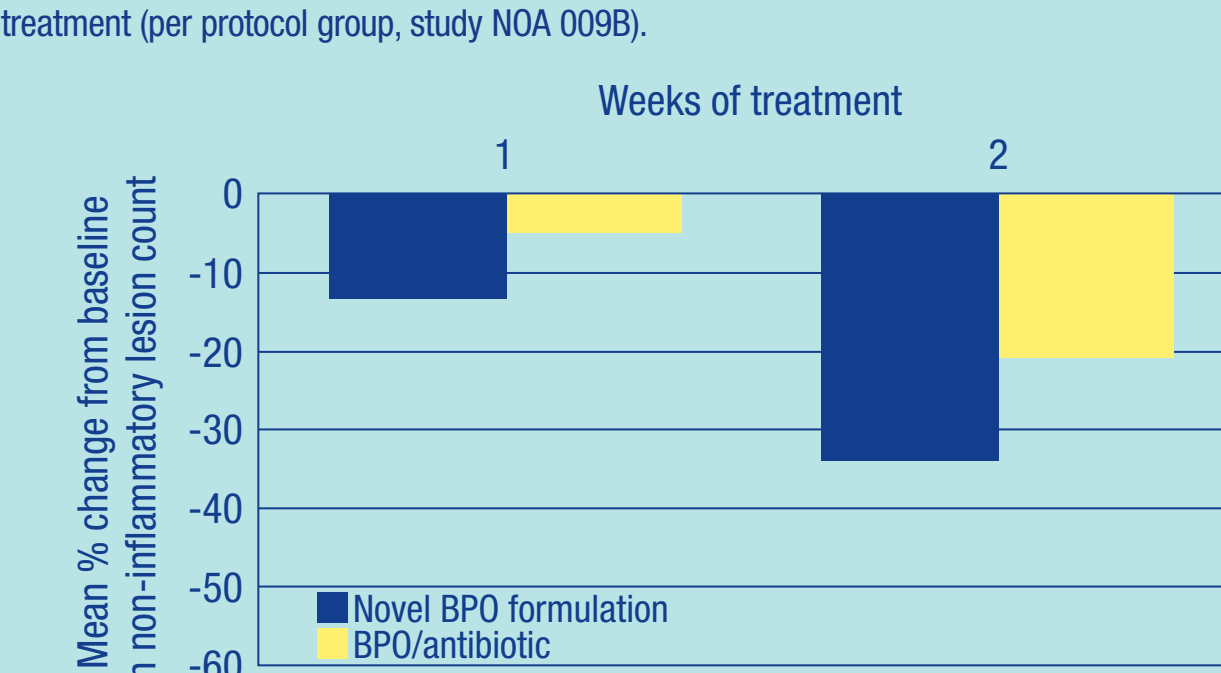
**Methods (study NOA 009b):** A randomized, split-face study was conducted in 34 subjects with mild to moderate facial acne, to compare the clinical efficacy of a prototype acne treatment system of 5% BPO in novel formulation and a salicylic acid-based toner with that of a prescription 5% BPO/antibiotic combination product, after application twice daily for 2 weeks.

**Results:** Of 34 enrolled subjects, 27 completed the study and were assessed for effectiveness at 2 weeks. The reduction in non-inflammatory lesion counts was greater for the side treated with the novel 5% BPO system (34% reduction) than the side treated with the prescription BPO/antibiotic product (21% reduction). The reduction in inflammatory lesion counts at 2 weeks was comparable for both sides (52% versus 50%) (Figures 9 and 10).

**FIGURE 9** In the follow-on clinical study, the reduction in inflammatory lesion count was greater with the novel BPO formulation than the BPO/antibiotic product in the first week of treatment (per protocol group, study NOA 009b).



**FIGURE 10** In the follow-on clinical study, the reduction in non-inflammatory lesion count was greater with the novel BPO formulation than the BPO/antibiotic product in the first 2 weeks of treatment (per protocol group, study NOA 009b).



## CONCLUSIONS

A novel BPO formulation has been designed to enhance both the bioavailability and penetration of BPO. It offers superior BPO solubility and is formulated in an anhydrous vehicle in order to further facilitate penetration into the follicles. The results of studies confirm that it penetrates the skin more readily than commercial BPO formulations, and can achieve greater bactericidal activity both on the surface of the skin and in follicles. These data suggest that the novel BPO formulation and system may result in similar or greater clinical efficacy than prescription BPO and BPO/antibiotic products. Further clinical studies are warranted to determine the degree to which these advantages may enhance clinical efficacy.

## REFERENCES

- Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol.* 2003;49(1 Suppl):S1-S37.
- Data on file, OMP, Inc., Long Beach, CA.
- UNEP (United Nations Environment Programme) Chemicals. OECD SIDS (Organisation for Economic Co-operation and Development Screening Information Dataset) document on benzoyl peroxide. Available at: <http://www.chem.unep.ch/irptc/sids/OECD/SIDS/BENZOYLPER.pdf>. Accessed September 26, 2006.
- Chellquist EM, Gorman WG. Benzoyl peroxide solubility and stability in hydric solvents. *Pharm Res.* 1992;9:1341-6.
- Technical Report #35847: A study of the efficacy of a skin product using scanning electron microscopy techniques. Structure Probe, Inc., West Chester, PA.
- McCullough JL. Final Report for Study OMP 05-03. In vitro percutaneous absorption of topical benzoyl peroxide formulations in human cadaver skin. OMP, Inc., Long Beach, CA.

## DISCLOSURES

Funded by OMP, Inc., Long Beach, CA.