Safety of a Novel Gel Formulation of Clindamycin Phosphate 1.2%–Tretinoin 0.025%: Results From a 52-Week Open-Label Study

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Acne affects as many as 50 million individuals in the United States. Topical therapy combining a retinoid and an antibiotic is recommended as a first-line therapeutic option for mild to moderately severe acne. Although treatment for extended durations may be required, little long-term safety data on these combination therapies are available.

This report summarizes the long-term safety and tolerability of a novel combination product for the treatment of acne vulgaris in participants 12 years and older. The combination treatment is a gel formulation containing a crystalline suspension of clindamycin phosphate 1.2%–tretinoin 0.025% (CLIN/RA). Two cohorts participated in a long-term (up to 52 weeks), multicenter, open-label, safety evaluation of CLIN/RA. Treatment duration was 6 months for the first cohort (N=442) and 12 months for the second cohort (N=213).

Overall, the CLIN/RA gel was well-tolerated; 92%, 91%, and 94% of participants reported no itching, burning, or stinging, respectively. The most frequent adverse events were acne (29/442; 7% [usually a flare]), sunburn (12/442; 3%), hypersensitivity (7/442; 2%), contact dermatitis (5/442; 1%), and application-site desquamation (3/442; 1%). These results confirm the safety of CLIN/RA gel for mild to moderately severe acne. The CLIN/RA gel fixed-dose combination provided minimal adverse events and a favorable safety profile for 2 agents with established efficacy for the treatment of acne vulgaris.

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Acne is a common and long-lasting disease affecting as many as 50 million individuals in the United States.[1] In recent years, multiple studies have demonstrated that topical therapies combining a retinoid with an antibiotic are more effective in treating mild to moderately severe acne than monotherapy with either a topical retinoid or topical antibiotic, with reported *P* values ranging from less than .001 to less than .05.[2-5] As a result, the combination of a topical retinoid with a topical antibiotic has become a preferred therapeutic option for patients with mild to moderately severe acne.[6,7]

Many patients with acne need long-term therapy, which may involve months of treatment with a

combination therapy or other medications to control their symptoms, followed by years of maintenance therapy to prevent recurrence. Thus, patients need acne therapies that are effective, safe, and tolerable over the long-term, and understanding the long-term impact of these therapies is important for effective and safe acne management. Unfortunately, the typical duration of trials of topical acne combination therapies is 12 weeks. One long-term study of a topical combination acne therapy has been published. It evaluated adapalene and benzoyl peroxide over 52 weeks and supported the efficacy and safety of a once-daily fixed-dose formulation of these agents in long-term acne management.[8] To our knowledge, there have been no published studies of combination acne therapy using a topical retinoid and a topical antibiotic for more than 14 weeks.[3,5,8-12] Thus, additional long-term studies of topical combination therapies are needed to elucidate the efficacy and safety of extended treatments with retinoids and antibiotics, both in combination and as monotherapy.

The only topical acne medication combining an antibiotic with a retinoid that has been approved by the US Food and Drug Administration for treatment of acne vulgaris in patients 12 years and older is a novel gel formulation containing a crystalline suspension of clindamycin phosphate 1.2%–tretinoin 0.025% (CLIN/RA). The efficacy, safety, and tolerability of this CLIN/RA formulation have been demonstrated in short-term (12-week) trials.[2,3,5] Given the need for long-term data, the current open-label study evaluated the safety of the CLIN/RA gel formulation for 52 weeks.

Methods

Study Design—A 52-week, multicenter, open-label, safety study involving 13 independent centers was conducted. Participants were analyzed in 2 cohorts. Cohort 1 comprised the entire study population that was followed for 0 to 6 months. Cohort 2 comprised 219 participants that completed 6 months of the study and chose to continue participating for up to 1 year. Acne severity and response to treatment were evaluated by the evaluator's global severity score (EGSS) rating system (Table 1).[13] Safety was evaluated by the cutaneous safety evaluation rating scale (Table 2), which scored erythema and scaling, and tolerability was measured by the tolerability evaluation rating scale (Table 3), which scored itching, burning, and stinging.[13]

The study conformed to the principles of the Declaration of Helsinki. All participants or their legal guardians gave informed consent. The protocol was reviewed and approved by the institutional review boards of the study centers involved.

Participant Selection—Study participants were required to be 12 years and older, with mild, moderate, or severe acne as determined by EGSS score.[13] Use of other topical retinoids, antibiotics, anti-inflammatory agents, or corticosteroids on the facial area was prohibited, as well as use of other medications that the investigators and sponsor deemed

Table 1.

Evaluator's Global Severity Score Rating System[13,a]

Score	Grade	Description
0	Clear	Normal clear skin with no evidence of acne vulgaris
1	Almost clear	Rare noninflammatory lesions, with rare noninflamed papules (papules must be resolving and may be hyperpigmented but not pink-red)
2	Mild	Some noninflammatory lesions, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	Noninflammatory lesions predominate, with multiple inflammatory lesions evident; several to many comedones and papules/pustules; there may or may not be 1 small nodulocystic lesion
4	Severe	Inflammatory lesions are more apparent; many comedones and papules/pustules; there may or may not be a few nodulocystic lesions
5	Very severe	Highly inflammatory lesions predominate; variable number of comedones; many papules/pustules; many nodulocystic lesions

[a]The evaluator's global severity score is a static assessment that is made without reference to the baseline score.

Table 2.

Cutaneous Safety Evaluation Rating Scale[13]

Score	Grade	Description
Erythema		
0	None	No evidence of erythema
1	Mild	Slight pink
2	Moderate	Definite redness
3	Severe	Marked erythema; bright red to dusky dark red
Scaling		
0	None	No scaling
1	Mild	Barely perceptible fine scales present to limited areas of the face
2	Moderate	Fine scales generalized to all areas of the face
3	Severe	Scaling and peeling of skin over all areas of the face

Table 3.

Tolerability Evaluation Rating Scale[13]

Score	Grade	Description
Itching		
0	None	No itching
1	Mild	Slight itching that is not bothersome
2	Moderate	Definite itching that is somewhat bothersome
3	Severe	Intense itching that may interrupt daily activities and/or sleep
Burning		
0	None	No burning
1	Mild	Slight burning sensation that is not bothersome
2	Moderate	Definite warm burning sensation that is somewhat bothersome
3	Severe	Hot burning sensation that causes definite discomfort and may interrupt daily activities and/or sleep
Stinging		
0	None	No stinging
1	Mild	Slight stinging sensation that is not bothersome
2	Moderate	Definite stinging sensation that is somewhat bothersome
3	Severe	Stinging sensation that causes definite discomfort and may interrupt daily activities and/or sleep

Table 4.

Participant Demographics by Cohort[13]

	Cohort 1 (Participated for 0–6 mo) (N=442)	Cohort 2 (Cohort 1 Participants Continuing Up to 12 mo) (N=213)
Age, y		
Mean (SD)	20.4 (8.41)	20.16 (8.27)
Range	12–52	12–51
Gender, n (%)		
Male	179 (40)	85 (40)
Female	263 (60)	128 (60)
Race/ethnicity, n (%)		
White	325 (74)	147 (69)
Black	33 (7)	11 (5)
Asian/Pacific Islander	10 (2)	8 (4)
Hispanic/Latino	62 (14)	38 (18)
American/Alaskan Native	10 (2)	8 (4)
Other (Indian, Native American, and Middle Eastern)	2 (0)	1 (0)
Baseline severity (EGSS)		
Mild	217 (49)	106 (50)
Moderate	166 (38)	79 (37)
Severe	59 (13)	28 (13)

Abbreviation: EGSS, evaluator's global severity score.

likely to interfere with the interpretation of the results. Topical benzoyl peroxide, oral retinoids, and oral antibiotics were permitted.[13]

Treatment—All participants were instructed to apply the CLIN/RA gel once daily at bedtime after cleansing their face.[13] Participants attended a baseline visit and monthly follow-up visits for the duration of the trial. At each visit, the investigator assessed EGSS, safety, tolerability, adverse events, concomitant medication use, and adherence.[13] To reflect routine clinical practice, participants could stop or restart therapy at the investigator's discretion.

Statistical Analysis—Primary safety analyses were based on the data from all participants who received at least 1 dose of study treatment, which comprised the intention-to-treat population. Safety was assessed by tabulations of adverse events, cutaneous safety evaluations, and tolerability evaluations. Adverse events are presented as the number of occurrences and as the percentages of the total participant population. Cutaneous safety evaluation scores (erythema, scaling) are presented as the percentages of participants with mild, moderate, or severe erythema or scaling as defined by the cutaneous safety evaluation rating scale (Table 2). Tolerability is presented as the percentages of participants reporting none, mild, moderate, or severe itching, burning, or stinging, as defined by the tolerability evaluation rating scale (Table 3).

Results

Demographics and Participant Disposition—A total of 442 participants enrolled in the trial. Table 4 summarizes the participant demographics. The

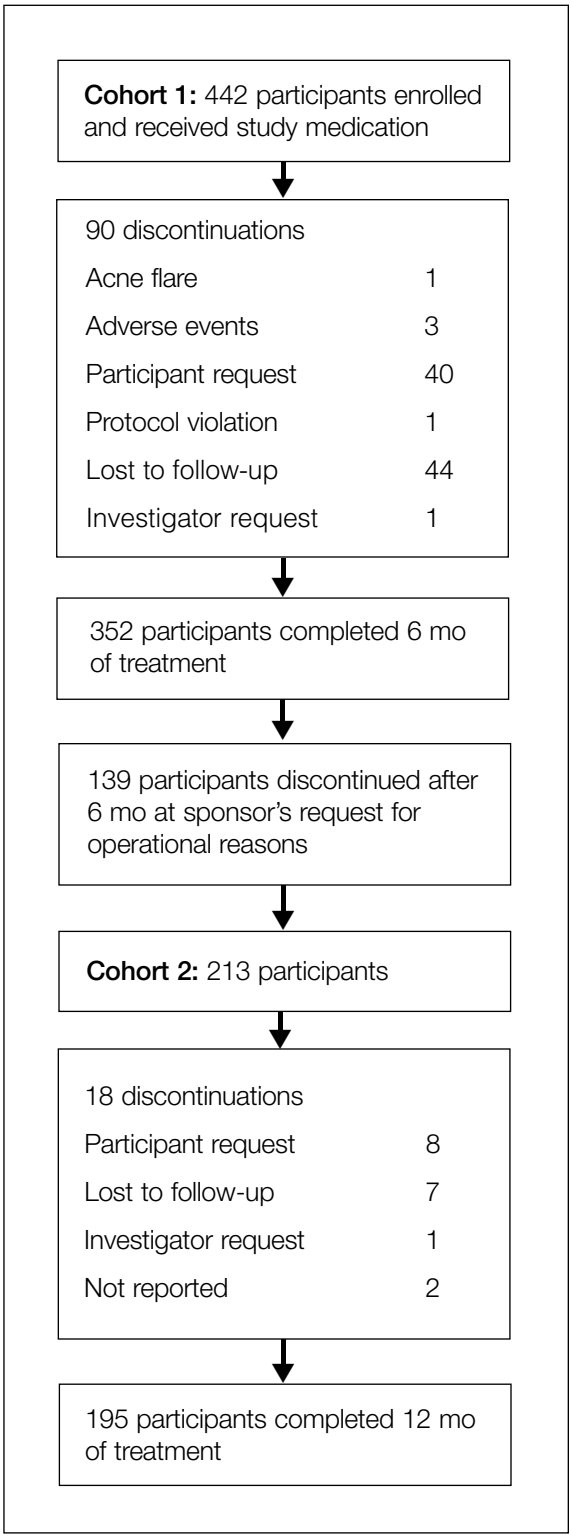


Figure 1. Summary of participant disposition.

participants comprised 2 cohorts for data analysis purposes. Cohort 1 (N=442) consisted of the entire enrolled study population and was included in the 0- to 6-month analysis. As previously stated, the first 219 participants who completed 6 months of the study and chose to continue participating were prospectively selected to comprise a cohort that was to be followed for up to 1 year. Ninety participants withdrew during the 0- to 6-month analysis period, leaving 352 participants for the second cohort. After 6 months, another 139 participants were discontinued at the sponsor's request to condense the number of sites participating in the 6- to 12-month phase, leaving 213 participants for the second cohort. Thus, the participants who remained after these discontinuations comprised cohort 2 (N=213) and were included in the 0- to 12-month analysis. A total of 18 participants withdrew from the second cohort during the second 6 months of follow-up. Age, gender, and race/ethnicity were similar between both cohorts. Discontinuations in both cohorts were primarily due to withdrawal of consent or lost to follow-up. Figure 1 summarizes the participant disposition.

Adverse Events—Adverse event rates were monitored for each quarter year, with adverse event data provided by 442 participants in the first quarter, 386 in the second quarter, 214 in the third quarter, and 203 participants in the fourth quarter. One participant from cohort 1 discontinued at 3 months but was followed for adverse events throughout the year and is included in the adverse event data for the entire year. A total of 32 of 442 participants (7.2%) reported 32 adverse events at any point during the treatment period that were considered to be at least possibly treatment related. The treatment-related adverse events primarily were application-site conditions that improved over time. Most treatment-related adverse events (23/32; 72%) occurred during the first quarter. The most frequent dermatologic adverse event in both cohorts was acne, which was reported by 7% (29/442) of participants and usually reported in association with an acne flare. Other common dermatologic adverse events reported at any point during the study in both cohorts were sunburn (12/442; 3%), hypersensitivity (7/442; 2%) contact dermatitis (5/442; 1%), and application-site desquamation (3/442; 1%). Figure 2 shows the rates of these adverse events by quarter. Adverse events caused 3 (<1%) discontinuations, of which 2 were considered to be at least possibly treatment related. All discontinuations due to adverse events occurred in cohort 1. A total of 8 serious adverse events occurred in 6 participants. No serious adverse event was considered to be treatment related. There were no deaths.

Cutaneous Safety—Erythema and scaling of mild severity were present in 24.2% and 13.6% of participants, respectively, at baseline. The incidence of at least mild severity increased for the first 1 to 2 months after the initiation of therapy, peaking at 25.2% and 22.6% for erythema and scaling,

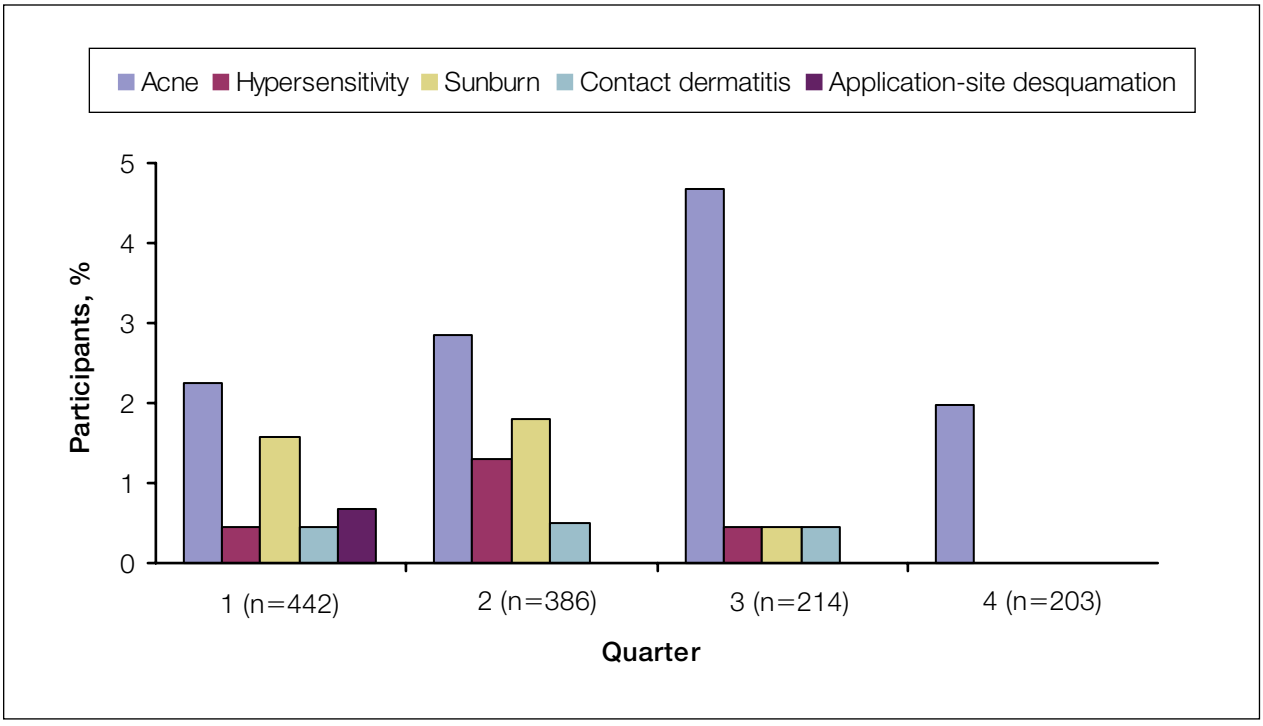


Figure 2. Summary of selected dermatologic adverse events over 12 months of treatment with clindamycin phosphate 1.2%–tretinoin 0.025% gel.

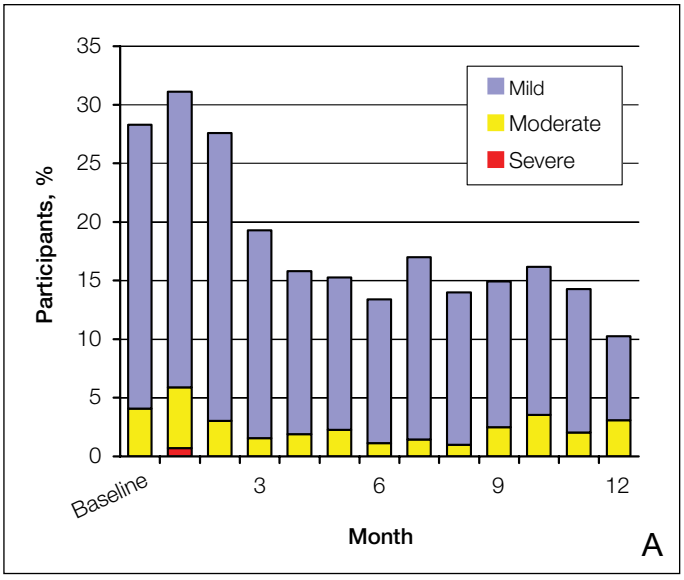
respectively, at 1 month and then declining over time. Over the last 6 months of the trial, the rates of mild severity ranged from 7.2% to 15.5% for erythema and 6.3% to 15.4% for scaling. The rates of moderate or severe erythema or scaling followed a similar pattern at a much lower incidence. Erythema and scaling rates peaked at 1 month at 5.2% and 4.0%, respectively, for moderate symptoms, and 0.7% and 0.5%, respectively, for severe symptoms. Figure 3 shows the rates of erythema and scaling by month and severity.

Tolerability—The CLIN/RA compound was well-tolerated by participants: the largest reported incidence at any study evaluation was 8.4% for itching (baseline), 8.5% for burning (month 1), and 5.7% for stinging (month 1). The percentages of participants with moderate or severe tolerability scores peaked at 1.1%, 2.1%, and 0.7% for itching, burning, and stinging, respectively. The peak occurred within the first 2 months of therapy, and then the incidence considerably declined. Figure 4 shows the itching, burning, and stinging rates by month and severity.

Comment

Combination therapy using a topical retinoid and topical antibiotic is a cornerstone of current acne treatment practices that is widely used in the management of mild to moderate acne. Effective acne therapy may require long-term combination therapy with a duration of months or years. However, long-term data on the safety of these therapies are lacking; the duration of prior published studies has not extended beyond 14 weeks.

Three recent publications have reported on a total of five 12-week studies evaluating combination acne therapies.[2,3,5] In two 12-week studies of the current CLIN/RA gel formulation involving more than 4500 participants reported by Schlessinger and colleagues,[2] 27% of participants reported adverse events, but the rates of most adverse events were similar for the CLIN/RA gel (both components as monotherapy) and vehicle. The incidence of mild or worse cutaneous safety or tolerability scores in the 12-week study was similar to the incidence seen during the first 12 weeks of the current 52-week study. Note that in the long-term study, tolerability improved and the adverse event rate declined and stabilized at a relatively low level after the first 3 months of treatment. In 2006, Leyden and colleagues[3] reported on two 12-week trials of a different combination medication, clindamycin 1% with tretinoin 0.025% in a hydrogel vehicle in 2219 participants with acne vulgaris. Treatment-related adverse events affected 19% of participants, primarily those participants receiving tretinoin, and 2% withdrew from the trial because of adverse events,[3] which is considerably higher than the 7% and less than 1% incidences of treatment-related adverse events and discontinuations due to



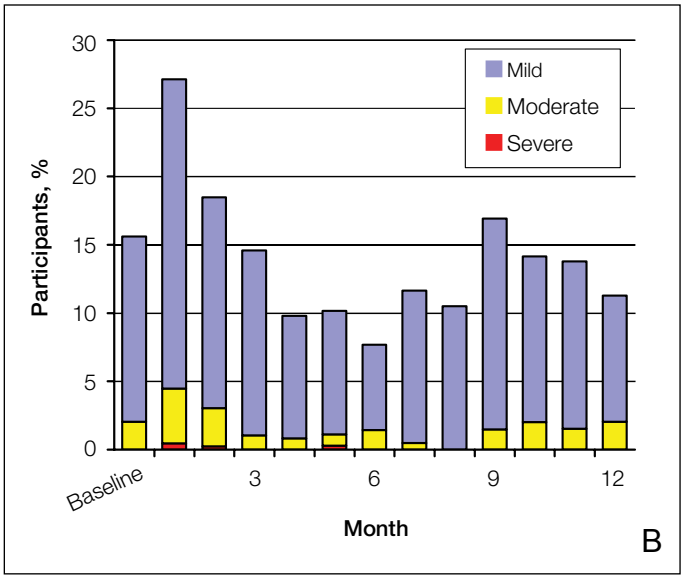
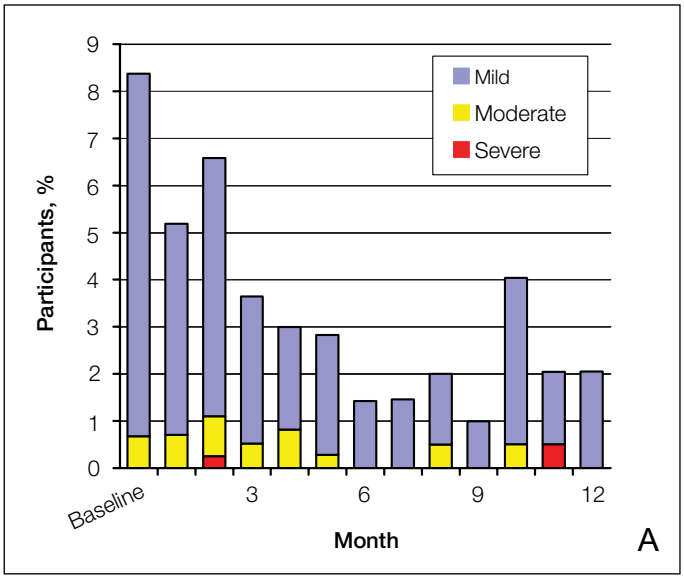


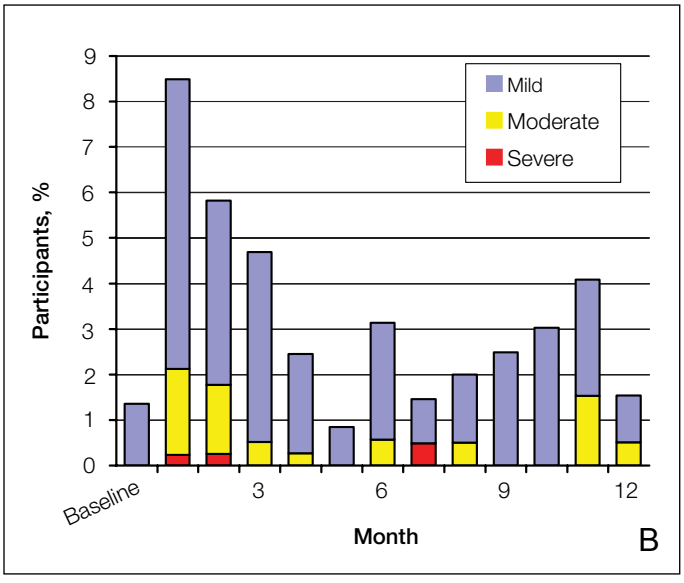
Figure 3. Cutaneous safety scores over 12 months of treatment with clindamycin phosphate 1.2%–tretinoin 0.025% gel, including percentage of participants with mild, moderate, or severe erythema (A) and scaling (B) by month. Cohort 1 consisted of 442 participants followed for 0 to 6 months. Cohort 2 consisted of 213 participants from cohort 1 who continued to participate for up to 1 year.

adverse events, respectively, seen in the current long-term study. Wolf and colleagues[5] reported on an evaluation of the combination of clindamycin and adapalene in 2003. Dermatologic adverse-event rates were similar to the current trial; 10.4% of participants in the combination treatment group consisting of 125 participants reported adverse events, and 0.8% discontinued due to adverse events.[5,9] Overall, the adverse-event rate and tolerability observed in the current trial are comparable with or better than those observed in other trials of topical acne therapy combining a retinoid with an antibiotic.

The novel gel formulation of CLIN/RA was safe and well-tolerated for 12 months. There were no unexpected adverse events. The incidence of cutaneous adverse events (erythema, scaling, itching, burning, stinging) was similar to phase 3 studies of other topical acne therapies combining a retinoid with an antibiotic[3,5,9-12] and is consistent with the adverse-event rates found in the 12-week CLIN/RA trials.[2,3,5] Itching, burning, and stinging were not reported by more than 9% of participants at any point in the study, and no more than 2.1% of participants reported that these symptoms were bothersome.

The relatively low levels of cutaneous irritation seen with CLIN/RA probably result from aspects of the gel formulation. First, the water-based gel used in the CLIN/RA formulation may be less irritating than an alcohol-based gel. Second, rather than using only solubilized tretinoin, the CLIN/RA formulation uses a stable combination of solubilized and crystalline tretinoin with a controlled particle size distribution:





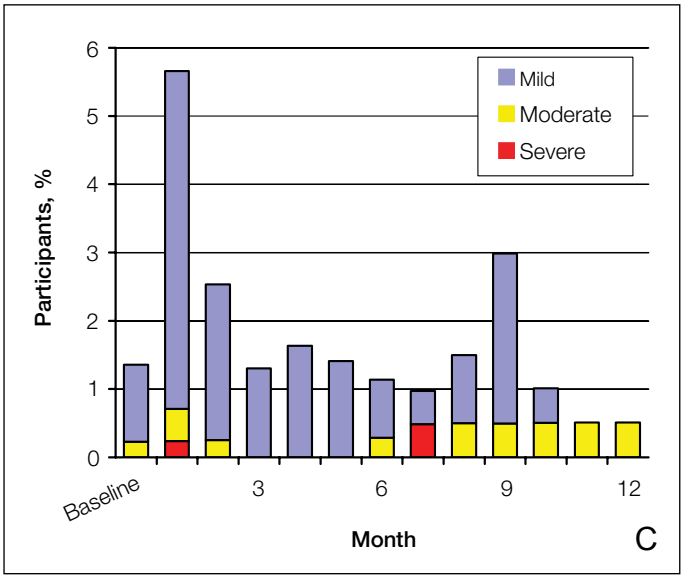


Figure 4. Tolerability scores by percentage of participants reporting mild, moderate, or severe itching (A), burning (B), or stinging (C) from treatment with clindamycin phosphate 1.2%–tretinoin 0.025% gel. Cohort 1 consisted of 442 participants followed for 0 to 6 months. Cohort 2 consisted of 213 participants from cohort 1 who continued to participate for up to 1 year.

the diameter is less than 20 μm for at least 90% of the particles and less than 10 μm for at least 50% of the particles. These characteristics are believed to minimize skin irritation by promoting rapid and selective localization of the tretinoin particles to the follicles, followed by slow release of the tretinoin.[6,14,15] In a single-center, phase 1, tolerability study, CLIN/RA gel was significantly less irritating than tretinoin gel, with irritancy scores of 14.12 and 23.25, respectively ($P<.001$ for each of the 3 paired comparisons), which suggests that the CLIN/RA gel formulation may provide a unique tretinoin delivery method that does not provoke the degree of irritation associated with standard solubilized formulations of tretinoin.[14]

Poor adherence is one of the major causes of acne treatment failure. Several medication-related factors can affect adherence, including tolerability, efficacy, and dosing simplicity. This study demonstrates that CLIN/RA gel provides excellent long-term tolerability, and earlier studies have shown that it is efficacious. In addition, as a combination therapy, CLIN/RA gel is simpler to use than 2 medications separately. Taken together, these factors suggest that CLIN/RA gel may promote improved adherence.

The current study is the first long-term (52-week) safety study of the treatment of acne with a topical retinoid used in combination with a topical antibiotic. The study demonstrates that the safety and tolerability found for this novel CLIN/RA gel in short-term (12-week) trials is maintained or improved for at least 1 year, with most adverse events occurring during the first 3 months of treatment. The CLIN/RA gel has a favorable long-term safety and tolerability profile for the treatment of mild to moderately severe acne, which may lead to improved adherence and therefore improved outcomes.

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