Tretinoin Cream 0.02% for the Treatment of Photodamaged Facial Skin: A Review of 2 Double-Blind Clinical Studies

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In extensive clinical studies and practical use since its US Food and Drug Administration approval in 1995, tretinoin emollient cream 0.05% has been shown to be safe and effective in the treatment of fine facial wrinkles, mottled hyperpigmentation, and skin roughness. To provide additional prescribing flexibility for various patient needs, a new lower concentration formulation, tretinoin cream 0.02% was chosen for further development.

Two multicenter, randomized, double-blind, vehicle-controlled clinical studies were conducted to evaluate the safety and efficacy of the lower concentration tretinoin formulation in the treatment of moderate-to-severe facial photodamage. Results indicate statistically significant improvement in fine wrinkling, coarse wrinkling, and yellowing with the use of tretinoin cream 0.02% at week-24 end point, compared with placebo. Therapy with tretinoin cream 0.02% was well tolerated overall and demonstrated a favorable safety profile. Both studies demonstrated that tretinoin cream 0.02% is safe and effective for the treatment of moderate-to-severe photodamaged facial skin.

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The relationship between chronic ultraviolet light exposure and skin damage is well established in the literature. The eventual clinical manifestations of photodamage, particularly on the face (eg, fine and coarse wrinkling; irregular pigmentation; changes in texture, elasticity, thickness), are now recognized as being associated with sun exposure and not as inevitable and unavoidable consequences of aging alone. In addition to undesirable cosmetic effects, photodamage also is now known to be associated with pathologic changes in the skin, including the development of both benign and malignant tumors.

Increasing numbers of individuals are seeking treatment for cosmetic and pathologic problems related to photodamaged facial skin. Topical tretinoin, a vitamin A derivative naturally found in the body, has been shown to be safe and effective for the reduction of fine facial wrinkling, mottled hyperpigmentation, and skin roughness in a number

of large-scale trials.[1-6] Histologic data[7] indicate that topical use of tretinoin emollient cream 0.05% produces increased epidermal thickness, increased granular layer thickness, stratum corneum compaction, and decreased melanin content, changes that are associated with visible and desirable improvements in the skin after 3 to 6 months of therapy. In addition, tretinoin has been found to induce collagen synthesis while inhibiting some metalloproteinases responsible for dermal collagen degradation.[8-9] Long-term use of tretinoin emollient cream 0.05% appears to maintain and improve photodamaged facial skin.[10-12] Mild-to-moderate skin reactions, such as erythema, peeling, and burning are the most commonly reported side effects. Generally, these reactions do not limit topical tretinoin use.

Some patients do not require the 0.05% concentration of tretinoin emollient cream; some cannot tolerate it; and some prefer a less occlusive vehicle, as this formulation is a water-in-oil formulation consisting primarily of mineral oil. For additional prescribing flexibility to meet these needs, a new formulation of tretinoin at 0.02% concentration was chosen for further development. This newer tretinoin formulation is a water-washable oil-in-water emulsion with different emulsifiers and preservatives than the original product.

We report the results from 2 pivotal, double-blind clinical trials for tretinoin cream 0.02%.

METHODS AND SUBJECTS

Study Design

The objective of the 2 multicenter, randomized, double-blind, vehicle-controlled, clinical studies was to evaluate the safety and efficacy of tretinoin cream 0.02% for the treatment of moderate-to-severe photodamaged facial skin.

A total of 180 subjects with moderate-to-severe photodamage were enrolled in each study. Subjects were randomly assigned to one of 2 double-blinded, parallel treatment groups (tretinoin cream 0.02% or vehicle), with 90 subjects in each study assigned to receive active drug and 90 subjects assigned to placebo for 24 weeks. The treatment regimen consisted of once-nightly application, using a general dosing guideline of 0.25 g per application. In addition, all subjects in both studies applied a moisturizing sunscreen daily, with additional emollients and sunscreens to be used as needed.

Evaluation

Clinical follow-up visits were scheduled after 2 and 4 weeks of therapy, and every 4 weeks thereafter until completion of the 24-week investigational period. The overall severity of photodamage rated on a scale of 0 to 9 (ie, 0=none, 9=severe) and individual signs of photodamage similarly rated on a scale of 0 to 9 (ie, fine wrinkling, coarse wrinkling, mottled hyperpigmentation, tactile roughness, yellowing, laxity) were graded by the investigators at each visit. A global evaluation of clinical improvement of photodamage was conducted at week 24. Self-assessment questionnaires were completed by all subjects at baseline and every 4 weeks thereafter.

Specific signs and symptoms of skin irritation such as erythema, peeling, dryness, and burning/stinging were graded at each visit. Adverse events were documented at each visit.

Skin surface replicas of the crow's feet and right cheek region and photographs using standardized techniques were obtained at baseline and at weeks 12 and 24. The baseline photographs and corresponding baseline grades were used for making subsequent clinical comparisons.

Study Subjects

Eligible subjects were Caucasian men and women from 45 to 70 years of age with moderate-to-severe photodamage of the facial skin.

Individuals were excluded from the study who had multiple visible facial actinic keratoses or any other skin condition (eg, rosacea, psoriasis) that might require concomitant therapy or potentially confound efficacy and safety evaluations. Also excluded from participation were pregnant or nursing women, as well as men or women with a history of basal or squamous cell carcinoma of the face or malignant melanoma at any site within the past 5 years; those who had prior dermatologic therapy that might affect study evaluations (eg, collagen or silicone injections); or those with known hypersensitivity to any of the study drug components. In subjects who had used topical or systemic retinoid therapy in the past, initiation of the investigational regimen was delayed until the previous therapy had been discontinued for at least 6 months. Prior to initiation of the study, Institutional Review Board approval and written informed consent were obtained from each participant.

RESULTS

Patient Characteristics

The study populations consisted of healthy Caucasian subjects between 45 and 70 years of age (Table 1). Of the 360 total subjects enrolled in both studies, 328 completed the studies, with all but 2 cases determined to be valid for safety evaluation. Most participants were women who exhibited signs of severe facial photodamage at baseline. In each of the studies, the 2 treatment groups were comparable in terms of age, gender, and baseline severity of photodamage.

Table 1.

Patient Characteristics

	Study 1			Study 2		
	Tretinoin Cream 0.02%	Vehicle	Total	Tretinoin Cream 0.02%	Vehicle	Total
Enrolled, n	90	90	180	90	90	180
Completed, n	77	83	160	82	86	168
Age*						
Mean, y	58.5	58.4	58.4	58.7	58.5	58.6
Range, y	45–69	45–69	45–69	45–70	43–70	43–70
Sex*						
Female, %	87	90	88	89	89	89
Male, %	13	10	12	11	11	11
Photodamage rating*						
Moderate, %	27	34	30	29	30	30
Severe, %	73	66	70	71	70	70
Total discontinued, n	13	7	20	8	4	12
Adverse event, n	4	0	4	2	1	3
Personal, n	7	3	10	1	1	2
Lost to follow up, n	2	4	6	5	2	7
Subjects valid for evaluation						
Safety, n	90	89	179	89	90	179
Efficacy, n	77	83	160	82	86	168

*Based on subjects valid for safety evaluation.

Efficacy

Primary Efficacy Measures—The primary efficacy measure was the investigators' evaluation of 6 individual clinical signs of photodamaged skin: fine wrinkling, coarse wrinkling, mottled hyperpigmentation, tactile roughness, yellowing (sallowness), and laxity (looseness).

Figure 1 shows a subject's improvement from baseline to week 24 with tretinoin 0.02% therapy. Table 2 shows the primary efficacy results at week 24 compared with baseline evaluation. Of the primary efficacy parameters, fine wrinkling demonstrated the greatest response to 0.02% tretinoin cream therapy when compared with vehicle alone in both studies ($P<.001$ in Study 1 and $P=.028$ in Study 2). In addition, both studies also indicated significantly greater responses with tretinoin cream 0.02% in the clinical signs of coarse wrinkling ($P=.033$ in Study 1 and $P=.015$ in Study 2) and yellowing ($P=.018$ in Study 1 and $P=.002$ in Study 2). For mottled hyperpigmentation, significantly greater improvement was demonstrated in the tretinoin cream 0.02% group compared with the control group in Study 2 ($P<.001$). Tactile roughness and laxity did not show a statistically significant improvement with tretinoin cream 0.02% compared with vehicle alone.

Secondary Efficacy Measures—Three secondary efficacy measures were used, each of which represents a composite assessment of clinical response at the end of therapy: (1) investigators' global evaluation of the subjects' clinical response at week 24 compared with

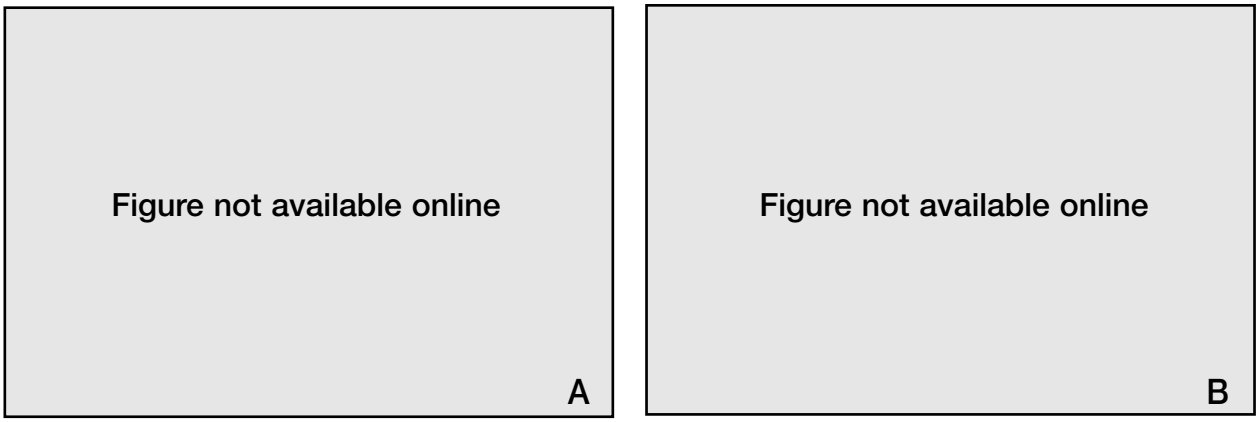

Figure 1. A subject at baseline (A) and after 24 weeks (B) of treatment with tretinoin cream 0.02%. This patient had mild improvement.

baseline, (2) investigators' evaluation of the overall severity of photodamage, and (3) subjects' self-assessment of overall appearance and feel of the skin at week 24 compared with baseline. Additional supporting measures of efficacy were subjects' self-assessment of individual signs of photodamage and objective skin replica measurements.

Investigators' Global Evaluation—According to global evaluation results at week 24 (Table 3), subjects in the tretinoin cream treatment groups exhibited significantly greater overall improvement in ratings of photodamaged skin (79% and 87% in Study 1 and Study 2, respectively) than did subjects in the control group (60% and 44% in Study 1 and Study 2, respectively; $P<.001$)(Figure 2). Among subjects who improved, the magnitude of rating improvement was greater in the tretinoin cream treatment groups. Furthermore, global evaluation results were similar regardless of the baseline severity rating of photodamage; thus, baseline severity was not a predictor of response to therapy.

Investigators' Evaluation of Overall Severity of Photodamage—Based on the mean change in the investigators' evaluation of overall severity of photodamage (0–9 scale) from baseline to week 24, use of tretinoin cream 0.02% produced significantly greater improvements in photodamaged skin compared with vehicle application ($P<.001$). In the tretinoin cream treatment groups, 68% and 71% of subjects in Study 1 and Study 2, respectively, demonstrated an overall reduction in photodamage severity at the end of therapy (Figure 2).

Subjects' Self-Assessment of Overall Appearance and Feel of Skin—In both studies, the majority of subjects in the active treatment and control groups graded their skin as "much improved" or "somewhat improved" at the end of therapy, with subjects who received tretinoin cream reporting more favorable responses than did vehicle-treated patients: 83% versus 64%, respectively, in Study 1; 83% versus 72%, respectively, in Study 2 (Table 4). In Study 1, the difference between tretinoin cream 0.02% and vehicle in the overall subject self-assessment results (mean scores of 3.1 and 2.7, respectively) reached statistical significance ($P<.001$)(Figure 3). Overall self-assessment results were consistent with the additional supporting measures.

Additional Supporting Measures—Additional supporting measures of efficacy were subject self-assessment of individual clinical signs of photodamage (ie, small wrinkles, tone [pink or rosy], color [brown spots], texture [roughness], tightness [pores]) and objective skin replica measures.

Individual self-assessment ratings also indicated consistently more favorable responses in tretinoin cream–treated subjects at week 24 compared with those of vehicle-treated subjects. The percentage of subjects from both studies who reported improvements—that is, ratings of "much improved" or "somewhat improved"—in the various self-assessment features ranged from 52% to 90% in the tretinoin cream groups compared with 36% to 72% in the vehicle groups. In Study 1, the differences between treatments were statistically significant for small wrinkles ($P=.005$), color ($P<.001$), texture ($P<.001$), and tightness ($P\leq.05$); and in Study 2, the differences between treatments were statistically significant for tone ($P=.004$) and pores ($P=.013$).

These findings were further supported by skin replica assessments comparing baseline to end-point data. These assessments, made on the basis of computer-assisted analyses of images taken from the crow's feet and cheek areas, showed statistically significant improvements in the tretinoin cream 0.02% group compared with the vehicle group.

Safety

Of the 360 subjects enrolled in both studies, 328 completed protocol, with all but 2 cases determined

Table 2.

Improvement From Baseline to Week 24 in Individual Clinical Signs of Photodamage

	Clinical Signs of Photodamage					
	Fine Wrinkling	Coarse Wrinkling	Tactile Roughness	Mottled Hyperpigmentation	Yellowing (Sallowness)	Laxity (Looseness)
Study 1						
Tretinoin cream 0.02% (n=77)						
Subjects improved,* %	66	43	55	73	51	35
Mean change from baseline†	-0.9	-0.5	-0.9	-1.2	-1.0	-0.5
Vehicle (n=83)						
Subjects improved,* %	37	25	52	61	48	36
Mean change from baseline†	-0.5	-0.3	-0.9	1.0	-0.7	-0.4
P value for treatment effect‡	<.001§	.033§	.787	.078	.018§	.282
Study 2						
Tretinoin cream 0.02% (n=82)						
Subjects improved,* %	57	38	85	72	59	38
Mean change from baseline†	-0.9	-0.5	-1.7	-1.1	-0.9	-0.5
Vehicle (n=86)						
Subjects improved,* %	40	22	71	30	35	22
Mean change from baseline†	-0.6	-0.3	-1.3	-0.4	-0.5	-0.3
P value for treatment effect‡	.028§	.015§	.055	<.001§	.002§	.053

*Improvement is defined as a reduction from baseline to week 24 of one or more units on a 0–9 scale with: 0=none, 1–3=mild, 4–6=moderate, and 7–9=severe.
†A negative mean change from baseline represents improvement.
‡Statistical results are based on the log-rank test stratified by investigator for the change from baseline to week 24. All tests are 2-sided and performed at the 0.05 significance level.
§Denotes statistically significant difference from vehicle (2-sided, $P \leq .05$).

to be valid for safety evaluation. Both studies showed good compliance rates with once-daily dosing, reflected in the fact that most subjects (>87%) completed at least 90% of applications.

Based on cutaneous irritation ratings and adverse event reports, tretinoin cream 0.02% demonstrated a favorable safety profile over the 24-week study period for the 2 trials. Skin irritation, while more prevalent in tretinoin cream-treated subjects than in vehicle-treated subjects, was generally mild and well tolerated. At each visit, the signs and symptoms of skin irritation (ie, erythema, peeling, dry-

Table 3.

Global Evaluation Ratings at Week 24

Rating Compared With Baseline	Study 1 Tretinoin Cream 0.02% (n=77)	Study 1 Vehicle (n=83)	Study 2 Tretinoin Cream 0.02% (n=82)	Study 2 Vehicle (n=86)
Improved, n (%)	61 (79)*	50 (60)	71 (87)*	38 (44)
Much improved	5 (6)	2 (2)	9 (11)	4 (5)
Improved	39 (51)	22 (27)	17 (21)	9 (10)
Slightly improved	17 (22)	26 (31)	45 (55)	25 (29)
No change, n (%)	16 (21)	33 (40)	11 (13)	48 (56)
Worse, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Mean scores†	3.4	2.9	3.3	2.6

*$P<.001$.
†1 indicates worse; 2, no change; 3, slightly improved; 4, improved; 5, much improved.

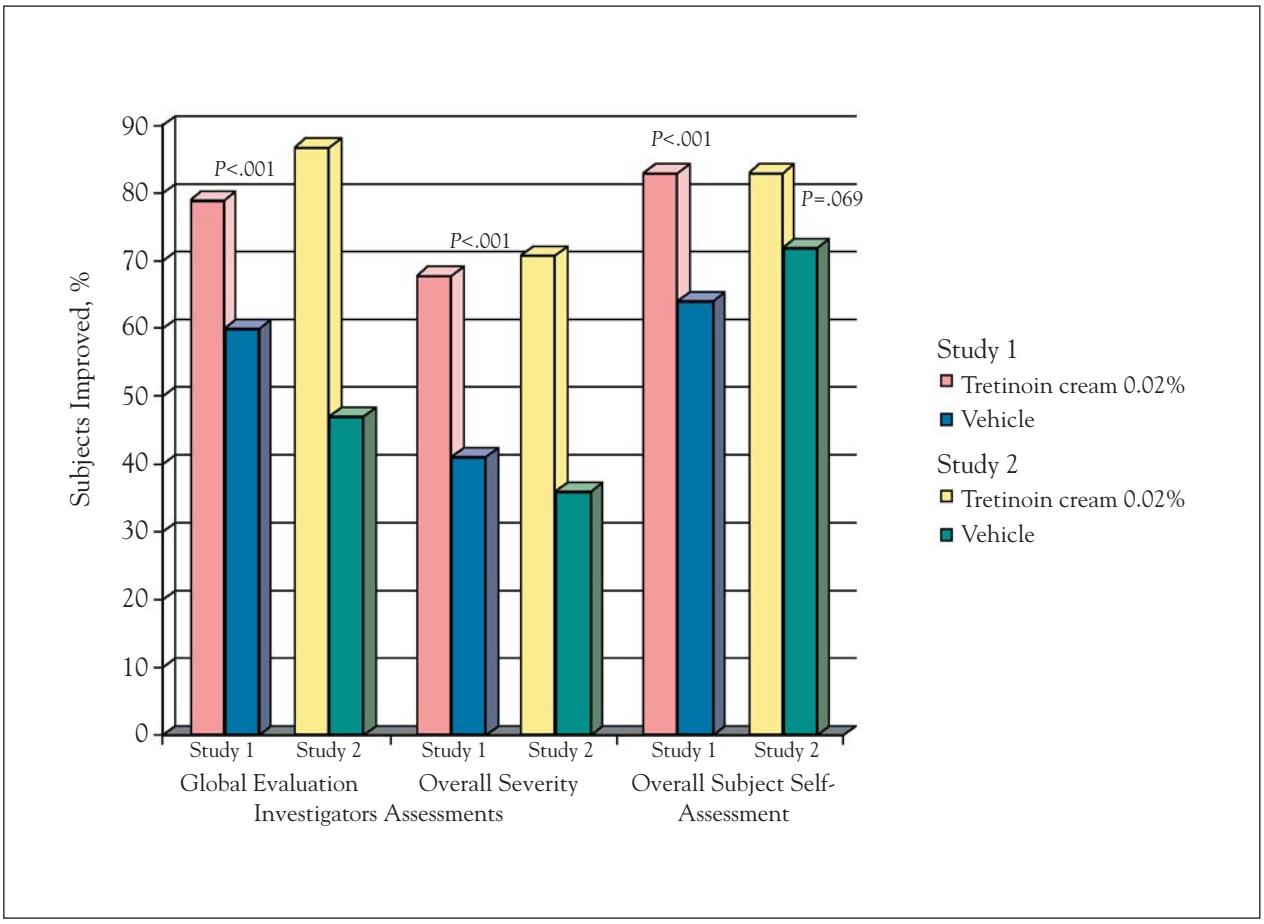

Figure 2. Secondary efficacy measures at week 24.

Table 4.

Overall Subject Self-Assessment Results

Rating Compared With Baseline	Study 1 Tretinoin Cream 0.02% (n=77)	Study 1 Vehicle (n=83)	Study 2 Tretinoin Cream 0.02% (n=82)	Study 2 Vehicle (n=85)
Improved, n (%)	64 (83)	53 (64)	68 (83)	61 (72)
Much improved	19 (25)	6 (7)	24 (29)	20 (24)
Somewhat improved	45 (58)	47 (57)	44 (54)	41 (48)
No change, n (%)	13 (17)	30 (36)	13 (16)	24 (28)
Worse, n (%)	0 (0)	0 (0)	1 (1)	0 (0)
Mean scores*	3.1†	2.7	3.1‡	3.0

*1 indicates worse; 2, no change; 3, somewhat improved; 4, much improved.
†$P<.001$ (tretinoin cream 0.02% vs vehicle).
‡$P=.069$ (tretinoin cream 0.02% vs vehicle).

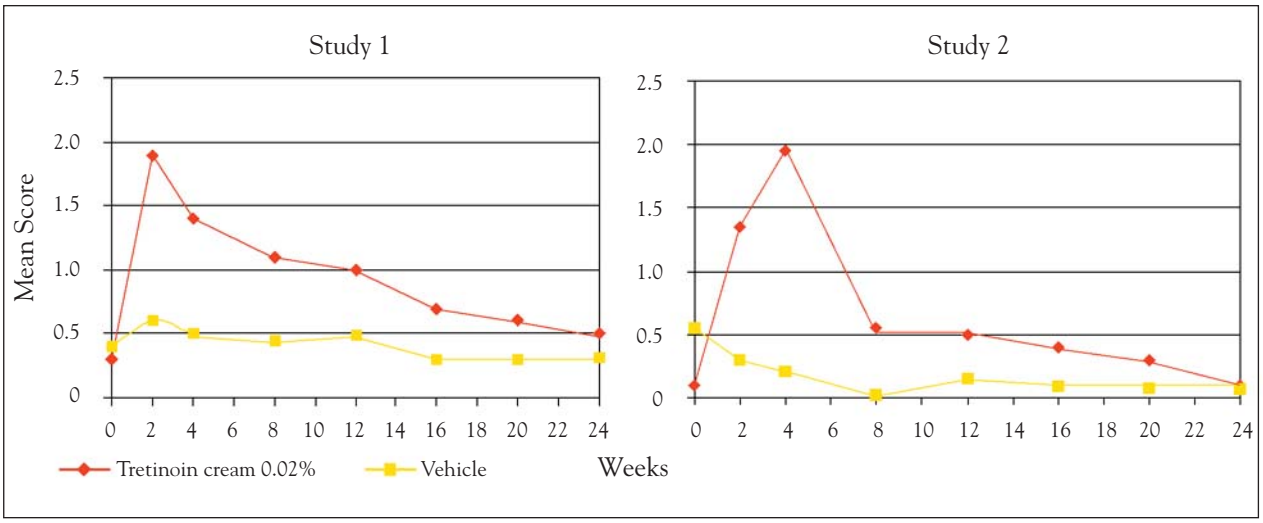

Figure 3. The time profile of overall skin irritation scores in Studies 1 and 2. Scores were on a 0–9 scale (0=none, 1–3=mild, 4–6=moderate, 7–9=severe).

ness, burning/stinging) were graded. These symptoms tended to peak during the first 4 weeks of the trial period and gradually declined to baseline levels by week 24 (Figure 3).

Although most subjects in the tretinoin groups experienced skin irritation symptoms of at least mild intensity, only 20% of subjects in Study 1 and 38% of subjects in Study 2 (versus 7% and 11% of vehicle-treated subjects in Study 1 and Study 2, respectively) had skin irritation reported as an adverse event related to tretinoin cream administration at the treatment site. Skin irritation was considered an adverse event only if it resulted in missed treatment applications, required topical steroid therapy, or was otherwise determined to be significant by the investigator.

Six study participants in the tretinoin groups (Study 1, 4 subjects; Study 2, 2 subjects) discontinued participation because of an adverse skin reaction (Table 1). In Study 1, two of the adverse events

leading to discontinuation were determined to be drug-related skin irritation or related symptoms, and in Study 2, one of these adverse skin reactions was considered to be possibly related to drug application.

Adverse events not associated with the treatment site were evenly distributed among the tretinoin and vehicle-only groups and did not prevent any subject from completing the study. The most frequently reported adverse event was upper respiratory infection, with a subject incidence rate of 16% and 7% in the tretinoin groups and 18% and 10% in the vehicle groups in Study 1 and Study 2, respectively. No laboratory testing was performed related to safety evaluations.

CONCLUSION

These 2 multicenter, randomized, double-blind, vehicle-controlled clinical trials demonstrate the efficacy and safety of tretinoin cream 0.02% in the treatment of moderate-to-severe photodamage of facial skin.

- The degree of overall clinical improvement as assessed by the clinical investigators was determined to be significantly greater in the tretinoin groups.
- Of the 6 individual clinical signs of photodamage evaluated by investigators, fine wrinkling demonstrated the greatest response to tretinoin cream 0.02% therapy when compared with vehicle alone in both studies. In addition, both studies also indicated significantly greater tretinoin cream–related responses in the clinical signs of coarse wrinkling and yellowing.
- Clinical observations by both investigators and subjects showed that, compared with vehicle-treated subjects, subjects treated with tretinoin cream 0.02% exhibited a significantly greater overall improvement in clinical signs of photodamage.
- Statistically significant differences were found with tretinoin cream 0.02% treatment in 22 of 27 efficacy parameters evaluated at the week-24 end point. The clinical benefits with tretinoin cream therapy were evidenced within 4 to 12 weeks after the start of treatment, depending on the specific parameter being evaluated.
- While improvement was observed in both treatment groups, global criteria and individual clinical signs and self-assessment parameters showed significantly greater improvement in the subjects who used tretinoin cream.
- These clinical differences were supported by independent findings from computer-generated skin replica measurements.
- Overall, therapy with tretinoin cream 0.02% was well tolerated and demonstrated a favorable safety profile over the 24-week investigational periods. Both studies showed good compliance rates with once-daily dosing, reflected in the fact that the majority of subjects completed at least 90% of applications.
- Although skin irritation was more prevalent in the tretinoin cream 0.02% treatment groups than in control subjects, symptoms were generally mild and well tolerated.

Tretinoin cream 0.02% is effective and safe when applied once-daily to subjects with moderate-to-severe photodamage of facial skin. This new formulation tretinoin cream 0.02% with a low irritation profile can be optimal for new patients starting tretinoin therapy or for patients who cannot tolerate the higher concentration tretinoin product.

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