

# Application Characteristics and Patient Preference of Triple-Combination vs Layered Topicals for Acne: Split-Face Study

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## ABSTRACT

**Background:** Although triple-combination therapies for acne are generally more efficacious than dual-combinations or topical monotherapy, this benefit may be offset by reduced adherence to a complicated treatment regimen. Clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% (CAB; Cabtreo®, Ortho Dermatologics) gel is the first triple-combination topical approved for the treatment of acne. By delivering multiple active ingredients as a fixed-dose combination, CAB gel may improve ease of use, which can benefit both treatment adherence and efficacy. The objective of this study was to compare the application characteristics of CAB gel with the layered application of its 3 individual active ingredients.

**Methods:** In this split-face study, adults with acne-prone skin (N=25), self-applied CAB gel (0.3 cc) to 1 side of the face and layered benzoyl peroxide cream, adapalene gel, and clindamycin gel (0.1 cc each) on the opposite side. CAB and clindamycin gels were compounded with pyranine, which fluoresces under blue light. Photos taken under blue light were used to assess the uniformity of product application, and participants rated the evenness, speed, and ease of the 2 application regimens, as well as overall preference.

**Results:** Investigator-assessed evenness of application favored CAB gel over layered application in 100% of participants. All participants rated the application of CAB gel as more uniform, easier, and faster. Most (96%) preferred CAB gel for use at home.

**Conclusion:** Fixed-dose CAB gel was applied more evenly than separate application of its 3 active ingredients. By addressing 3 of the main acne pathogenic pathways in a single, easy-to-apply formulation, CAB gel may improve the efficacy of and adherence to acne treatment.

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## INTRODUCTION

In the treatment of acne, therapies that address multiple pathophysiological pathways are recommended for most patients.<sup>1</sup> Combination therapies are generally more efficacious; in a meta-analysis of 221 clinical trials of 37 different acne interventions, triple-combination therapies incorporating a topical or oral antibiotic, topical retinoid, and benzoyl peroxide were consistently more efficacious than 2-product combinations or topical monotherapy.<sup>2</sup> However, the real-world effectiveness of combining multiple products is less certain, as the addition of products to a treatment regimen increases the cost and complexity of treatment, both of which have been associated with decreases in treatment adherence.<sup>3,4</sup>

The effectiveness of topical acne treatment is further impacted by a medication's physical properties. Aesthetic characteristics such as ease and uniformity of application, spreadability, and skin feel can influence patient acceptance of and adherence to treatment<sup>5-9</sup> as well as drug delivery, efficacy, and tolerability.<sup>8,10</sup>

A thin, uniform film of the drug is ideal as it allows for greater absorption and penetration of active ingredients without leaving greasy or sticky residues on the skin.<sup>11,12</sup> In contrast, thick or uneven applications may contain drugs that are never able to contact, much less penetrate, the skin;<sup>8</sup> and excess drug remaining on the skin can contribute to treatment-related irritation.<sup>13</sup> Beyond these clinical implications, excessively thick applications can be economically wasteful by decreasing the number of applications available from a given amount of product.

Clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% (CAB; Cabtreo®, Ortho Dermatologics) gel is the first fixed-dose triple-combination topical treatment approved by the US Food and Drug Administration (FDA) for the treatment of acne, and is indicated for patients 12 years of age and older.<sup>14</sup> The active ingredients in CAB address 3 of the 4 pathophysiological mechanisms in acne (Table 1),<sup>1,15-17</sup> and are

TABLE 1.

## Pathogenesis of Acne and Treatment With Triple-Combination CAB Gel

Pathogenic Factors in Acne	CAB Active Ingredients		
	Clindamycin	Adapalene	Benzoyl Peroxide
Inflammation	X	X	X
Epithelial hyperproliferation	--	X	--
<i>C. acnes</i> proliferation	X	--	X

Active ingredients in CAB gel address 3 of the 4 pathogenic factors in acne: adapalene normalizes epithelial hyperproliferation; clindamycin and benzoyl peroxide reduce *C. acnes* viability; all 3 active ingredients have anti-inflammatory properties.<sup>1,15-17</sup>

CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%.

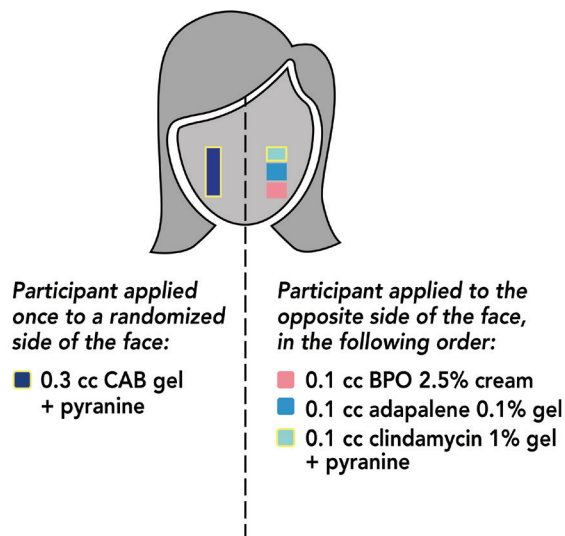
delivered in a single, aqueous gel that is pH-balanced for the skin and contains propylene glycol, a hydrating humectant.<sup>14</sup> In phase 2 and two phase 3 clinical trials, CAB demonstrated superior efficacy compared with vehicle and dyad combinations of the active ingredients, with a favorable safety and tolerability profile.<sup>19,20</sup> By delivering multiple active ingredients as a fixed-dose combination, CAB gel may improve ease of use, which has been shown to improve both treatment adherence and efficacy.<sup>3,4,18</sup> The objective of this study was to compare the application characteristics of fixed-combination CAB gel to the layered application of its 3 individual active ingredients.

## MATERIALS AND METHODS

Healthy adults (18-45 years of age) of all Fitzpatrick skin types, with acne-prone skin but no skin texture abnormalities that would interfere with product application or facial photography, were eligible for participation in this 1-day study. The study was conducted in accordance with the International Conference on Harmonization, the Declaration of Helsinki, and Good Clinical Practice Guidelines, and was approved by the Allendale Institutional Review Board (Old Lyme, CT). All participants provided written informed consent prior to any procedures.

A schematic of the method for assessing the application characteristics of CAB gel vs its individual active ingredients is shown in Figure 1. In this split-face study, participants were randomized to self-apply 0.3 cc CAB gel to one side of the face and 0.1 cc each of the individual active ingredients to the opposite side of the face in the following order: generic benzoyl peroxide 2.5% cream, adapalene 0.1% gel (Differin®; Galderma), and generic clindamycin 1% gel. To mimic how patients might apply the products in a real-world setting, there was no wait time between the application of the 3 ingredients. CAB gel and generic clindamycin gel were compounded with a fixed amount of fluorescent dye (pyranine) for post-application visualization of products on the skin. Pyranine (D&C green no. 8; solvent green no. 7) is the dye used in yellow highlighter pens; in dermatology, it is used as a dye in topical drugs, cosmetics, and personal care products, as well as for visualization of skin damage caused by detergent irritants (eg, sodium lauryl sulfate).<sup>21-23</sup> It was chosen as the fluorescent dye for this study as it is water soluble, non-toxic, and non-irritating to the skin at the concentrations

**FIGURE 1.** Split-face application of single product vs layered application of individual active ingredients. Generic formulations used, except for CAB gel and adapalene 0.1% gel (Differin®; Galderma). CAB gel and clindamycin 1% gel were compounded with similar amounts of fluorescent pyranine.

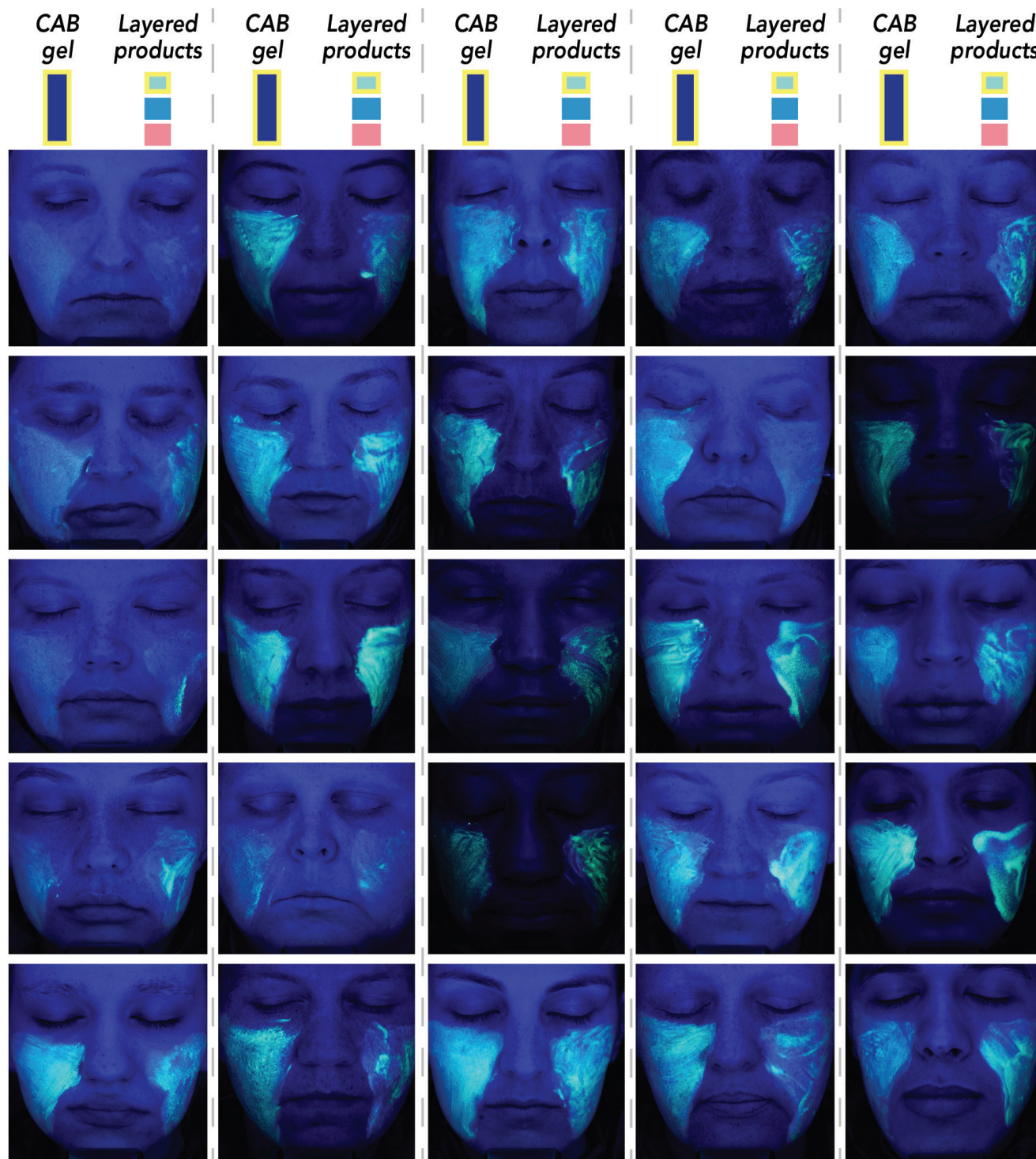


BPO, benzoyl peroxide; CAB, clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1%.

used. Importantly, pyranine was added to CAB and generic clindamycin gel so that the same amount of dye was applied to each side of the face despite the different application volumes of the 2 products. Because pyranine fluoresces under blue light, digital photographs (Visia-CR, Canfield Scientific) were taken of the front of the face before and 10 minutes after product application under both standard and blue lighting.

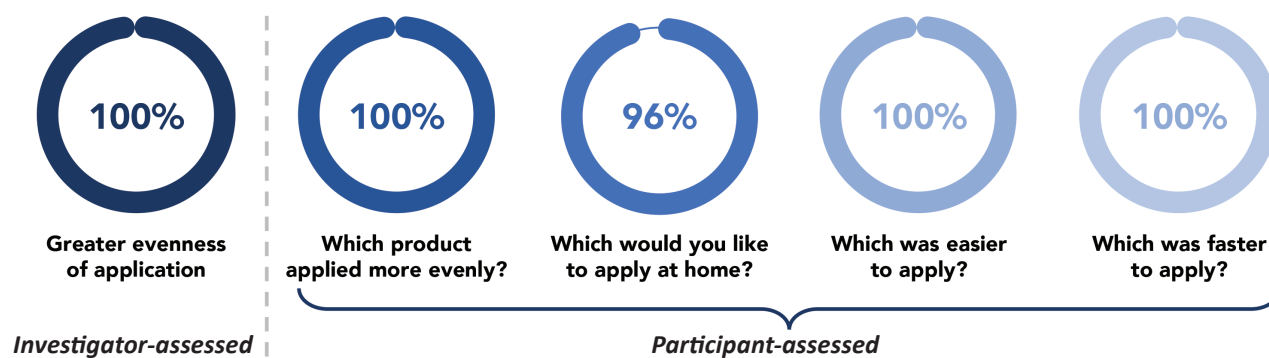
From the blue-light photographs, the blinded investigator assessed which side of the face demonstrated more uniform study product application in real time. After washing all products from their faces, participants viewed both standard-lighting and blue-light photographs before answering the following questions: Which product applied more evenly? Which product would you like to apply at home? Which product was easier to apply? Which product was faster to apply? Responses were analyzed using descriptive statistics.

**FIGURE 2.** Participant photographs. CAB gel and layered products were randomized to application to opposite sides of the face. Select photographs have been flipped so that all images show CAB gel on participants' right side (left side of photo) and layered products on participants' left side (right side of photo).



CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%.



**FIGURE 3.** Assessment of application characteristics favoring CAB gel over layered application.

Percentages indicate responses in favor of CAB gel over layered application of individual ingredients. CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%.

## RESULTS

Twenty-five healthy adults (mean age 30.8 years; range 18-45 years) were enrolled in and completed the study. The majority were female ( $n=24$ ; 96%) and/or White ( $n=19$ ; 76%). Three participants each were Black (12%) or Hispanic (12%).

Post-application blue-light frontal photographs of all 25 participants are shown in Figure 2. Based on the photographs, the investigator assessed CAB gel as demonstrating more uniform product application in 25/25 participants (100%; Figure 3). In addition, participants widely preferred application characteristics of CAB gel vs layered application of the 3 individual active ingredients. All participants (25/25; 100%) assessed CAB gel as easier to apply, faster to apply, and applying more evenly. All but one participant (24/25; 96%) indicated that they would prefer to apply CAB gel at home (Figure 3). Assessment of photographs taken under blue light confirmed that there was no fluorescence on the skin prior to product application, and standard-lighting photos confirmed that the products were not visible after application (photos not shown).

## DISCUSSION

Combination treatment is recommended for most patients with acne,<sup>1</sup> but as treatment regimens become more complex, patient adherence declines.<sup>3,4</sup> CAB gel, the first fixed-dose triple-combination topical treatment approved by the FDA for acne, combines 3 active ingredients into 1 easy-to-use formulation.<sup>14</sup> In this split-face study, CAB gel demonstrated a more uniform application and was widely preferred over the layered application of its individual active ingredients.

Several factors about the design of this study must be considered when interpreting the results. Due to the small sample size, an assessment of spreadability on different skin types (eg, dry, oily) could not be performed, limiting extrapolation to a broader

population. Although this study was conducted in a controlled clinical setting, the findings are likely to be representative of real-world use because all participants self-applied both CAB gel and the individual ingredients. Evaluation of differences in application of CAB gel vs layered products is limited by the fact that uniformity of spread was not quantified, though the more uniform distribution of CAB was readily visible in all participants (Figure 3). In the layered application of 3 products, only the last product applied (clindamycin gel) included fluorescent dye, and thus the uniformity of spread for the other ingredients could not be assessed. Nevertheless, because an equal amount of fluorescent dye was applied to both sides of the face, the results point to overall more favorable application characteristics with fixed-combination CAB gel vs layered application of multiple products.

The ability to form a thin, uniform layer on the skin is necessary for topical medications to rapidly provide a standard dose across the intended treatment area.<sup>11,12</sup> In this study, areas of more intense fluorescence indicate regions of thicker application, which may represent “hot spots” of higher drug concentrations at the skin surface that may increase the likelihood of treatment-related irritation.<sup>13</sup> Conversely, areas of relatively decreased intensity indicate regions of lower drug concentration, where treatment effectiveness might be diminished. CAB is formulated using a polymeric gel that melts upon contact with salts on the skin to provide even distribution and optimized delivery of active ingredients. BPO and adapalene are micronized and suspended, while clindamycin is dissolved in the gel, which may improve tolerability by allowing for the use of lower drug concentrations. The uniform application of CAB gel vs separate, layered application of active ingredients suggests a greater likelihood that all 3 drugs are reaching the intended target, potentially maximizing their therapeutic potential.

Delivering topical combination therapies as fixed-dose formulations provides several additional benefits over layered application of individual ingredients. Layering products can reduce the skin permeation of active ingredients. In one example, layering tazarotene cream on top of halobetasol propionate cream reduced the concentration of tazarotene that permeated human cadaverous skin tissue compared with the application of tazarotene cream alone.<sup>24</sup> Compared with the application of 3 separate products, CAB gel demonstrated greater ease of application and reduced application time, attributes that are consistently cited among the most important for topical treatments for dermatological conditions such as acne, atopic dermatitis, and plaque psoriasis,<sup>25,26</sup> and that have also been shown to be important for patients' quality of life.<sup>26</sup> Collectively, superior application characteristics, improved patient preference, and decreased treatment complexity/inconvenience can all have positive impacts on treatment adherence,<sup>3,4,25-27</sup> which is essential for successful acne treatment.

## CONCLUSION

CAB gel demonstrated a more uniform spread and was preferred by participants over the layered application of its 3 active ingredients. Ease of use and greater uniformity of application are associated with users' acceptance and use of a topical product. Simplifying acne treatment with fixed-dose topical combinations can improve drug delivery as well as patient acceptance of the therapeutic regimen, increasing the likelihood that patients adhere to treatment. Together, these benefits of CAB gel may be expected to improve efficacy in the treatment of acne.

## DISCLOSURES

Zoe Diana Draelos MD received funding from Ortho Dermatologics to conduct the research presented in this article.

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