A Combined Analysis of 2 Randomized Clinical Studies of Tretinoin Gel 0.05% for the Treatment of Acne

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Acne vulgaris is a widely prevalent skin disorder primarily treated with retinoids, which have been shown to cause skin irritation. This report describes the combined analysis of 2 similar phase 3 studies designed to evaluate the efficacy and safety of an aqueous gel formulation of tretinoin relative to its vehicle (both studies) and a marketed microsphere formulation of tretinoin (one study) for once-daily topical treatment of acne. Randomized participants 10 years and older with mild to moderate acne (N=1537) received tretinoin gel 0.05% (n=674), tretinoin gel microsphere 0.1% (n=376), or vehicle (n=487) once daily for 12 weeks. Tretinoin gel was more effective than vehicle in reducing inflammatory (P<.001) and noninflammatory (P<.001) lesion counts over 12 weeks. Treatment success rate (global severity score, 0 or 1) was significantly greater in the tretinoin gel 0.05% group compared with the vehicle group (P<.001). The efficacy rate of tretinoin gel 0.05% was approximately 12% less than tretinoin gel microsphere 0.1%. Adverse events (AEs) were generally mild to moderate and rarely resulted in participant discontinuation. Incidence of skin-related AEs in the tretinoin gel 0.05% group (31%) was significantly lower compared with the tretinoin gel microsphere 0.1% group (52%)(P<.001). Thus, tretinoin gel 0.05% applied once daily is a well-tolerated and effective therapy for acne vulgaris and is associated with a low incidence of skin-related AEs.

Cutis. 2009;83:146-154.

Acne vulgaris is the world's most common skin disorder, afflicting 30% to 85% of adolescents.[1] The disorder frequently appears in adults as well, but the incidence rate diminishes with age. Acne is a long-term process that begins during puberty and is caused by androgenic stimulation of sebum secretion coupled with the plugging of follicles by keratinization. Together, excess sebum production and follicular keratinization lead to the initiation of comedogenesis and the proliferation of *Propionibacterium acnes*. The microcomedone is the precursor to inflammatory (papules, pustules, nodules) and noninflammatory (open and closed comedones) lesions.[2,3] Acne is characterized by eruptions composed of comedones, cysts, papules, and pustules, predominantly on the face, back, and chest. Treatment of the disorder focuses primarily on preventing microcomedone formation and resolving existing lesions.[1]

Topical retinoids, which have been the mainstay of acne therapy for more than 30 years, interfere with the abnormal follicular desquamation associated with acne[4] and prevent obstruction of the pilosebaceous outlet.[5] Retinoids also have anti-inflammatory properties, presumably from their actions on toll-like receptors and cytokine production.[4]

Accepted for publication November 25, 2008.
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This study was sponsored by Coria Laboratories, Ltd, a division of DFB Pharmaceuticals, Inc. Dr. Webster is a consultant for Allergan, Inc; Coria Laboratories, Ltd; Cutanea Life Sciences; Galderma Laboratories, LP; OrthoNeutrogena; and Stiefel Laboratories, Inc. Drs. Cargill and Slade are employees of DFB Pharmaceuticals, Inc. Dr. Quiring is a consultant for Coria Laboratories, Ltd.
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Tretinoin (all-*trans*-retinoic acid) was the first prescription retinoid approved for the treatment of acne vulgaris. It normalizes keratinization, inhibits comedone formation, and has anti-inflammatory properties, but it also can cause skin irritation.[1] Various concentrations of tretinoin have been approved in the United States in several formulations, including creams, liquids, gels, microsponges, and a cream and a gel within a liquid polymer matrix, each designed to reduce irritation.[6]

An aqueous gel formulation containing a 0.05% concentration of tretinoin has been developed for the treatment of acne vulgaris. The gel contains excipients that are commonly found in moisturizers (soluble collagen, sodium hyaluronate) and skin hydration products (glycerin).

We report the combined results of 2 studies independently conducted to evaluate the efficacy and safety of tretinoin gel 0.05%. Both studies were investigator blinded and randomized, enrolling participants 10 years and older with mild to moderate acne. While both studies compared tretinoin gel 0.05% with vehicle, 1 of the 2 studies also compared it with tretinoin gel microsphere 0.1%. The combined analysis of these 2 studies provides a robust assessment of tretinoin gel 0.05% in the treatment of acne.

Methods

Study Design—Two 12-week, randomized, investigator-blinded, vehicle-controlled phase 3 studies evaluated the efficacy and safety of tretinoin gel 0.05% in the treatment of mild to moderate acne, with study visits at weeks 1, 2, 4, 8, and 12. All participants met the inclusion and exclusion criteria; they were assigned a unique number and dispensed randomized study medication.

Participants applied pea-sized amounts of medication in a thin layer to the face once daily prior to bedtime. Spot treatments were not permitted in either study, and only facial lesions were considered in the efficacy assessments.

Designated personnel distributed the test articles according to a randomization schedule. In the first study, participants were randomized (2:2:1) to 1 of 3 treatment groups: tretinoin gel 0.05%, tretinoin gel microsphere 0.1%, or vehicle, respectively. In the second study, participants were randomized (1:1) to receive tretinoin gel 0.05% or vehicle. Because of differences in coloration and packaging, the personnel dispensing, collecting, and otherwise accounting for the medications were not involved with the evaluation of the participants. Further, participants and the relevant study staff were instructed not to discuss or show the assigned tubes to the investigators or to any other site personnel performing clinical assessments.

At each visit, investigators performed counts of inflammatory (papules, pustules) and noninflammatory (open and closed comedones) lesions. Additionally, they provided a global severity score ranging from 0 (clear) to 5 (severe) in whole-unit increments. Adverse events (AEs), whether observed by the investigator or reported by the participant, and dosing compliance, as reported by the participants and estimated from tube weights, were recorded.

All sites were approved by an institutional review board and each participant or his/her legal representative read and signed an informed consent prior to participating in the study. Participants younger than 18 years provided their assent in addition to a parent or legal guardian providing informed consent. Both studies complied with the Declaration of Helsinki and Good Clinical Practice.

Study Population—For both trials, eligible participants were 10 years and older, of any race and either sex, and presented with mild to moderate acne. Participants were required to have 15 to 40 inflammatory facial lesions; 30 to 125 noninflammatory facial lesions; and a global severity score of 2 (mild), 3 (mildly moderate), or 4 (moderate).

Exclusion criteria included pregnancy or breastfeeding, presence of other dermatologic conditions (eg, acne conglobata, acne fulminans), specified medications without appropriate washout (eg, corticosteroids or antibiotics on the facial area), use of therapies or treatments with potential to interfere in the interpretation of the study results, and potentially toxic doses of oral vitamin A.

Statistical Analysis—The primary objective was to evaluate tretinoin gel 0.05% for superiority relative to vehicle and to evaluate its noninferiority to tretinoin gel microsphere 0.1%. Data from the 2 studies were analyzed both separately and after pooling. The intention-to-treat study population was used for analysis; intention to treat was defined as all participants who were randomized and dispensed study medication. Analyses were performed using SAS®; 2-tailed hypothesis testing was conducted at $P=.05$. No adjustments for multiple comparisons were made.

Efficacy Evaluations—The superiority of tretinoin gel 0.05% relative to vehicle was evaluated between treatment groups by comparing the change from baseline to week 12 in the absolute counts for inflammatory and noninflammatory lesions. The global severity score at week 12 was dichotomized into either successes (score, 0 or 1) or failures (all other scores) and compared between treatment groups. (The analyses of absolute lesion counts and global severity scores were considered primary.) The

secondary end points, the percentage change from baseline to week 12 in inflammatory and noninflammatory lesion counts, also were reported.

The absolute and percentage change in lesion counts were rank transformed and submitted to an analysis of variance, with factors of treatment and analysis center. Percentage change in the least squares means and corresponding *P* values were reported using the results of the rank-transformed counts. The last-observation-carried-forward method was used to extrapolate missing lesion counts and global severity scores for participants who missed a visit or prematurely discontinued from the study. Additionally, the analysis of the dichotomized global severity score using last observation carried forward at week 12 was performed with the Cochran-Mantel-Haenszel test, stratified by analysis center.

Data from the first trial were used to test the noninferiority of tretinoin gel 0.05% to tretinoin gel microsphere 0.1%. The percentage change from baseline to week 12 in lesion counts (inflammatory, noninflammatory, total) and the dichotomized global severity score at week 12 were compared between the tretinoin gel 0.05% and tretinoin gel microsphere 0.1% treatment groups. Noninferiority testing used the 1-tailed 97.5% confidence interval approach with a noninferiority margin of 10% for the difference between the percentage change in lesion counts (inflammatory, noninflammatory, total) and the dichotomized global severity score.

Safety Evaluations—Safety was evaluated by summarizing AEs and manually reviewing concomitant medications. Adverse events were assigned a system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA)–based coding; their severity, seriousness, and relationships to study medications also were recorded. The Fisher exact test was used to compare the proportion of participants in each treatment group that reported AEs.

Results

Participant Disposition—Overall, for both studies, 1537 participants were recruited from 45 sites in the United States: 674 of the participants were treated with tretinoin gel 0.05%, 376 participants were treated with tretinoin gel microsphere 0.1%, and 487 participants were exposed to vehicle.

Baseline Characteristics—The mean participant age was 18.9 years (age range, 10–65 years), and participants primarily were female and Caucasian. Overall, the 3 treatment groups had a similar distribution of participants by age, sex, race, baseline lesion counts, and global severity scores (Table 1).

Efficacy—It was apparent from the first posttreatment evaluation (week 1) that tretinoin gel 0.05% caused a greater reduction compared with vehicle in mean inflammatory (Figure 1A) and noninflammatory (Figure 1B) lesion counts. Furthermore, tretinoin gel 0.05% was effective in reducing inflammatory and noninflammatory lesion counts by more than 20% within 4 weeks, and this improvement continued with persistent treatment.

The absolute and percentage change in mean inflammatory and noninflammatory lesion counts from baseline to week 12 were significantly greater in the tretinoin gel 0.05% group than the vehicle group ($P<.001$)(Table 2). Also, participants treated with tretinoin gel 0.05% had a significantly greater success rate than the vehicle-treated participants ($P<.001$)(Table 3). Taken together, these data demonstrate that tretinoin gel 0.05% was superior to its vehicle in the treatment of facial acne.

The results from the first study for the percentage change from baseline in mean inflammatory and noninflammatory lesion counts for the tretinoin gel 0.05% and tretinoin gel microsphere 0.1% treatment groups are shown in Figure 2. Treatment success based on the dichotomized global severity score was 21% in the tretinoin gel 0.05% group and 32% in the tretinoin gel microsphere 0.1% group. The lower 97.5% confidence limit for the difference between the tretinoin gel 0.05% and tretinoin gel microsphere 0.1% treatment groups in the percentage change from baseline to week 12 in inflammatory, noninflammatory, total lesions, and dichotomized global severity scores was −13.05%, −12.51%, −12.84%, and −17.63%, respectively. Thus, the results from this one study failed to show noninferiority of tretinoin gel 0.05% to tretinoin gel microsphere 0.1%.

Safety—No participants died during the studies; 106 (15%) participants treated with tretinoin gel 0.05%, 38 (10%) treated with tretinoin gel microsphere 0.1%, and 62 (13%) treated with vehicle withdrew from the study. Adverse events accounted for withdrawal of 8 (1%) participants treated with tretinoin gel 0.05% and 3 (1%) treated with tretinoin gel microsphere 0.1%. Serious AEs were reported in 3 participants treated with tretinoin gel 0.05% and 3 participants treated with tretinoin gel microsphere 0.1%.

Most AEs were mild in severity; there were few serious AEs and none were related to treatment. Table 4 presents a general overview of the pooled safety data. Overall, more participants reported AEs and treatment-related AEs in the 2 active groups than the vehicle group. However, the percentage of participants who experienced 1 or more AEs was greater in the tretinoin gel microsphere 0.1% group than the tretinoin gel 0.05% group. In addition,

Table 1.

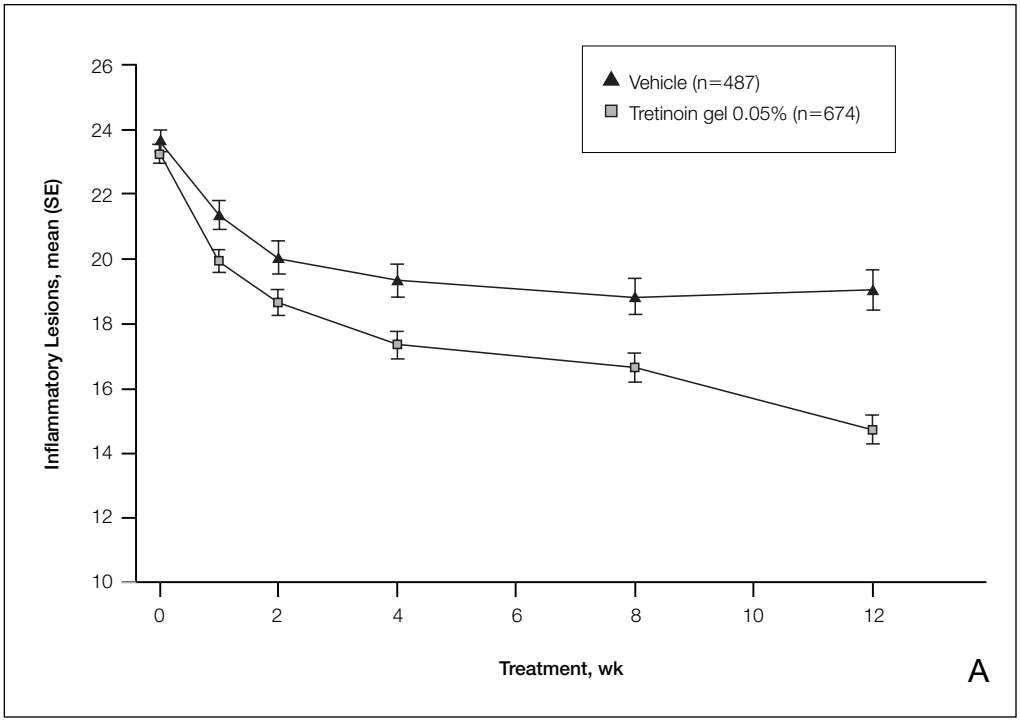
Participant Demographic and Baseline Characteristics

Variable	Treatment Group			
	Tretinoin Gel 0.05%	Tretinoin Gel Microsphere 0.1%	Vehicle	Total
Participants, n	674	376	487	1537
Mean age, y (range)	18.7 (10.1–53.0)	18.9 (10.2–45.0)	19.3 (10.0–65.0)	18.9 (10.0–65.0)
Sex, n (%)				
Male	327 (49)	167 (44)	237 (49)	731 (48)
Female	347 (51)	209 (56)	250 (51)	806 (52)
Race, n (%)				
Caucasian	508 (75)	262 (70)	369 (76)	1139 (74)
Black	94 (14)	69 (18)	77 (16)	240 (16)
Asian	20 (3)	10 (3)	12 (2)	42 (3)
Other	52 (8)	35 (9)	29 (6)	116 (8)
Lesion counts, mean (SD)				
Inflammatory	23.2 (7.6)	23.6 (7.0)	23.6 (7.3)	23.4 (7.3)
Noninflammatory	51.2 (21.9)	48.2 (19.6)	52.6 (23.0)	50.9 (21.8)
Global severity score, n (%)[a]				
2 (mild)	97 (14)	90 (24)	49 (10)	236 (15)
3 (mildly moderate)	400 (59)	203 (54)	276 (57)	879 (57)
4 (moderate)	177 (26)	82 (22)	162 (33)	421 (27)

Abbreviation: SD, standard deviation.
[a]One participant did not have data in the tretinoin gel microsphere 0.1% group.

the percentage of participants who interrupted/discontinued treatment due to AEs was greater in the tretinoin gel microsphere 0.1% group than the tretinoin gel 0.05% group. The incidence of treatment-related AEs was greater in the tretinoin gel microsphere 0.1% group compared with the tretinoin gel 0.05% group.

Because most treatment-related AEs associated with retinoids consist of skin and subcutaneous tissue disorders, skin-related AEs reported by at least 5% of participants in 1 or more of the treatment groups were tabulated (Table 5). Not surprisingly, the incidence of skin-related AEs was significantly greater in the active treatment groups than in the vehicle group ($P<.001$). However, the percentage of participants experiencing skin-related AEs in the tretinoin gel 0.05% group was significantly less than the tretinoin gel microsphere 0.1% group ($P<.001$). Specifically, participants in the tretinoin gel microsphere 0.1% group experienced significantly greater rates of exfoliative dermatitis, dry skin, erythema, scaly rash, and skin burning sensation than the tretinoin gel 0.05% group ($P<.001$ for all comparisons). The most commonly reported skin-related AE within



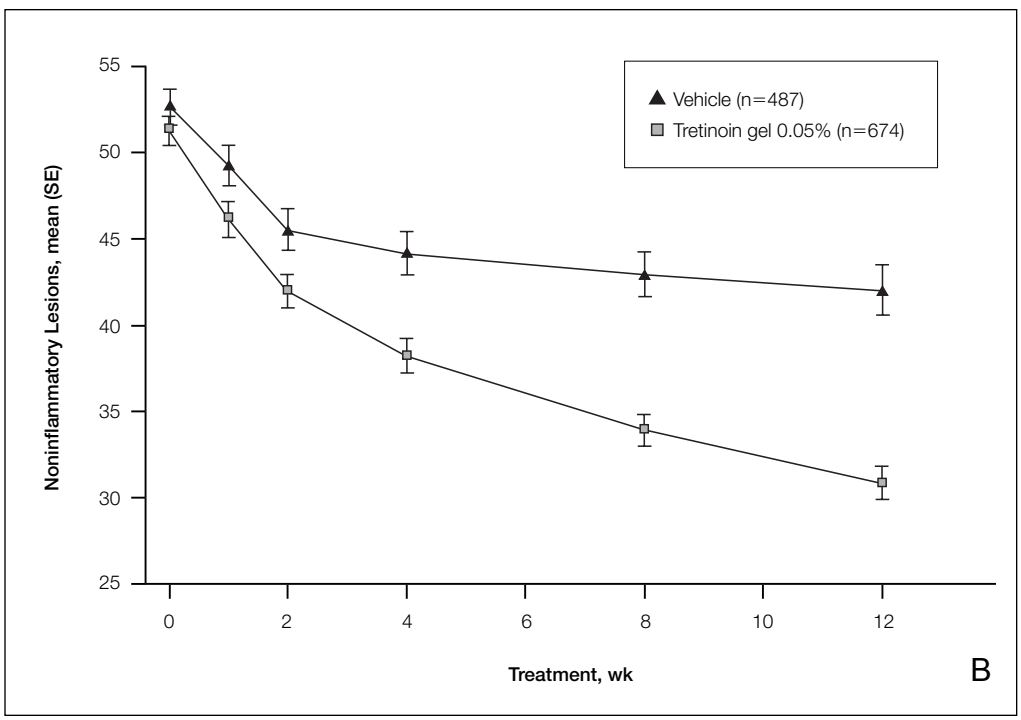


Figure 1. Mean inflammatory (A) and noninflammatory (B) lesion counts (standard error [SE]) at each evaluation for tretinoin gel 0.05% versus vehicle. $P<.001$ at week 12 for both inflammatory and noninflammatory lesions.

both active treatment groups was dry skin, with an incidence of 16% for the tretinoin gel 0.05% group and 30% for the tretinoin gel microsphere 0.1% group. With the exception of this event, all of the other commonly reported skin-related AEs in the tretinoin gel 0.05% group occurred at frequencies of 8% or less, while most of the other commonly reported AEs in the tretinoin gel microsphere 0.1% group occurred at frequencies of 15% or more.

Comment

The efficacy, safety, and improved tolerability of the tretinoin gel 0.05% formulation has been demonstrated in this combined analysis of pooled data from 2 pivotal studies. This formulation contains a 0.05% concentration of active tretinoin and excipients that are commonly found in moisturizers (soluble collagen, sodium hyaluronate) and skin hydration products (glycerin).

Table 2.

Summary of Efficacy Outcomes for Tretinoin Gel 0.05% Versus Vehicle: Lesion Counts

Treatment Group	Mean Lesion Count[a] (SD) Baseline	Week 12	Absolute Change From Baseline[b]	Percentage Change From Baseline	*P* Value
Inflammatory Lesions					
Tretinoin gel 0.05% (n=674)	23.2 (7.6)	14.7 (11.4)	7.6	36	<.001
Vehicle (n=487)	23.6 (7.3)	19.0 (14.0)	4.2	19	
Noninflammatory Lesions					
Tretinoin gel 0.05% (n=674)	51.2 (21.9)	30.8 (24.7)	19.6	40	<.001
Vehicle (n=487)	52.6 (23.0)	42.0 (31.7)	10.1	20	

Abbreviations: SD, standard deviation; ANOVA, analysis of variance.

[a]Lesion counts presented as raw values; *P* values derived from ANOVA on rank-transformed data, with factors of treatment and analysis center.

[b]Least squares means from ANOVA, with factors of treatment and analysis center.

Tretinoin gel 0.05% was found to be effective and statistically superior to its vehicle in the treatment of facial acne. The reduction in inflammatory and noninflammatory lesion counts in the tretinoin gel 0.05% group was apparent from the first post-treatment evaluation at week 1. By week 4, lesion counts in the tretinoin gel 0.05% group were reduced by more than 20% and continued to decline with persistent treatment. The efficacy of tretinoin gel 0.05% in reducing lesion counts was only modestly lower (≈12%) than tretinoin gel microsphere 0.1%. Although the clinical study failed to show noninferiority of tretinoin gel 0.05% to tretinoin gel microsphere 0.1%, the difference between treatment groups in inflammatory and noninflammatory lesion counts exceeded the noninferiority threshold by only a small margin (approximately 3% for each lesion type). One obvious reason for the greater efficacy of the microsphere product is that it contains twice the concentration of tretinoin, but it also is known that the formulation of tretinoin may play an important part in both the efficacy and safety of the product.[7] Relative to its vehicle, tretinoin gel 0.05% demonstrated superiority at week 12 in the reduction of lesion counts (absolute change from baseline in inflammatory and noninflammatory lesions) as well as in the analysis of the dichotomized global severity scores.

A major drawback to retinoid therapy is its potential to cause irritation of the treatment area, a side effect that is generally dose dependent.[5] Retinoid therapy has been associated with irritation, exfoliation, dryness, and scaling, especially during the first 3 to 4 weeks of treatment. The analyses of the combined studies described herein indicate that the incidence of skin-related AEs after treatment with tretinoin gel 0.05% is considerably lower than tretinoin gel microsphere 0.1%. Furthermore, the incidence rates observed with tretinoin gel 0.05% in this combined analysis are 50% to 75% lower than those rates reported in the literature for other marketed tretinoin formulations, all containing the active ingredient at half the concentration of tretinoin gel (ie, 0.025%).[8,9]

Retinoids attack comedone formation and are central to acne therapy. In fact, many experts believe that, if properly used, topical retinoids are effective as long-term monotherapy.[10] As a group, topical retinoids induce irritation, which becomes a limiting factor in compliance for many patients.[5] For long-term diseases such as acne that are not life threatening and are widely prevalent among younger populations, a prescribing clinician often will choose therapies based, at least in part, on tolerability in an attempt to ensure greater compliance. Thus, treatment with topical acne medications that have proven efficacy and are associated with fewer skin-related side effects should result in greater patient compliance and, likely, greater overall effectiveness. Furthermore, Piacquadio and Kligman[7] have noted that the safety, efficacy, and compliance associated with retinoids are formulation dependent.

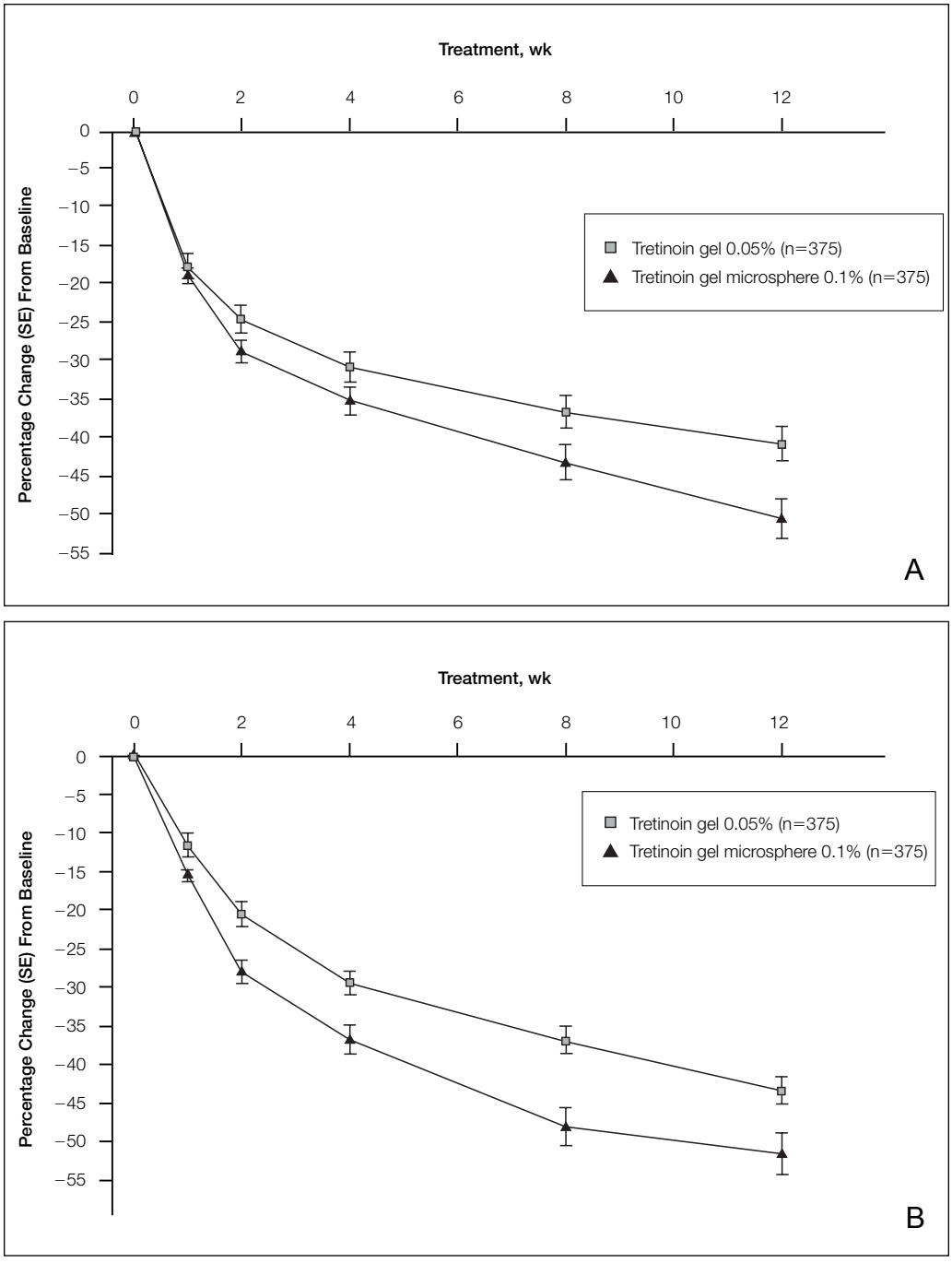


Figure 2. Percentage change from baseline (standard error [SE]) in inflammatory (A) and noninflammatory (B) lesion counts at each evaluation for tretinoin gel 0.05% versus tretinoin gel microsphere 0.1%. One participant was excluded from the tretinoin gel microsphere 0.1% group.

The aqueous gel formulation of tretinoin described here is an effective therapy for acne that exhibits a clinically relevant, local tolerance profile resulting in low levels of skin irritation.

Conclusion

The results of the combined analysis of pooled data from these studies demonstrate that tretinoin gel 0.05%, when administered once daily, is an effective, safe, well-tolerated therapy for acne, exhibiting a favorable irritation profile.

Acknowledgments—The authors wish to thank Illuminated Research LLC for medical writing contributions and the following investigators: Lawrence L. Anderson, MD, Tyler, Texas; Jerry Bagel, MD, East Windsor, New Jersey; Alicia Barba, MD, Miami, Florida; Susan Barker, MD, Temple Terrace, Florida; Morrisa Baskin, MD, Wenatchee, Washington; Karl Beutner, MD, Vallejo, California; Debra Breneman, MD, Cincinnati, Ohio; Suzanne Bruce, MD, Houston, Texas; Coyle Connolly, DO, Linwood, New Jersey; Ponciano Cruz Jr, MD, Irving, Texas;

Table 3.

Summary of Efficacy Outcome for Tretinoin Gel 0.05% Versus Vehicle: Success/Failure[a]

Treatment Group	Success, n (%)	Failure, n (%)	*P* Value[b]
Tretinoin gel 0.05% (n=674)	117 (17)	557 (83)	<.001
Vehicle (n=487)	49 (10)	438 (90)	

Abbreviation: CMH, Cochran-Mantel-Haenszel.
[a]Global severity score was based on a scale of 0 (clear) to 5 (severe). A score of 0 or 1 at week 12 was rated as a success; all other scores were rated as a failure.
[b]*P* value derived from CMH test stratified by analysis center.

Table 4.

Combined Analysis of Adverse Event (AE) Characteristics

	Treatment Group		
Parameter	Tretinoin Gel 0.05% (n=674)	Tretinoin Gel Microsphere 0.1% (n=376)	Vehicle (n=487)
No. of AEs reported	684	642	230
Participants reporting ≥1 AEs, n (%)	336 (50)	245 (65)	141 (29)
Participants with a serious AE, n (%)	3 (<1)	3 (<1)	1 (<1)
Participants who interrupted/ discontinued treatment due to AEs, n (%)	47 (7)	45 (12)	2 (<1)
Severity of AE, n (%)[a]			
Mild	495 (72)	466 (73)	150 (65)
Moderate	165 (24)	163 (25)	77 (33)
Severe	24 (4)	13 (2)	3 (1)
Treatment-related AE, n (%)[b]	357 (52)	428 (67)	30 (13)

[a]Percentage based on number of AEs.
[b]Relationship of AE to study drug was determined by the investigator and includes events possibly, probably, and definitely related to study drug.

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Table 5.

Combined Incidence of Skin-Related Adverse Events[a]

Adverse Event	Treatment Group: Tretinoin Gel 0.05% (n=674)	Tretinoin Gel Microsphere 0.1% (n=376)	Vehicle (n=487)	*P* Value[b]
Skin related, n (%)	208 (31)	196 (52)	25 (5)	<.001
Exfoliative dermatitis	37 (5)	80 (21)	4 (1)	<.001
Dry skin	109 (16)	112 (30)	8 (2)	<.001
Erythema	47 (7)	67 (18)	1 (<1)	<.001
Scaly rash	14 (2)	29 (8)	1 (<1)	<.001
Skin burning sensation	53 (8)	57 (15)	82 (17)	<.001

[a]Common adverse events experienced by ≥5% of participants in at least 1 treatment group.
[b]Overall *P* value derived from Fisher exact test.

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