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Efficacy and Safety of a Fixed-Dose Clindamycin Phosphate 1.2%, Benzoyl Peroxide 3.1%, and Adapalene 0.15% Gel for Moderate-to-Severe Acne: A Randomized Phase II Study of the First Triple-Combination Drug

Linda F. Stein Gold

Henry Ford Health, lstein1@hfhs.org

Hilary Baldwin

Leon H. Kircik

Jonathan S. Weiss

David M. Pariser

See next page for additional authors

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Authors

Linda F. Stein Gold, Hilary Baldwin, Leon H. Kircik, Jonathan S. Weiss, David M. Pariser, Valerie Callender, Edward Lain, Michael Gold, Kenneth Beer, Zoe Draelos, Neil Sadick, Radhakrishnan Pillai, Varsha Bhatt, and Emil A. Tanghetti



Efficacy and Safety of a Fixed-Dose Clindamycin Phosphate 1.2%, Benzoyl Peroxide 3.1%, and Adapalene 0.15% Gel for Moderate-to-Severe Acne: A Randomized Phase II Study of the First Triple-Combination Drug

Linda Stein Gold¹ · Hilary Baldwin^{2,3} · Leon H. Kircik^{4,5,6} · Jonathan S. Weiss^{7,8} · David M. Pariser^{9,10} · Valerie Callender^{11,12} · Edward Lain¹³ · Michael Gold¹⁴ · Kenneth Beer¹⁵ · Zoe Draelos¹⁶ · Neil Sadick^{17,18} · Radhakrishnan Pillai¹⁹ · Varsha Bhatt¹⁹ · Emil A. Tanghetti²⁰

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Abstract

Background A three-pronged approach to acne treatment—combining an antibiotic, antibacterial, and retinoid—could provide greater efficacy and tolerability than single or dyad treatments, while potentially improving patient compliance and reducing antibiotic resistance.

Objectives We aimed to evaluate the efficacy and safety of triple-combination, fixed-dose topical clindamycin phosphate 1.2%/benzoyl peroxide (BPO) 3.1%/adapalene 0.15% (IDP-126) gel for the treatment of acne.

Methods In a phase II, double-blind, multicenter, randomized, 12-week study, eligible participants aged ≥ 9 years with moderate-to-severe acne were equally randomized to once-daily IDP-126, vehicle, or one of three component dyad gels: BPO/adapalene; clindamycin phosphate/BPO; or clindamycin phosphate/adapalene. Coprimary endpoints were treatment success at week 12 (participants achieving a ≥ 2 -grade reduction from baseline in Evaluator's Global Severity Score and clear/almost clear skin) and least-squares mean absolute changes from baseline in inflammatory and noninflammatory lesion counts to week 12. Treatment-emergent adverse events and cutaneous safety/tolerability were also assessed.

Results A total of 741 participants were enrolled. At week 12, 52.5% of participants achieved treatment success with IDP-126 vs vehicle (8.1%) and dyads (range 27.8–30.5%; $P \leq 0.001$, all). IDP-126 also provided significantly greater absolute reductions in inflammatory (29.9) and noninflammatory (35.5) lesions compared with vehicle or dyads (range inflammatory, 19.6–26.8; noninflammatory, 21.8–30.0; $P < 0.05$, all), corresponding to $> 70\%$ reductions with IDP-126. IDP-126 was well tolerated, with most treatment-emergent adverse events of mild-to-moderate severity.

Conclusions Once-daily treatment with the novel fixed-dose triple-combination clindamycin phosphate 1.2%/BPO 3.1%/adapalene 0.15% gel demonstrated superior efficacy to vehicle and all three dyad component gels, and was well tolerated over 12 weeks in pediatric, adolescent, and adult participants with moderate-to-severe acne.

Clinical Trial Registration ClinicalTrials.gov identifier NCT03170388 (registered 31 May, 2017).

1 Introduction

The pathogenesis of acne, one of the most common dermatologic disorders, is a multifactorial process involving follicular proliferation of *Cutibacterium acnes* (formerly *Propionibacterium acnes*), abnormal keratinization, and

increased sebum production and inflammation [1, 2]. Effective treatment, which requires pharmacologic targeting of one or more of these pathophysiologic mechanisms, includes various prescription oral and topical treatments such as benzoyl peroxide (BPO), retinoids (topical tretinoin, adapalene, tazarotene, trifarotene; oral isotretinoin), antibiotics (e.g., erythromycin, clindamycin, minocycline, doxycycline, sarecycline), and hormonal therapies [2]. Adherence rates to oral or topical acne treatments, however, are typically poor and reasons for low adherence include complex regimens, lack of efficacy, and adverse effects [3, 4]. Combining treatments

✉ Linda Stein Gold
LSTEIN1@hfhhs.org

Extended author information available on the last page of the article

Key Points

Combining three acne treatments (an antibiotic, antibacterial, and retinoid) within an easy-to-use topical formulation could improve efficacy, tolerability, and treatment adherence. This is the first study of clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15% (IDP-126) gel, which once approved will be the first triple-combination, fixed-dose topical acne treatment.

Results from this multi-center, randomized, double-blind study in children, adolescents, and adults with moderate-to-severe acne showed that over half of participants treated with IDP-126 gel achieved treatment success by week 12, with over 70% reductions in inflammatory and noninflammatory lesions.

Overall, IDP-126 demonstrated significantly greater efficacy vs vehicle gel and the three component dyad gels and was well tolerated over 12 weeks of daily use—making it a potential new treatment option in the acne armamentarium.

in an easy-to-use, fixed-dose formulation can improve treatment adherence by reducing complex drug regimens [3, 5]. Furthermore, combining topical treatments that target multiple processes of acne pathogenesis may improve efficacy [6] and is a recommended treatment strategy for the majority of patients with acne per the US treatment guidelines published in 2016 [2].

Clindamycin phosphate 1.2%/BPO 3.1%/adapalene 0.15% gel (IDP-126), once approved, will be the first triple-combination fixed-dose topical acne treatment. Formulated as an aqueous gel, with no alcohol, preservatives, occlusive agents, or surfactants, it is pH balanced for the skin and contains propylene glycol, a hydrating humectant. As a smaller particle size allows for better penetration of the pilosebaceous unit [7, 8], BPO and adapalene have been micronized. Additionally, all ingredients are contained within a polymeric gel to allow for even distribution on the skin. As vehicle formulation can affect the tolerability of topical treatments [7], the use of micronized ingredients contained within a polymeric gel may also provide better tolerability. Although combining multiple acne treatments into one formulation can be difficult, as some retinoids, such as tretinoin, are more susceptible to oxidative breakdown in the presence of BPO, adapalene is more stable than tretinoin under such conditions [9].

Several dyad formulations containing BPO/adapalene or BPO/clindamycin have been approved in the USA [10],

but IDP-126 will be the first to combine all three ingredients. While the dyad combinations of BPO with adapalene or clindamycin result in greater lesion reductions than the individual treatments alone, irritation may be an issue with certain combinations [11–14]. Improved efficacy has also been demonstrated following the use of BPO/clindamycin in the morning with the retinoid tazarotene in the evening [15], though complex regimens can impact patient adherence. The objective of this phase II study was to evaluate the efficacy, safety, and tolerability of IDP-126, a novel once-daily clindamycin phosphate 1.2%/BPO 3.1%/adapalene 0.15% fixed-dose gel, in patients with moderate-to-severe acne.

2 Methods

2.1 Study Design

In this phase II, multicenter, randomized, double-blind, parallel-group, vehicle-controlled study, participants 9 years of age or older with moderate (Evaluator's Global Severity Score [EGSS] 3) or severe (EGSS 4) acne were enrolled from 31 study centers in the USA and four in Canada. Eligible participants also needed to have the following facial lesions: ≥ 30 to ≤ 100 inflammatory (pustules, papules, and nodules), ≥ 35 to ≤ 150 noninflammatory (closed and open comedones), and two or fewer nodules. Ranges were selected to enroll patients with a baseline number of lesions while minimizing large variations across the treatment arms. CeraVe® hydrating cleanser, CeraVe® moisturizing lotion (L'Oreal, New York, NY, USA), and sunscreen were provided as needed for optimal moisturization/cleaning of the skin.

Participants were equally randomized to receive one of five treatments to be applied to the face once daily for 12 weeks: clindamycin phosphate 1.2%/BPO 3.1%/adapalene 0.15% gel (IDP-126); one of the three component dyads formulated with the same active drug concentration and within the same vehicle as IDP-126 (BPO 3.1%/adapalene 0.15% gel; clindamycin phosphate 1.2%/BPO 3.1% gel; clindamycin phosphate 1.2%/adapalene 0.15% gel); or vehicle gel. Identically labeled/packaged study drug kits were dispensed to participants at baseline and weeks 4 and 8 by study center staff, based on a randomization code assigned by the central randomization system. This study was carried out in accordance with principles of Good Clinical Practice and the Declaration of Helsinki. At all investigational sites, the study protocol was approved by the relevant independent ethics committees or institutional review boards. All participants or their legal guardians provided written informed consent.

2.2 Study Assessments

Efficacy evaluations comprised counts of inflammatory and noninflammatory lesions and treatment success, defined as the proportion of participants achieving a ≥ 2 -grade reduction from baseline in EGSS and a score of 0 (clear) or 1 (almost clear). Assessments were performed at screening, baseline, and weeks 2, 4, 8, and 12 (treatment end). The EGSS was scored as follows: 0 = Normal, clear skin with no evidence of acne; 1 = Rare noninflammatory lesions present, with rare noninflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red); 2 = Some noninflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions); 3 = Noninflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be one nodulocystic lesion; 4 = Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be up to two nodulocystic lesions. Participants also completed an Acne-Specific Quality of Life (Acne-QoL) questionnaire covering four domains (self-perception, role-emotional, role-social, and acne symptoms) at baseline and week 12; a higher score in any domain indicates improved health-related quality of life [16]. Investigator-assessed cutaneous safety (scaling, erythema, hypopigmentation, and hyperpigmentation) and participant-reported tolerability (itching, burning, and stinging) were evaluated via a 4-point scale where 0 = none and 3 = severe. Treatment compliance was defined as participants missing ≤ 5 consecutive days of dosing and applying 80–120% of expected applications. Adverse events (AEs) were evaluated throughout the study.

2.3 Statistical Analyses

The coprimary endpoints were the percentage of participants achieving treatment success at week 12 and the absolute changes from baseline to week 12 in inflammatory and non-inflammatory lesion counts. Treatment success at week 12 was analyzed using a logistic regression test with factors of treatment group and analysis center. Significant skewness was observed in the change from baseline analyses of non-inflammatory and inflammatory lesions, and as such, a non-parametric method was used to rank transform the data prior to the analysis of covariance. For the analysis of covariance, treatment and analysis center were factors and the respective baseline lesion counts were a covariate.

Secondary and post hoc analyses included treatment success and a ≥ 2 -grade reduction in EGSS by study visit, percent changes from baseline in inflammatory and non-inflammatory lesion counts by study visit, and quality-of-life assessments at week 12. For all post hoc analyses of

treatment success and a ≥ 2 -grade EGSS reduction, the Firth option was added (used to apply Firth's Penalized Likelihood to the logistic regression) because of convergence issues.

For all efficacy assessments, values were adjusted for multiple imputations and pairwise tests were performed to compare IDP-126 with the three component dyads (BPO/adapalene, clindamycin/BPO, clindamycin/adapalene) and vehicle gel. Missing efficacy data were handled based on estimation using the Markov Chain Monte Carlo multiple imputation method. Acne-QoL questionnaire results and cutaneous safety and tolerability assessments were summarized using descriptive statistics with no imputation of missing values.

No formal sample size calculation was performed for this study as the sample size was based only on clinical considerations and the numbers of participants enrolled in each treatment arm were considered sufficient to evaluate the safety and tolerability of IDP-126 vs the dyads or vehicle. All statistical analyses were conducted using SAS[®] software, version 9.3 or later (Cary, NC, USA). Statistical significance was based on two-tailed tests of the null hypothesis resulting in $P \leq 0.05$. Adverse events were classified using the Medical Dictionary for Regulatory Activities terminology for the safety population. No interim analyses were performed. The intent-to-treat population consisted of all randomized participants who received the study drug. The safety population was defined as all randomized participants who used the study drug at least once and had at least one post-baseline safety evaluation.

3 Results

3.1 Participants

Screening began on 5 October, 2017 and the last study visit occurred on 23 April, 2019. A total of 741 participants were randomized to IDP-126, one of the three component dyad gels, or vehicle gel, with 740 comprising the intent-to-treat population (one excluded participant was not dispensed the study drug; Fig. 1). Of these, $\geq 85\%$ participants in each treatment group completed the study. The most common reasons for study discontinuation were AEs, lost to follow-up, and participant request. Discontinuation because of AEs occurred in 0–5.3% of participants across treatments. A total of 725 participants were included in the safety population.

Baseline demographics and disease characteristics are shown in Table 1. Participants were similar across treatment arms: the mean age was approximately 19.5 years, the majority were female (61.2%) and White (69.2%), and most had moderate (EGSS 3) disease (range 79.3–86.0%). Treatment compliance across treatment groups was $\geq 93\%$.

3.2 Efficacy and Quality of Life

Across all 12 coprimary efficacy comparisons, IDP-126 gel was significantly more efficacious than each of its dyad components and vehicle (Table 2). Over half of participants (52.5%) achieved treatment success at week 12 with IDP-126, significantly greater than the three dyad gels (range 27.8–30.5%; $P \leq 0.001$, all) and vehicle gel (8.1%; $P < 0.001$). Absolute mean reductions in inflammatory and noninflammatory lesions from baseline to week 12 were also significantly greater with IDP-126 vs all dyads and vehicle (Table 2).

In the by-study visit analyses, significant differences in treatment success were seen as early as week 4 with IDP-126 vs vehicle ($P < 0.01$) and maintained throughout the study (see eFig. 1 of the Electronic Supplementary Material [ESM]). By study end, over half of IDP-126-treated participants (58.7%) also achieved a ≥ 2 -grade reduction from baseline in EGSS, significantly more than the three dyads (35.8–37.0%) and vehicle (12.5%; $P \leq 0.001$, all).

In terms of least-squares mean percent changes in acne lesion counts, IDP-126 had significantly greater reductions in inflammatory and noninflammatory lesions than vehicle gel at all study visits ($P < 0.05$, all), with over 70% reductions achieved by week 12 (Fig. 2). Additionally, significant

differences between IDP-126 and each of its component dyads were observed at week 12 (Fig. 2 footnote). Images depicting acne improvement in IDP-126-treated participants are shown in Fig. 3. Improvements in Acne-QoL scores at week 12 were numerically greater for the IDP-126 group vs all three dyad gels and vehicle in all four domains, with the largest improvements seen in the domains of self-perception and role-emotional (Fig. 4).

3.3 Safety

A greater proportion of participants treated with IDP-126 and BPO/adapalene reported treatment-emergent AEs (TEAEs) compared with clindamycin/BPO, clindamycin/adapalene, or vehicle (Table 3). Treatment-emergent AEs were mostly mild or moderate in severity for all groups and more TEAEs were considered related to treatment in the IDP-126 and BPO/adapalene groups. The most commonly reported TEAEs related to treatment were application-site pain and dryness. A total of four participants experienced one serious AE each, none of which was considered related to treatment ($n = 1$ in IDP-126 group [sickle cell anemia with crisis]; $n = 3$ in clindamycin/adapalene [enteritis; hyperbilirubinemia; induced abortion]). Discontinuations because of TEAEs were highest in the BPO/adapalene group

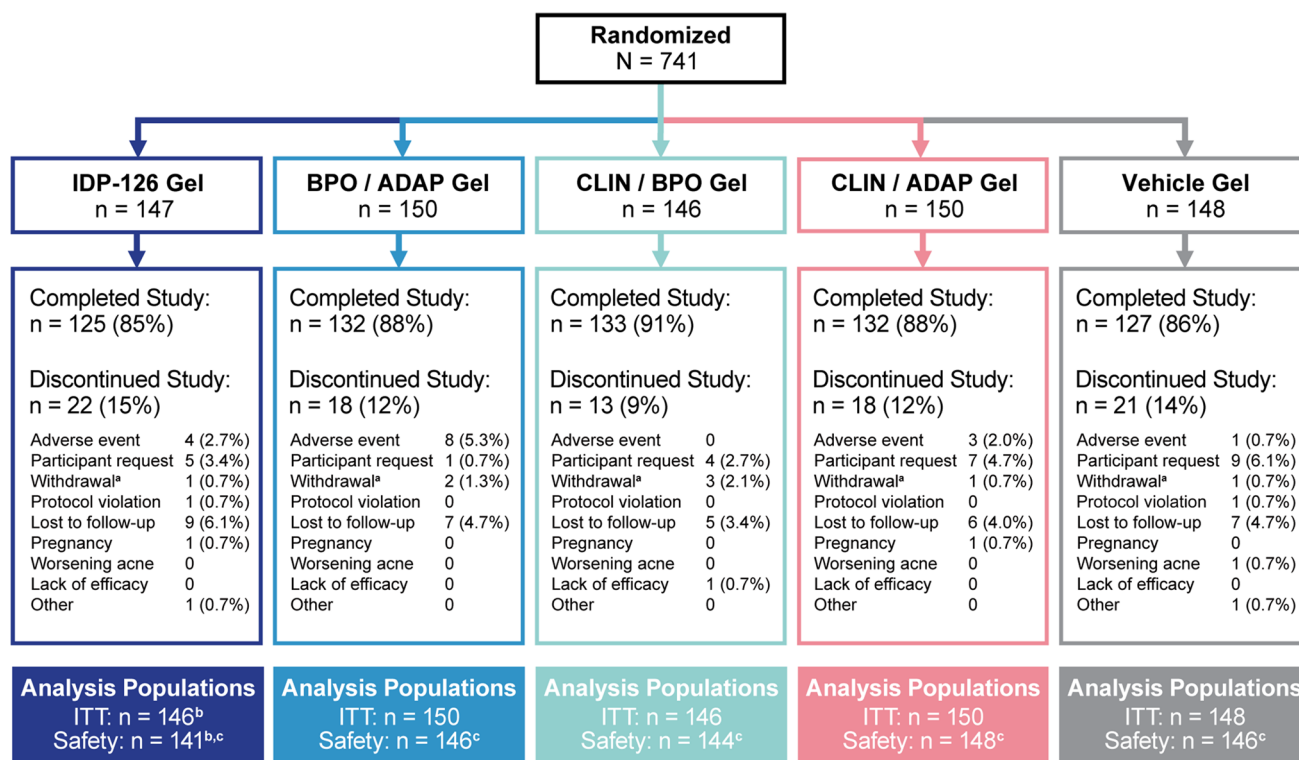


Fig. 1 Participant disposition. ^aWithdrawal by parent or guardian. ^bOne excluded participant was not dispensed the study drug. ^cExcluded participants had no post-baseline safety evaluations. ADAP

adapalene 0.15%, BPO benzoyl peroxide 3.1%, CLIN clindamycin phosphate 1.2%, IDP-126 clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15%, ITT intent to treat

Table 1 Baseline demographics and characteristics (ITT population)

	IDP-126 gel (n = 146)	BPO/ADAP gel (n = 150)	CLIN/BPO gel (n = 146)	CLIN/ADAP gel (n = 150)	Vehicle gel (n = 148)
Age, mean (SD), y	19.9 (7.0)	19.2 (8.0)	19.6 (6.9)	19.4 (6.5)	19.6 (7.1)
Age, median (range), y	17.0 (11–46)	17.0 (10–60)	17.0 (10–45)	17.0 (11–50)	17.0 (11–47)
Female, n (%)	94 (64.4)	86 (57.3)	91 (62.3)	93 (62.0)	89 (60.1)
Ethnicity, Hispanic/Latino, n (%)	33 (22.6)	30 (20.0)	29 (19.9)	27 (18.0)	34 (23.0)
Race, n (%)					
Black	24 (16.4)	26 (17.3)	30 (20.5)	20 (13.3)	26 (17.6)
White	98 (67.1)	109 (72.7)	101 (69.2)	109 (72.7)	95 (64.2)
Asian	10 (6.8)	6 (4.0)	8 (5.5)	9 (6.0)	17 (11.5)
Other ^a	14 (9.6)	9 (6.0)	7 (4.8)	12 (8.0)	10 (6.8)
Inflammatory lesion count, mean (SD)	39.0 (11.8)	39.0 (10.2)	40.0 (12.8)	38.2 (7.9)	38.2 (9.2)
Noninflammatory lesion count, mean (SD)	51.8 (20.3)	48.0 (14.7)	49.2 (17.6)	51.1 (18.4)	50.7 (18.7)
Evaluator's Global Severity Score, n (%)					
3: moderate	124 (84.9)	119 (79.3)	124 (84.9)	129 (86.0)	127 (85.8)
4: severe	22 (15.1)	31 (20.7)	22 (15.1)	21 (14.0)	21 (14.2)

ADAP adapalene 0.15%, BPO benzoyl peroxide 3.1%, CLIN clindamycin phosphate 1.2%, IDP-126 clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15%, ITT intent to treat, SD standard deviation

^aAmerican Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, and other/multiple

Table 2 Coprimary endpoints at week 12 (ITT population)

	IDP-126 gel (n = 146)	BPO/ADAP gel (n = 150)	CLIN/BPO gel (n = 146)	CLIN/ADAP gel (n = 150)	Vehicle gel (n = 148)
Treatment success ^a , %	52.5	27.8***	30.5***	30.3***	8.1***
Absolute change from baseline, LS mean					
Inflammatory lesions	– 29.9	– 26.7*	– 24.8**	– 26.8*	– 19.6***
Noninflammatory lesions	– 35.5	– 29.9**	– 27.8***	– 30.0**	– 21.8***

Multiple imputation was used to impute missing values

ADAP adapalene 0.15%, BPO benzoyl peroxide 3.1%, CLIN clindamycin phosphate 1.2%, EGSS Evaluator's Global Severity Score, IDP-126 clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15%, ITT intent to treat, LS least squares

* $P < 0.05$; ** $P < 0.01$; *** $P \leq 0.001$ vs IDP-126

^aDefined as a ≥ 2 -grade reduction from baseline in EGSS and a score of 0 (clear) or 1 (almost clear)

(Table 3). A total of five participants experienced a system organ class gastrointestinal disorder AE (one participant in the clindamycin/adapalene group had two AEs): one constipation (IDP-126); one gastritis (IDP-126); one dyspepsia (clindamycin/adapalene); one enteritis (clindamycin/adapalene); one vomiting (clindamycin/adapalene); and one diarrhea (vehicle). None of these AEs was considered by the investigator to be related to treatment and all were mild to moderate in severity with the exception of enteritis.

Across all active treatment groups, there were transient increases in severity from baseline at weeks 2 or 4 for

several of the cutaneous safety and tolerability assessments (see eFig. 2 of the ESM). Mean scores for all treatments at all visits, however, were ≤ 0.6 (score of 1 = mild). By week 12, $< 6\%$ of participants in any treatment group experienced a severe rating on any cutaneous safety or tolerability assessment; participant-reported burning and stinging had the highest rates of severe events, both of which were highest in the BPO/adapalene group (Table 3). In the IDP-126 group, there were no reports of severe scaling, erythema, hypopigmentation, and itching and $< 5\%$ of participants reported severe hyperpigmentation, burning, and stinging.

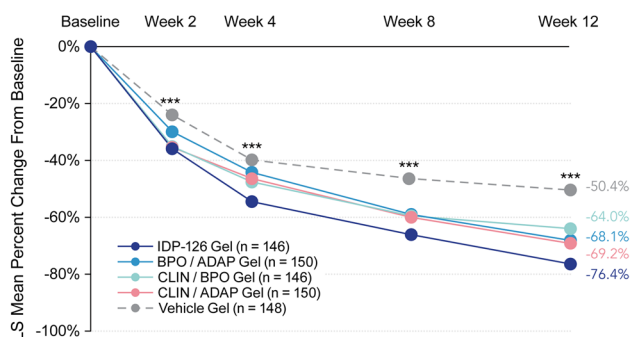
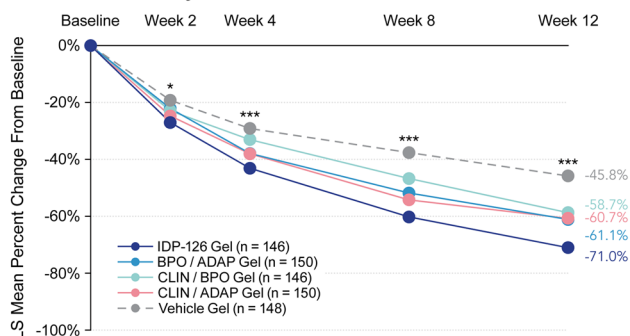
A. Inflammatory Lesions**B. Noninflammatory Lesions**

Fig. 2 Least-squares (LS) mean percent reductions in **a** inflammatory lesions and **b** noninflammatory lesions (intent-to-treat [ITT] population). Multiple imputation was used to impute missing values. * $P < 0.05$; *** $P < 0.001$ vehicle vs clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15% (IDP-126). Data not shown: P -values for IDP-126 vs dyads were significant ($P < 0.05$) as follows: inflammatory lesions: benzoyl peroxide 3.1%, (BPO)/adapalene 0.15% (ADAP) at weeks 2, 4, 8, and 12; clindamycin phosphate 1.2%, (CLIN)/BPO at weeks 4 and 12; CLIN/ADAP at weeks 4, 8, and 12. Noninflammatory lesions: BPO/ADAP at weeks 8 and 12; CLIN/BPO at weeks 4, 8, and 12; CLIN/ADAP at weeks 4, 8, and 12. All active dyad treatments were significant vs vehicle at weeks 8 and 12 for both inflammatory and noninflammatory lesions ($P < 0.01$, all); additionally, CLIN/BPO and CLIN/ADAP were significant vs vehicle at weeks 2 and 4 for inflammatory lesions ($P < 0.05$, all) and BPO/ADAP and CLIN/ADAP were significant vs vehicle at week 4 for noninflammatory lesions ($P < 0.01$, both).

4 Discussion

In this phase II study, IDP-126, the novel fixed-dose triple-combination clindamycin phosphate 1.2%/BPO 3.1%/adapalene 0.15% gel, was evaluated over 12 weeks in participants with moderate-to-severe acne. IDP-126 demonstrated superior efficacy on all three coprimary endpoints compared with the three dyad component combinations and vehicle gel and was well tolerated.

The three drugs that make up IDP-126 were chosen in order to target the multiple processes of acne pathogenesis. Topical retinoids, such as adapalene, are a mainstay of acne treatment; they normalize keratinocyte proliferation, block several inflammatory pathways, promote comedolysis, and

reduce microcomedonal formation. While they are generally well tolerated, their use can be limited by dryness, irritation, and erythema [8, 17]. Adapalene—a third-generation retinoid that modulates cellular keratinization, differentiation, and proliferation [8, 18]—has the advantage of being one of the most tolerable retinoids [19] that also retains its stability in the presence of BPO [9]. Benzoyl peroxide is an antibacterial agent with mild comedolytic activity, keratolytic effects, and good efficacy and tolerability [2, 20–22]; it is unaffected by *C. acnes* resistance, [20] and has been used in combination with topical and oral antibiotics because of its ability to reduce resistant *C. acnes* populations [23]. Topical or oral antibiotics reduce *C. acnes* colonization and proliferation [24], and clindamycin, a lincosamide, is a widely studied and commonly used antibiotic with anti-inflammatory effects [1]. It has been used for acne treatment for over 30 years [1] and has shown better efficacy in comparison to erythromycin [2]. The addition of clindamycin to BPO not only increases antibiotic activity [22], but may also moderate the irritating effects or withdrawals from AEs observed with BPO [12, 14]. Altogether, the combination of these three acne treatments targets three of the four acne pathogenic pathways and may reduce the antibiotic resistance and adverse cutaneous effects observed with monotherapy.

In the present study, over half of IDP-126-treated participants achieved treatment success at week 12, with a rate that was 1.7–1.8 times greater than with the component dyads. The inclusion of all dyad combinations within the same vehicle formulation as IDP-126 was a strength in this study, in that it allowed for assessing the contribution of the active drug components while minimizing study arms. However, the exclusion of the component monads prevented the determination of the direct contributions of each active treatment to calculate the synergistic treatment effect. Though synergy cannot be directly assessed in this study, treatment success rates with IDP-126 appeared to be greater than the expected additive effect, as each of the dyad combinations had rates less than two-thirds of IDP-126.

At week 12, IDP-126 demonstrated over 70% reductions in acne lesions. Significantly greater percent reductions in inflammatory and noninflammatory lesions were observed as early as week 2 with IDP-126 vs vehicle gel, suggesting a fast therapeutic action. As BPO, retinoids, and antibiotics act primarily as antibacterial and/or anti-inflammatory agents, it would be expected that inflammatory lesions would be reduced more than noninflammatory lesions with IDP-126. In this study, however, there were similar reductions in both inflammatory and noninflammatory acne. This may be due to the comedolytic properties of BPO as well as the ability of clindamycin to reduce *C. acnes* populations. It is likely that using these products together with adapalene targets both inflammatory and noninflammatory acne. Similar results were observed in a 12-week acne study where clindamycin/

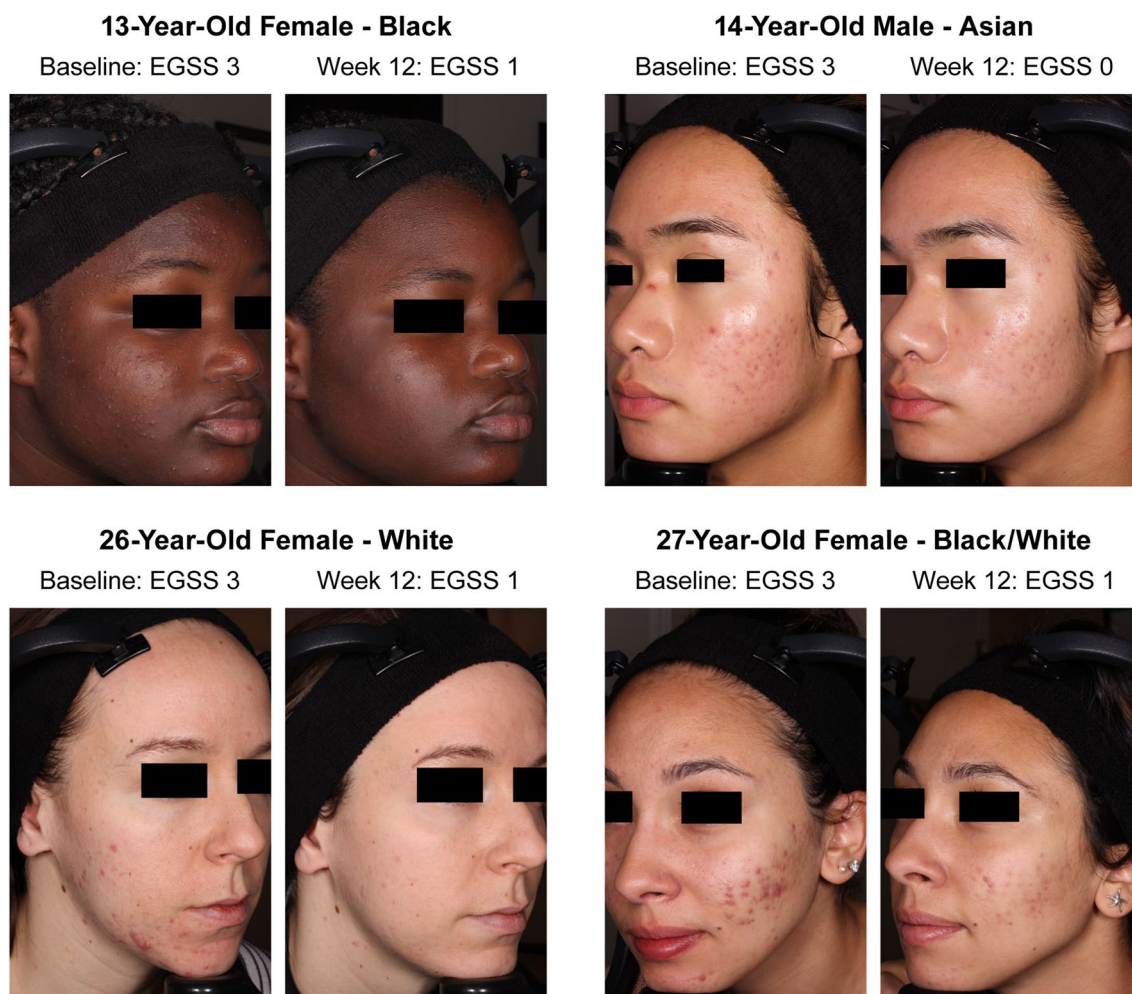


Fig. 3 Acne improvements with clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15% (IDP-126). Individual results may vary. EGSS Evaluator's Global Severity Score (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe)

BPO gel was applied in the morning and tazarotene 0.1% cream was also applied at night [25].

In context with other 10-week to 12-week clinical studies that examined various combinations and dosages of commercially available dyads containing BPO and clindamycin or adapalene, IDP-126 had greater numeric percent changes in inflammatory and noninflammatory lesions (− 76.4% and − 71.0%, respectively) than the other dyads (range − 42% to − 68.7% and − 21.9% to − 68.3%) [11–13, 26–31]. IDP-126 treatment success rates were also numerically greater than dyads in other 12-week clinical studies (52.5% vs a range of 21.5–33.7%) [13, 26–29]. As expected, the component dyads in the present study performed comparably to other commercially available dyads, which further highlights the efficacy of the triple-combination IDP-126 gel. Direct comparisons, however, cannot be made between IDP-126 and other currently approved dyad treatments, as no head-to-head or facial-splitting studies were conducted. Further, there were design differences across the studies (phase II or

phase III; differing percentages of participants with moderate or severe acne and other patient backgrounds; differing definitions of treatment success), as well as differences in the drug dosages, combinations, and vehicle formulations.

Limitations of this study and its design are similar to other clinical trials of acne. Assessments of acne severity via the EGSS may result in inter-observer bias or variation. Treatment duration in the study was limited to 12 weeks, and longer treatment would better reflect real-world patient experiences. Finally, results from this study may not be generalizable to diverse real-world practice populations, which may differ in race, age, and sex. Future post hoc analyses evaluating these populations of interest can address this limitation.

In the past, there has not been a formulation containing BPO, a retinoid, and a topical antibiotic—possibly because of concerns regarding tolerability (BPO and retinoids) and/or antibacterial resistance (antibiotics). In the present study, this triple combination demonstrated good tolerability with once-daily use. As expected, there were slight increases from

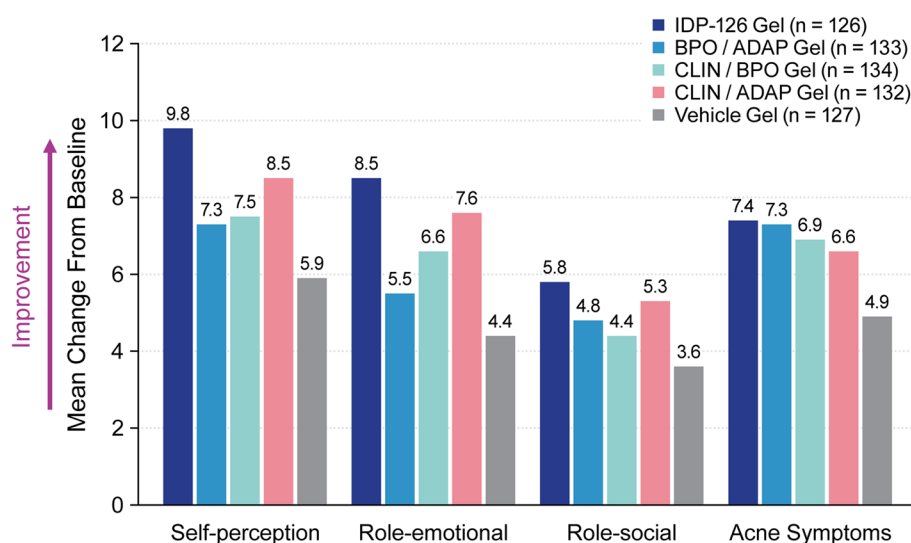


Fig. 4 Acne-Specific Quality of Life Questionnaire at week 12 (intent-to-treat population). No imputation of missing values. Higher scores for each domain reflect improved health-related quality of life. Self-perception domain assesses the extent facial acne has affected a particular area of self-perception (e.g., feeling self-conscious, feeling unattractive, dissatisfaction with self-appearance). Role-emotional domain assesses the emotional effect or impact of facial acne (e.g., annoyance at spending time on face, worry/concern about medications working fast enough, bothersomeness of needing cover-up).

baseline to week 12 in scaling, burning, and stinging mean scores with IDP-126. Transient increases at weeks 2 and 4, however, were lower with IDP-126 than the BPO/adapalene dyad. Furthermore, there were no instances of severe scaling, erythema, or itching with IDP-126, whereas the BPO/adapalene or clindamycin/adapalene dyads had instances of severe ratings; IDP-126 also had fewer severe cases of burning and stinging than BPO/adapalene. Rates of discontinuations because of TEAEs were at least twofold higher with BPO/adapalene than any of the other treatment groups.

The combination of clindamycin, BPO, and adapalene in IDP-126 appears to have a slightly better safety and tolerability profile than the BPO/adapalene combination. This may be a result of the IDP-126 vehicle formulation, the combination of active ingredients, or both. In terms of vehicle formulation, as noted previously, IDP-126 is a gel that uses a polymeric technology to provide a more uniform distribution of all ingredients. It is also possible that the multiple anti-inflammatory properties of clindamycin [1] can provide a moderating effect on the cutaneous safety and tolerability of BPO and adapalene. This rationale is supported by a meta-analysis that showed clindamycin combined with BPO had lower odds of patient withdrawal/discontinuation because of AEs than BPO alone or BPO/adapalene combinations [14]. These results are supported by the AEs and AE-related discontinuations reported in this phase II study, as well as

Role-social domain assesses the impact of facial acne on a respondent's intersocial relationships (e.g., going out in public, meeting new people, socializing). Acne symptoms assesses the physical symptoms experienced by facial acne (e.g., bumps on face, scabbing, worry about scarring); the acne symptom domain score correlates inversely with acne severity. ADAP adapalene 0.15%, BPO benzoyl peroxide 3.1%, CLIN clindamycin phosphate 1.2%, IDP-126 clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15%

the cutaneous safety/tolerability data, as the lowest rates of related AEs were observed with clindamycin/BPO and the highest rates with BPO/adapalene. In addition, topical antibiotics such as clindamycin are an attractive treatment option as they may reduce the risk of systemic side effects that are seen with oral antibiotics [2]. Though cases of diarrhea, bloody diarrhea, and colitis have been reported with the use of clindamycin (oral or topical) [32], instances of gastrointestinal AEs were rare in the present study and none were deemed related to treatment.

An issue with common antibiotic acne treatments such as erythromycin, clindamycin, and tetracyclines is the development of *C. acnes* resistance [2, 33]. While a topical minocycline 4% foam (approved in the USA for monotherapy) has been introduced as having a decreased risk for the development of resistance, more research is needed to determine the potential for the development of drug-resistant bacteria with this formulation [34]. To prevent the development of resistance, antibiotic monotherapy is not recommended [2, 35]. However, combining an antibiotic with BPO is recommended, as studies have shown that BPO reduces the risk of antibiotic resistance [2, 23].

While there are many treatment options available, acne is a chronic disease that requires long-term treatment [2, 4]. Regimens with side effects, low efficacy, or high complexity (e.g., using several treatments at one time, taking

Table 3 Summary of AEs and safety/tolerability assessments

Participants, <i>n</i> (%)	IDP-126 gel (<i>n</i> = 141)	BPO/ADAP gel (<i>n</i> = 146)	CLIN/BPO gel (<i>n</i> = 144)	CLIN/ADAP gel (<i>n</i> = 148)	Vehicle gel (<i>n</i> = 146)
Reporting any TEAE	51 (36.2)	52 (35.6)	26 (18.1)	40 (27.0)	22 (15.1)
Reporting any SAE ^a	1 (0.7)	0	0	3 (2.0)	0
Discontinued study drug due to TEAE ^b	4 (2.8)	8 (5.5)	0	3 (2.0)	2 (1.4)
Severity of TEAEs					
Mild	26 (18.4)	25 (17.1)	16 (11.1)	20 (13.5)	11 (7.5)
Moderate	18 (12.8)	22 (15.1)	10 (6.9)	17 (11.5)	10 (6.8)
Severe	7 (5.0)	5 (3.4)	0	3 (2.0)	1 (0.7)
Relationship to study drug					
Related	28 (19.9)	32 (21.9)	3 (2.1)	18 (12.2)	2 (1.4)
Unrelated	23 (16.3)	20 (13.7)	23 (16.0)	22 (14.9)	20 (13.7)
Related TEAEs reported by $\geq 2\%$ of participants in any treatment group					
AS pain	11 (7.8)	16 (11.0)	1 (0.7)	5 (3.4)	1 (0.7)
AS dryness	9 (6.4)	8 (5.5)	2 (1.4)	9 (6.1)	0
AS exfoliation	5 (3.5)	3 (2.1)	0	2 (1.4)	1 (0.7)
AS irritation	3 (2.1)	4 (2.7)	1 (0.7)	3 (2.0)	0
AS erythema	2 (1.4)	2 (1.4)	1 (0.7)	5 (3.4)	0
AS dermatitis	2 (1.4)	3 (2.1)	0	2 (1.4)	0
AS pruritus	3 (2.1)	2 (1.4)	1 (0.7)	1 (0.7)	0
TEAEs leading to permanent withdrawal of study drug and/or early discontinuation (in $\geq 1\%$ of participants in any treatment group)					
AS pain	2 (1.4)	5 (3.4)	0	2 (1.4)	0
AS dermatitis	0	2 (1.4)	0	0	0
Sunburn	0	2 (1.4)	0	0	0
AS acne	0	0	0	0	2 (1.4)
Grade 3 (severe) cutaneous safety and tolerability assessments ^c					
Scaling	0	2 (1.4)	0	2 (1.4)	0
Erythema	0	2 (1.4)	0	3 (2.0)	0
Hypopigmentation	0	0	0	0	0
Hyperpigmentation	2 (1.4)	3 (2.1)	2 (1.4)	3 (2.0)	1 (0.7)
Itching	0	1 (0.7)	0	0	1 (0.7)
Burning	6 (4.3)	8 (5.5)	0	1 (0.7)	0
Stinging	3 (2.1)	6 (4.1)	0	0	0

ADAP adapalene 0.15%, AE adverse event, AS application site, BPO benzoyl peroxide 3.1%, CLIN clindamycin phosphate 1.2%, IDP-126 clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15%, SAE serious adverse event, TEAE treatment-emergent adverse event

^aNone of the SAEs were considered related to the study drug

^bOne participant in the vehicle gel group discontinued the study drug, but not the study, because of a TEAE

^cInvestigator-assessed evaluations were scaling, erythema, hypopigmentation, and hyperpigmentation; participant-assessed evaluations were itching, burning, and stinging

multiple doses in a day) can adversely affect treatment adherence [3, 4]. The results from the present study have demonstrated that IDP-126 was not only well tolerated with low rates of discontinuations due to TEAEs, it was also efficacious and fast acting, providing significantly greater lesion reductions vs vehicle as early as week 2. Together with the simple once-daily treatment regimen, this fixed-dose triple-combination may also help improve treatment adherence.

5 Conclusions

Once-daily treatment with the novel fixed-dose triple-combination clindamycin phosphate 1.2%/BPO 3.1%/adapalene 0.15% gel (IDP-126) in an elegant delivery system demonstrated superior efficacy to vehicle gel and three dyad component gels over 12 weeks in pediatric, adolescent, and adult participants with moderate-to-severe acne. IDP-126 was also fast acting, significantly reducing lesion counts vs

vehicle as early as week 2 and was safe and well tolerated. The good efficacy and safety profiles of the only fixed-dose triple-combination—containing three of the recommended acne treatments (benzoyl peroxide, a topical retinoid, and a topical antibiotic)—demonstrate that IDP-126 is a potential new treatment option in the acne armamentarium.

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Declarations

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Ethics approval This study was carried out in accordance with principles of Good Clinical Practice and the Declaration of Helsinki. At all investigational sites, the study protocol was approved by the relevant independent ethics committees or institutional review boards. All participants or their legal guardians provided written informed consent.

Consent to participate All participants or their legal guardians provided written informed consent before entering the clinical trial from which the data were derived.

Consent for publication Additional informed consent was obtained from all individual participants for whom identifying information/photographs are included in this article.

Availability of data and material Available upon request.

Code availability Not applicable.

Authors' contributions All authors made substantial contributions to the conception or design of the work; drafted the work/revised it critically; approved the version to be published; and agree to be accountable for all aspects of this work.

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Authors and Affiliations

Linda Stein Gold¹ · Hilary Baldwin^{2,3} · Leon H. Kircik^{4,5,6} · Jonathan S. Weiss^{7,8} · David M. Pariser^{9,10} · Valerie Callender^{11,12} · Edward Lain¹³ · Michael Gold¹⁴ · Kenneth Beer¹⁵ · Zoe Draelos¹⁶ · Neil Sadick^{17,18} · Radhakrishnan Pillai¹⁹ · Varsha Bhatt¹⁹ · Emil A. Tangheiti²⁰

¹ Henry Ford Hospital, 6530 Farmington Rd, Ste 101, West Bloomfield, Detroit, MI 48322, USA

² The Acne Treatment and Research Center, Brooklyn, NY, USA

³ Robert Wood Johnson University Hospital, New Brunswick, NJ, USA

⁴ Indiana University School of Medicine, Indianapolis, IN, USA

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- | | |
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| <p>⁵ Physicians Skin Care, PLLC, Louisville, KY, USA</p> <p>⁶ Icahn School of Medicine at Mount Sinai, New York, NY, USA</p> <p>⁷ Georgia Dermatology Partners, Snellville, GA, USA</p> <p>⁸ Gwinnett Clinical Research Center, Inc., Snellville, GA, USA</p> <p>⁹ Eastern Virginia Medical School, Norfolk, VA, USA</p> <p>¹⁰ Virginia Clinical Research, Inc., Norfolk, VA, USA</p> <p>¹¹ Callender Dermatology and Cosmetic Center, Glenn Dale, MD, USA</p> <p>¹² Howard University College of Medicine, Washington, DC, USA</p> | <p>¹³ Austin Institute for Clinical Research, Austin, TX, USA</p> <p>¹⁴ Tennessee Clinical Research Center, Nashville, TN, USA</p> <p>¹⁵ University of Miami Miller School of Medicine, Miami, FL, USA</p> <p>¹⁶ Dermatology Consulting Services, PLLC, High Point, NC, USA</p> <p>¹⁷ Weill Cornell Medical College, New York, NY, USA</p> <p>¹⁸ Sadick Dermatology, New York, NY, USA</p> <p>¹⁹ Bausch Health US, LLC, Petaluma, CA, USA</p> <p>²⁰ Center for Dermatology and Laser Surgery, Sacramento, CA, USA</p> |
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