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 ORIGINAL ARTICLE

Early and Sustained Acne Lesion Reductions With Fixed-Dose Clindamycin Phosphate 1.2%/Adapalene 0.15%/Benzoyl Peroxide 3.1% Gel

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ABSTRACT

Background: A once-daily, three-pronged approach using an antibiotic, antibacterial, and retinoid may provide faster acne improvement versus monotherapy or dual-combination products. This post hoc analysis compared threshold acne lesion reductions with clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% (CAB) gel—the first FDA-approved triple-combination topical acne product—to its dyads and vehicle.

Methods: Phase 2 (N=741; NCT03170388) and phase 3 (N=183; N=180; NCT04214639; NCT04214652), double-blind, 12-week studies randomized participants aged ≥9 years with moderate-to-severe acne to once-daily CAB or vehicle gel; the phase 2 study included three additional dyad gel arms. The pooled percentage of participants achieving ≥33%, ≥50%, and ≥75% reduction in inflammatory and noninflammatory acne lesions was evaluated.

Results: As early as week 4 in the phase 2 study, ≥33% reduction in inflammatory lesions occurred in a significantly greater percentage of CAB gel-treated participants (82.7%) than with the 3 dyads and vehicle (61.1-69.8%; $P<0.05$, all). These early reductions were sustained throughout the study, with significantly ($P<0.05$) more CAB-treated participants achieving ≥50% reduction in inflammatory lesions versus dyads and vehicle from weeks 4-12. By week 12, CAB led to substantial reductions of ≥75% in significantly more participants than dyads and vehicle (65.8% vs 49.9-51.2% and 21.6%; $P<0.05$, all). Similar trends were observed for noninflammatory lesions in the phase 2 study and for inflammatory and noninflammatory lesions in the phase 3 studies.

Conclusions: Lesion count reductions were significantly greater with CAB versus its dyads and vehicle gel as early as week 4, with substantial reductions observed after 12 weeks of treatment. This faster-acting and sustained efficacy of CAB gel—coupled with its optimized formulation, once-daily dosing, and tolerability—may positively impact treatment adherence.

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INTRODUCTION

Acne vulgaris is a common dermatologic condition that can have a profound psychosocial impact on patients' quality of life.[1,2] While several oral and topical drugs are currently available for acne therapy, treatment can be challenging owing to the chronic nature of acne and its multifactorial underlying pathology.[1] Treatment is further hindered by low adherence typical of acne therapies,[3-6] with multiple factors contributing to nonadherence including side effects, difficulty incorporating the treatment routine, and treatment cost.[7] Additionally, many acne medication regimens currently available may take weeks or months to produce an improvement discernible by patients. This lag between treatment initiation and acne improvement noticeable to patients can further reduce adherence, potentially contributing to treatment failure.[1,8]

Combination therapies that simultaneously target multiple processes of acne pathogenesis are recommended in the US for the majority of patients with acne.[9] A three-pronged combination approach using once-daily application of an antibiotic, antibacterial agent, and retinoid may provide faster improvement than stand alone or dual combination products. The first triple-combination, fixed-dose acne treatment approved by the US Food and Drug Administration, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide (BPO) 3.1% (CAB; Cabtreo™; Ortho Dermatologics) gel, has been evaluated in three 12-week studies of participants with moderate-to-severe acne.[10,11] In a phase 2 study, once-daily CAB was well tolerated and demonstrated efficacy that was significantly superior to vehicle and three dyad combinations of the active ingredients.[10] Two identical randomized, phase 3, double-blind, vehicle-controlled trials confirmed the efficacy, safety, and tolerability of CAB.[11] Further, the onset of action with CAB was rapid: percent reductions from baseline in acne lesions were significantly greater with CAB than vehicle gel as early as week 2 in the phase 2 study (both inflammatory and noninflammatory lesions, $P<0.05$, both)[10] and phase 3 studies (inflammatory lesions only; $P<0.05$ all).[12] This is important as treatments associated with fast and substantial or complete clearance of acne lesions are highly desirable to patients with acne[13] and can promote treatment adherence.[6]

While the literature on what is considered "acne improvement" by patients is scarce, one analysis of data from >4,000 patients suggests that a 10-15% reduction in acne lesions is relevant to patients.[14] Using data from three clinical studies of CAB gel, the objective of this post hoc analysis was to determine the percentage of participants meeting threshold reductions of inflammatory and noninflammatory acne lesions of at least 33%, 50%, and 75% following treatment with CAB gel compared to its three dyads (BPO/adapalene, clindamycin phosphate/BPO, and clindamycin phosphate/adapalene) and vehicle gel.

MATERIALS AND METHODS

Study Design and Participants

These analyses included data from a phase 2 (NCT03170388) and two phase 3 (NCT04214639; NCT04214652), double-blind, 12-week studies.[10,11] Eligible participants were aged ≥9 years with moderate-to-severe acne (a score of 3 or 4 on the Evaluator's Global Severity Score [EGSS]). 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. Participants were randomized either 1:1 (phase 2 study) or 2:1 (phase 3 studies) to receive once-daily clindamycin phosphate 1.2%/adapalene 0.15% gel/BPO 3.1% (CAB) or vehicle gel; the phase 2 study included three additional dyad gel randomization arms: BPO 3.1%/adapalene 0.15%; clindamycin phosphate 1.2% /BPO 3.1%; and clindamycin phosphate 1.2%/adapalene 0.15%. For optimal moisturization, cleaning, and protection of the skin, CeraVe® hydrating cleanser, CeraVe® moisturizing lotion (L'Oreal, New York, NY), and sunscreen were provided as needed.

Studies were carried out in accordance with the 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.

Study Assessments and Post Hoc Statistical Analyses

For each study, efficacy evaluations included least-squares mean percent change from baseline in inflammatory and noninflammatory lesion counts. Assessments were performed at screening, baseline, and weeks 2, 4, 8, and 12 (treatment end). Data from the phase 3 studies were pooled prior to analysis. When significant skewness was observed for lesion counts, a nonparametric method was used in which data were rank transformed prior to an analysis of covariance, with factors of treatment group and analysis center and covariate of baseline lesion count. Lesion counts at weeks without significant skewness were based on non-rank-transformed data. For all efficacy assessments, multiple imputation was used to impute missing values using the Markov Chain Monte Carlo method.

For this post hoc analysis, the percentage of participants achieving ≥33%, ≥50%, and ≥75% thresholds in lesion reduction were evaluated at baseline and each assessment week for the phase 2 and pooled phase 3 studies. All statistical analyses were performed using SAS® version 9.3 or later. Statistical significance was set at $P<0.05$.

RESULTS

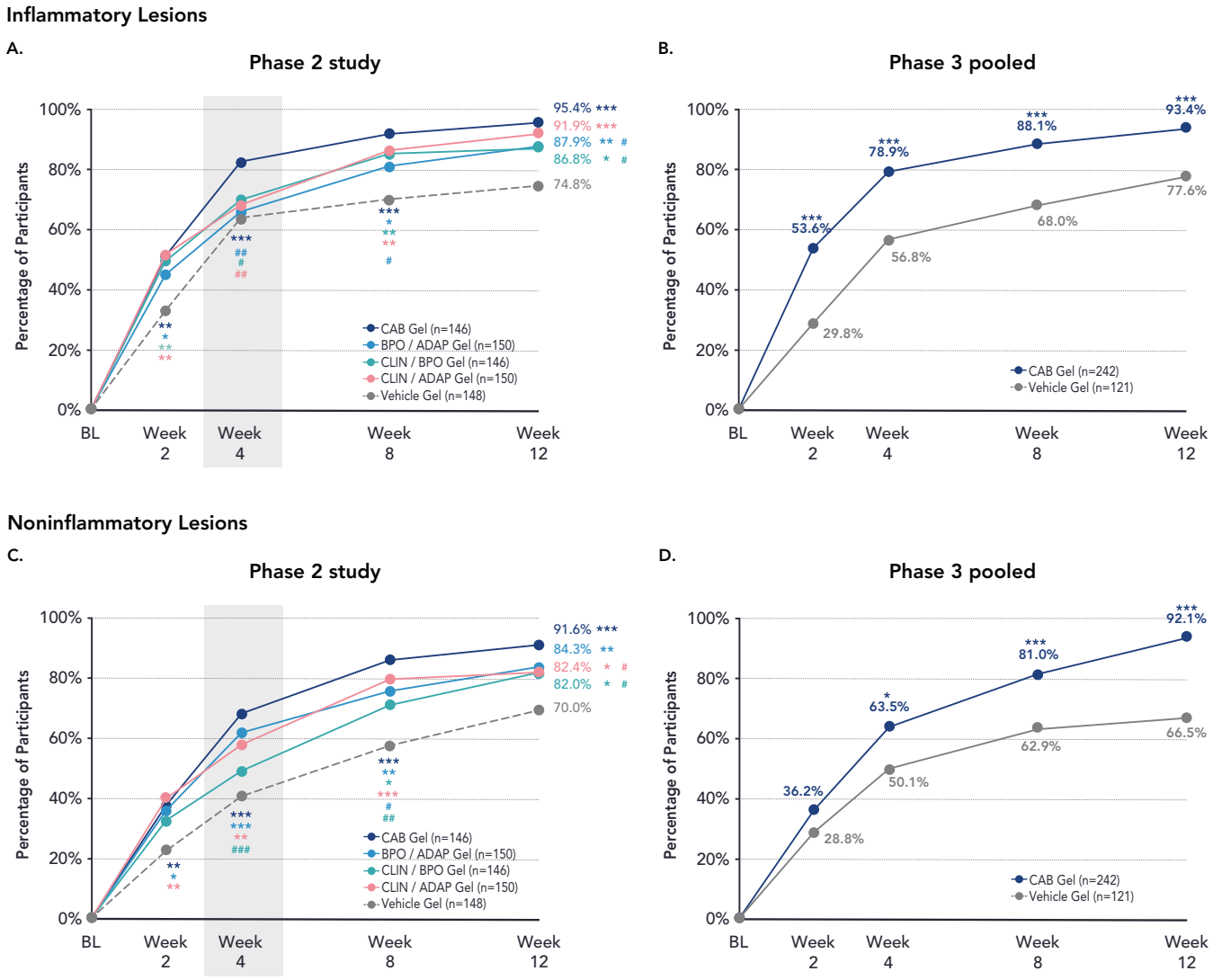
Participant Disposition and Demographics

Detailed baseline demographics and disease characteristics for the individual studies have been previously published.[10,11] A total of 741 and 363 participants were randomized to the phase 2 and the phase 3 studies (pooled), respectively. Participants across all arms/treatment groups of the studies ranged in age from 19.2 to 21.4 years and were predominantly female (phase 2: 61.2%; pooled phase 3: 58.4%), White (69.2%; 73.6%), and had moderate disease (EGSS 3, 84.2%; 91.2%). Treatment compliance was ≥91% in all studies.

Efficacy: ≥33% Reductions

Lesion count reductions of at least one-third occurred rapidly with CAB treatment. By the second post-baseline visit (week 4) in the phase 2 study, 82.7% of participants treated with CAB had at least a 33% reduction in inflammatory lesions, significantly greater than all three dyads and vehicle (dyads, range: 65.9–69.8%; vehicle: 64.1%; $P<0.05$, all; Figure 1A). Similar trends in early reductions in lesion counts were also observed for noninflammatory lesions in the phase 2 study (Figure 1C) and for

FIGURE 1. One-Third Reduction in Lesion Counts (ITT Population, Pooled).



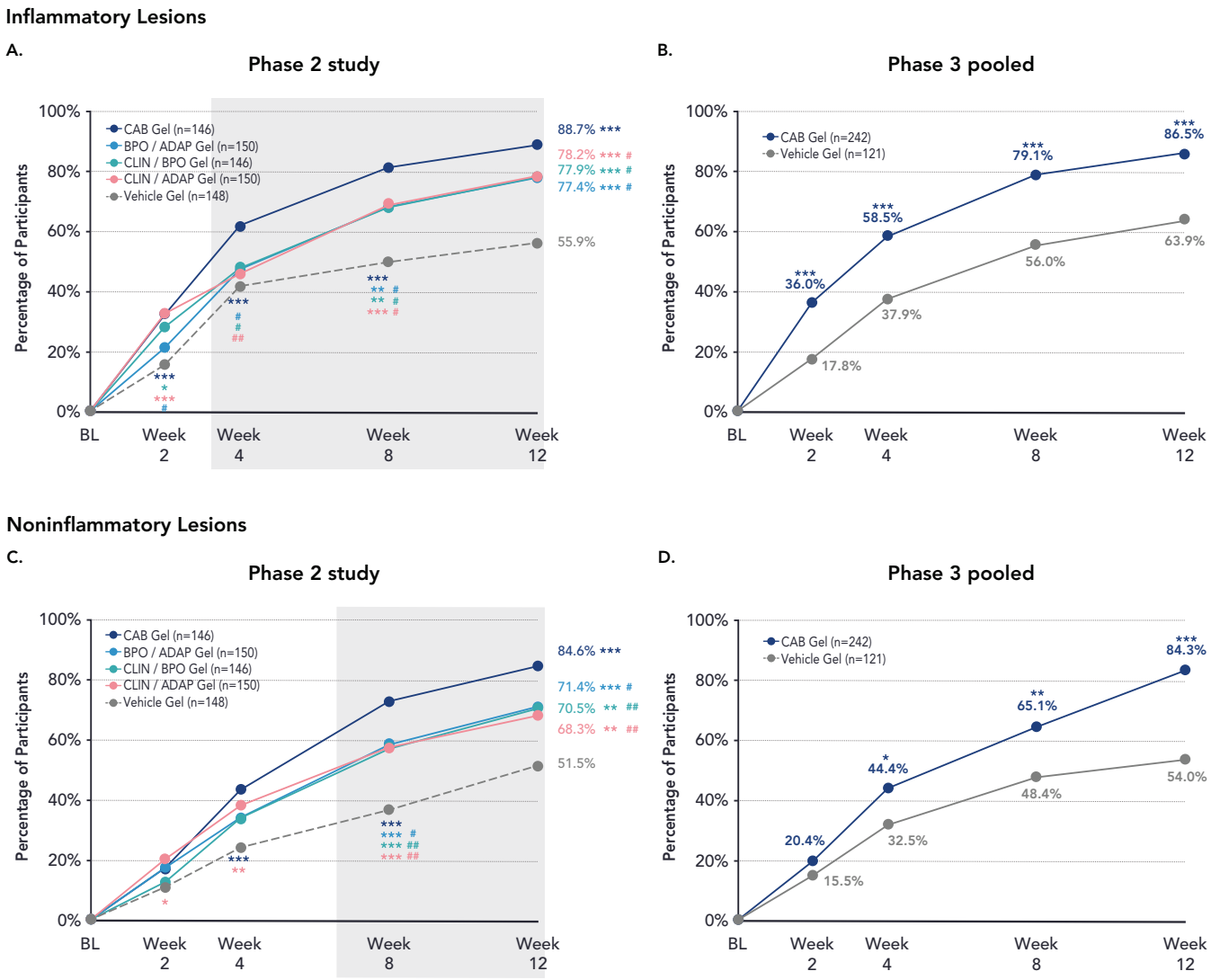
*P<0.05, **P≤0.01, ***P<0.001 active treatment vs vehicle.
#P<0.05, ##P<0.01, ###P≤0.001 dyads vs CAB.
ADAP, adapalene; BPO, benzoyl peroxide; CLIN, clindamycin phosphate; CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%.
Grey shading at week 4 represents the earliest time point at which CAB produced lesion reductions of ≥33% in a significantly greater percentage of participants compared to at least one of the dyads.

both inflammatory and noninflammatory lesions in the phase 3 studies (Figure 1B, D). By study end at week 12, CAB maintained a higher percentage of patients achieving at least 33% reduction in lesion counts versus the dyads and vehicle, with significant differences versus two of three dyads and vehicle for both inflammatory and noninflammatory lesions (Figure 1 A-D).

Efficacy: ≥50% Reductions

At least one-half reduction in lesion counts with CAB treatment occurred early and was sustained throughout the study. Significantly more participants achieved a one-half reduction in inflammatory lesions with CAB versus dyads as early as week 4, with statistical separation from vehicle occurring as early as

FIGURE 2. One-Half Reduction in Lesion Counts (ITT Population, Pooled).



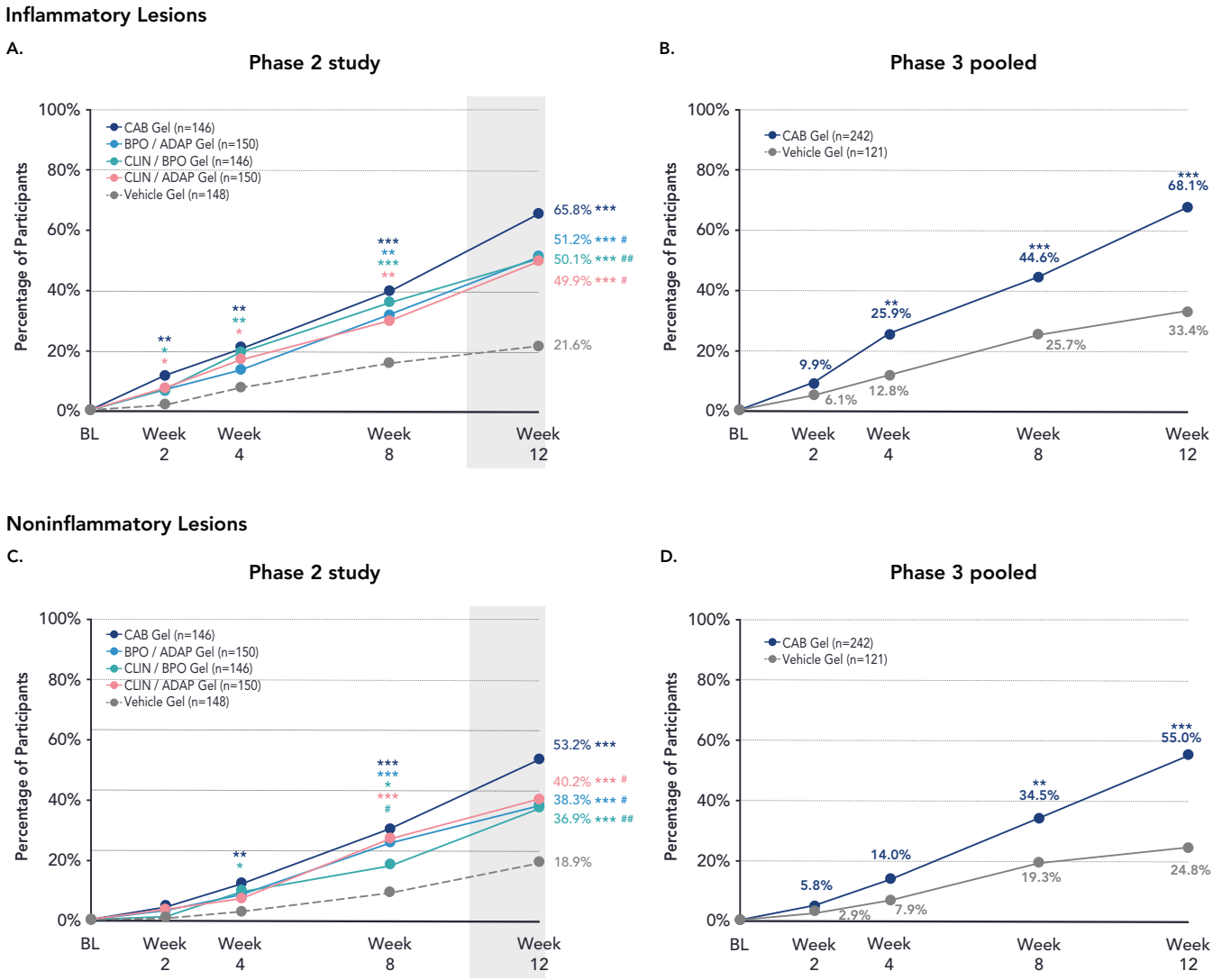
*P<0.05, **P≤0.01, ***P≤0.001 active treatment vs vehicle.
#P<0.05, ##P<0.01, ###P≤0.001 dyads vs CAB.
ADAP, adapalene; BPO, benzoyl peroxide; CLIN, clindamycin phosphate; CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%.
Grey shading represents the time points at which CAB produced ≥50% lesion reductions in a significantly greater percentage of participants compared to dyads.

week 2 (week 4, CAB: 61.4%; dyads, range: 45.8–47.4%; vehicle: 41.8%; P<0.05, all; Figure 2A). This significant reduction with CAB treatment was maintained at weeks 8 and 12 (81.0% and 88.7%, respectively) versus the dyads and vehicle (range, week 8: 49.6–68.7%; week 12: 55.9–78.2%; P<0.05, all)—a finding replicated in the pooled, phase 3 studies (Figure 2B). Similarly, ≥50% reduction in noninflammatory lesions across the studies occurred in significantly more CAB-treated participants compared to the dyads at weeks 8 and 12 and compared to vehicle at weeks 4 through 12 (Figure 2C, D; P<0.05, all).

Efficacy: ≥75% Reductions

Substantial reductions in lesion counts were achieved by the end of the study at week 12, with nearly two-thirds of participants treated with CAB (65.8%) in the phase 2 study achieving ≥75% reduction in inflammatory lesions, significantly higher than dyads and vehicle (49.9–51.2% and 21.6%; P<0.05, all; Figure 3A). Similar trends in substantial reductions (≥75%) in lesion counts were observed for noninflammatory lesions in the phase 2 study (Figure 3C) and both inflammatory and noninflammatory lesions in the phase 3 studies (Figure 3B, D).

FIGURE 3. Three-Fourths Reduction in Lesion Counts (ITT Population, Pooled).



*** $P \leq 0.001$ active treatment vs vehicle.
# $P < 0.05$, ## $P \leq 0.01$ dyads vs CAB.
ADAP, adapalene; BPO, benzoyl peroxide; CLIN, clindamycin phosphate; CAB, clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%.
Grey shading represents the earliest time point at which CAB produced ≥75% lesion reductions in a significantly greater percentage of participants compared to dyads.

DISCUSSION

Poor treatment adherence typical of acne therapies[3-6] poses a major hurdle to treatment success[3,4] and is exacerbated by the months-long lag in acne improvement discernable by patients following treatment initiation.[4] This post hoc analysis of a phase 2 and two pooled phase 3 trials showed that, as early as week 4, a significantly greater number of participants had at least a 33% reduction in acne lesion counts with the fixed-dose, triple-combination CAB gel compared to constituent dyads and vehicle gel. Lesion count reduction with CAB gel further improved with subsequent study visits, culminating in substantial and significant reductions of at least 75% after 12 weeks of CAB treatment compared to dyads and vehicle gel. This fast-acting feature of CAB—coupled with its optimized efficacy, once a day application, and good tolerability—may positively impact treatment adherence, positioning CAB gel as a desirable treatment option for patients with moderate-to-severe acne.

This post hoc analysis demonstrating rapid and significant acne lesion reductions of varying magnitudes with CAB extends findings from these studies, in which significantly greater reductions in inflammatory and noninflammatory lesions were

observed with CAB treatment versus vehicle gel as early as week 2[10] or week 4.[11] The fast therapeutic action of CAB may be attributed in part to its constituent antibiotic clindamycin phosphate, antimicrobial BPO, and retinoid adapalene, which target three of the four acne pathological mechanisms. Briefly, adapalene modulates cellular keratinization, differentiation, and proliferation, BPO has antimicrobial and mild comedolytic activity along with keratolytic effects, and clindamycin has antibiotic activity.The three drugs in this fixed-dose combination CAB gel may act together to achieve rapid effects on acne lesion counts. Additionally, adapalene and BPO within the polymeric dispersion formulation of CAB are micronized; this allows for even distribution of these active ingredients over the skin and improves penetration into the pilosebaceous unit, thereby potentially boosting treatment efficacy and enabling the rapid therapeutic action of CAB.[15,16]

Comparing these CAB data on acne lesion count reductions of a specific magnitude to those of other commercially available topical dyads containing BPO plus clindamycin or a retinoid is challenging as studies infrequently report such measures. Even so, the percentage of participants achieving thresholds in lesion count reductions was generally higher with CAB compared with commercially available dyads, including clindamycin phosphate 1.2%/BPO 5% gel, adapalene 0.1%/BPO 2.5% gel, clindamycin phosphate 1.2%/tretinoin 0.025% gel, and clindamycin 1%/tretinoin 0.025% hydrogel.[13,17-20] While comparisons cannot be made in the absence of parallel-group studies, a unique design of the phase 2 study of CAB was the inclusion of additional treatment arms with all three dyad combinations within the same vehicle formulation, allowing for a head-to-head comparison. In this study, CAB treatment produced acne lesion count reductions of specific magnitudes (≥33%, 50%, and 75%) in a significantly greater percentage of participants versus all three dyads, demonstrating the benefit of the triple combination over traditional dyad combinations.

Notably, CAB also had a relatively fast onset of action on inflammatory lesions compared to the three dyads in the phase 2 study. Lesion count reductions of both ≥33% and ≥50% occurred in a significantly greater percentage of participants with CAB gel compared to all three dyads as early as week 4 (P<0.05, all), earlier than for noninflammatory lesions (week 8: ≥33% reduction, P<0.05 for two dyads; ≥50% reduction, P<0.05, all). The relatively faster therapeutic effect of CAB on inflammatory lesions could be because BPO, adapalene, and clindamycin all have anti-inflammatory properties. This rapid reduction in inflammatory lesions is crucial: a reduction in inflammatory lesions, which are erythematous and perceivable at a greater viewing distance, is more likely to have a greater impact on patient perception of treatment efficacy[1] and in turn, may promote treatment adherence with CAB gel. Further, the impact of acne on patient quality of life is related to the patient's perception of disease severity, rather than the physician's objective clinical assessment.[21] This rapid reduction in inflammatory lesion counts may thus also have a positive impact on patient quality of life.

A limitation of this post hoc analysis is that it did not include a global measure of acne improvement, such as an assessment of treatment success via EGSS (which have been presented previously for the phase 2 and phase 3 studies[10,11]). However, as treatment success is evaluated as a binary measure (success/failure), it is not possible to evaluate multiple thresholds as was done for this analysis of lesion reductions. Further, it is important to note that the CAB studies were not powered to detect differences in the percentage of patients achieving minimum lesion count reductions between treatment groups. Therefore, P values from the post hoc analyses in this manuscript are for informative purposes only.

CONCLUSION

Therapeutic effect of the fixed-dose, triple-combination clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% (CAB) gel on moderate-to-severe acne was rapid and sustained. As early as week 4, acne lesion count reductions of at least 33% and 50% occurred in a significantly greater percentage of participants treated with CAB versus its dyads and vehicle gel. Further, substantial reductions of at least 75% were observed after 12 weeks of CAB treatment. This fast-acting and sustained efficacy of CAB—coupled with its optimized formulation, once a day application, and good tolerability—may positively impact treatment adherence.

DISCLOSURES

Julie Harper has received honoraria from Aclaris, Almirall, BioPharmX, Cassiopea, Cutanea, Dermira, Foamix, Galderma, LaRoche-Posay, Ortho Dermatologics, and Sun Pharma. Leon Kircik has served as either a consultant, speaker, advisor, or investigator for Allergan, Almirall, Epi Health, Galderma, Novartis, Ortho Dermatologics, and Sun Pharma. Michael Gold has acted as an investigator, advisor, speaker, and consultant for Ortho Dermatologics. Adelaide A. Hebert has received honoraria from Galderma, LEO Pharma, Almirall, Cassiopea, Ortho Dermatologics, Cutanea, Ferrer, Pfizer, and Demira. The UTHealth McGovern Medical School had received research grants from Cassiopea, Demira, and Ortho Dermatologics. Jeffrey L Sugarman is a consultant and speaker for Arcutis, Ortho Dermatologics, Bausch Health, Bristol Myers Squibb, Regeneron, Sanofi, Verrica, Incyte, and Pfizer. Lawrence Green has served as an investigator, consultant, or speaker for Almirall, Cassiopea, Galderma, Ortho Dermatologics, Sol Gel, Sun Pharma, and Vyne. Linda Stein Gold has served as investigator/consultant or speaker for Ortho Dermatologics, LEO Pharma, Dermavant, Incyte, Novartis, AbbVie, Pfizer, Sun Pharma, UCB, Arcutis, and Lilly. Hilary Baldwin has served as an advisor,

investigator, and on speakers' bureaus for Almirall, Cassiopea, Foamix, Galderma, Ortho Dermatologics, Sol Gel, and Sun Pharma. Eric Guenin is an employee of Ortho Dermatologics and may hold stock and/or stock options in its parent company. James Q. Del Rosso has served as a consultant, investigator, and/or speaker for Ortho Dermatologics, AbbVie, Amgen, Arcutis, Cutera, Dermavant, EPI Heath, Galderma, Incyte, JEM Health, La Roche-Posay, LEO Pharma, Lilly, L'Oreal, MC2 Therapeutics, Pfizer, Strata, Sun Pharma, and UCB.

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