Bioequivalence of 2 Formulations of Tretinoin Emollient Cream 0.05%: Efficacy and Tolerability in Fine Wrinkling and Mottled Hyperpigmentation

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Topical tretinoin (0.05%) improves fine facial wrinkles, mottled hyperpigmentation, and tactile roughness, which improve the skin's appearance. Efficacy appears to be dose dependent, but higher doses of tretinoin (ie, 0.1%) have demonstrated corresponding increases in cutaneous side effects occurring in the first few weeks of treatment. This study compared the bioequivalence of a newer tretinoin emollient cream 0.05% (tre-A) with the discontinued brand 0.05% formulation (tre-B) and vehicle in 420 participants with mild to moderate facial photoaging over 24 weeks. Both active formulations were effective in treating fine facial wrinkles (70.5%–74.4% success rate) and mottled hyperpigmentation (82.8%–88.0% success rate). Results for tre-A and tre-B were bioequivalent and significantly superior to vehicle ($P<.001$ and $P\leq.002$, respectively). The majority of adverse events (AEs) were mild to moderate (94% [300/318]) and were not drug related (97% [308/318]). The newer tre-A formulation is now commercially available with the fragrance and quarternium-15 having been removed from the original formulation.

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Retinoids are perhaps the most commonly used treatments to improve the signs of photodamage, fine wrinkles, mottled hyperpigmentation, and tactile roughness. However, despite the large number of retinoid compounds that are available, few have been studied in detail in patients with photodamaged skin. In concentrations greater than 0.02%, tretinoin cream has proven to be

beneficial in the treatment of mild to severe photodamage on the face and forearms.[1] The efficacy of tretinoin emollient cream 0.05% in reversing photodamage and improving the skin's clinical appearance has been widely studied and clearly demonstrated in long-term, large-scale, double-blind clinical studies.[2-9] Reductions in fine wrinkles, mottled hyperpigmentation, and roughness can occur as early as 2 weeks into treatment.[10] Benefits can be sustained with continued use or reversed with treatment cessation.[9] In prior studies, tretinoin emollient cream 0.05% showed significant improvements in fine wrinkles and skin structure over 12 to 24 weeks in participants with evidence of photoaging ($P<.05$ vs vehicle).[4,5] Topical tretinoin (0.05% and 0.1%) also has been evaluated in long-term studies.[3,11] Most improvement occurs over the first 6 to 12 months and is maintained with long-term treatment.[11]

Unfortunately, tretinoin emollient cream 0.05% was discontinued in 2006, leaving dermatologists with only a lower concentration tretinoin emollient cream (0.02%) approved for fine facial wrinkles. The beneficial effects of tretinoin have been shown to be dose dependent. Two large, 24-week, multicenter, double-blind studies showed that the 0.05% formulation was more effective than tretinoin 0.01% or 0.001%.[6,8] Seventy-eight percent of participants demonstrated overall improvement after treatment with the 0.05% cream, with no significant difference between vehicle (44% improvement) and tretinoin 0.01% and 0.001%.[8]

A newer formulation of tretinoin emollient cream 0.05% recently has been developed. This study examines the bioequivalence of the newer formulation and the discontinued formulation prior to commercialization.

METHODS

This randomized, double-blind, balanced, parallel study evaluated 420 male and female participants (age range, 40–75 years) with Fitzpatrick skin types I to IV and mild to moderate facial photoaging. Participants were treated once daily for 24 weeks with either the newer tretinoin emollient cream 0.05% formulation (tre-A [Refissa, Spear Pharmaceuticals, Inc]), the discontinued tretinoin emollient cream 0.05% formulation (tre-B [Renova, Ortho Dermatologics), or vehicle.

Assessments

Fine winkles and mottled hyperpigmentation were graded at baseline and week 24 by a single-blinded dermatologist using a 10-point grading scale (0=no damage; 2−3=mild; 4−5=moderate; 6−7=moderate/severe; 8−9=severe). Irritation and erythema of the facial skin were assessed at baseline and weeks 4, 12, and 24 using a 5-point scale (0=none; 1=minimal; 2=mild; 3=moderate; 4=severe). Participant self-assessment was performed at week 24 compared to baseline using a 4-point grading scale (4=much improved; 3=somewhat improved; 2=same; 1=worse).

Inclusion and Exclusion Criteria

The main inclusion criteria included Fitzpatrick skin type I to IV and participants had to have mild to moderate (grades 3−5) or moderate to severe (grades 6−7) fine wrinkles, and mild to moderate (grades 2−5) or moderate to severe (grades 6−7) hyperpigmentation. Women of childbearing potential had to be nonpregnant, nonbreastfeeding, and willing to avoid pregnancy during the course of the study. Participants were asked to refrain from the use of other moisturizers, topical facial medications, skin peels, and facials during the 24-week treatment period.

The main exclusion criteria included all other grades of fine wrinkles and pigmentation, other Fitzpatrick skin types, and active acne or severe acne-prone skin. Participants with a history of allergic or hypersensitivity reactions to tretinoin or any creams, lotions, ointments, gels, or cosmetics were not included in the study; concurrent use of drugs known to cause photosensitivity also was not permitted.

Statistical Analysis and Bioequivalence

Evaluation of bioequivalence was conducted on an efficacy-valid population. Participants were eligible for the efficacy-valid analysis if they demonstrated consistent use of the study drug throughout the 24-week period, missed no more than 30% of the required applications of the study drug, and were present for the week-24 visit and used drug up until the final visit. Tests for statistical superiority, skin irritation, and safety were conducted on intent-to-treat participants, defined as those who were eligible for the study, enrolled, and used the study product. Those participants who did not complete the week-24 visit were considered treatment failures. Participants were encouraged to complete the study and use the study product as instructed, but failure to use the product as instructed did not disqualify participants from the intent-to-treat population. The study was considered valid if both of the products (reference or test) showed superiority over vehicle for each bioequivalence parameter and if the reference and test products also demonstrated bioequivalence.

All statistical analyses were performed using SAS version 8. Frequency tabulations, percentages, means, standard deviations, and sample sizes were presented to characterize and describe the clinical results, as appropriate. Statistical comparisons of age were conducted with a 1-way analysis of variance. Additionally, the

likelihood ratio test was used to analyze gender, while the Cochran-Mantel-Haenszel test was used to analyze initial evaluations of fine wrinkling and mottled hyperpigmentation. The statistical superiority of tre-A and tre-B over vehicle in the improvement of fine wrinkling and mottled hyperpigmentation at week 24 was assessed using a 1-sided Fisher exact test of proportions.

The bioequivalence of tre-A and tre-B was based on the proportion of participants who experienced improvement in fine wrinkling and mottled hyperpigmentation. Treatment success was defined as a change from baseline of 1 or more points. Effects were considered statistically significant ($P \leq .05$) and bioequivalent if the 90% confidence interval of the difference in success rates was contained within the interval −0.20 to +0.20). (See Peters et al[12] for a general review on bioequivalence).

Statistical comparison of participant self-assessment was calculated by adding a score to each group and statistically comparing the number in each group.

RESULTS

Participant disposition, demographics, and baseline characteristics are shown in Figure 1 and Table 1. Of the 420 participants included in the study, 382 (91%)(122 tre-A; 125 tre-B; 135 vehicle) were considered efficacy valid.

Efficacy

Table 2 summarizes the proportion of participants in each active treatment group showing improvement in fine wrinkling and mottled hyperpigmentation as well as the results of the bioequivalence analysis. Active treatments were comparable with no statistically significant difference and bioequivalent. For tre-A, 70.5% (86/122) of participants showed improvement in fine wrinkling and 82.8% (101/122) showed improvement in mottled hyperpigmentation at week 24 compared to tre-B with 74.4% (93/125) improvement in fine wrinkling (90% confidence limit: −14.1% to −6.2%) and 88.0% (110/125) improvement in mottled hyperpigmentation (90% confidence limit: −13.4% to 3.0%). The slight differences between the 2 active groups were not statistically different. Both active treatments showed a statistically significant treatment effect over vehicle ($P < .001$ and $P \leq .002$)(Figure 2).

Moreover, 69% (86/125) of participants assessed themselves as somewhat improved to much improved after

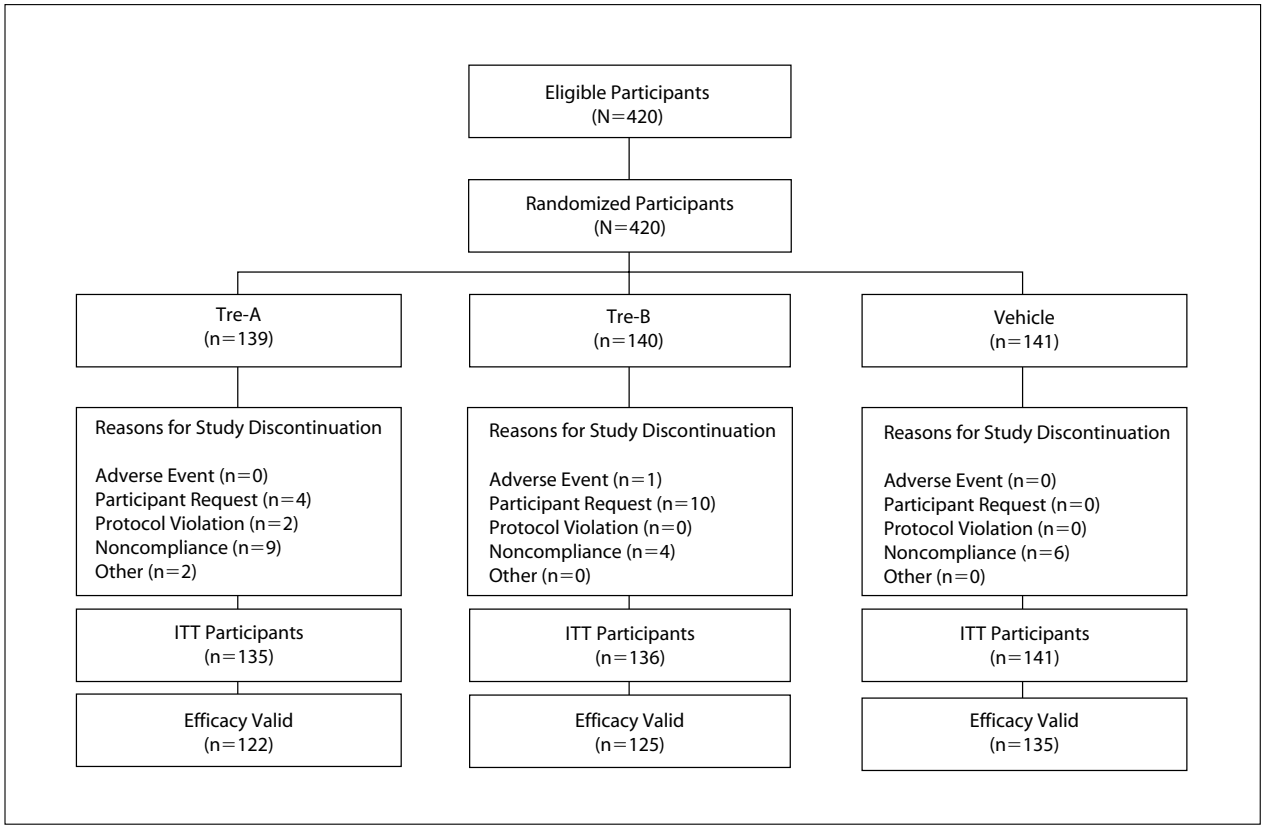

Figure 1. Participant disposition. Tre-A indicates tretinoin emollient cream 0.05% (Refissa); Tre-B, tretinoin emollient cream 0.05% (Renova); ITT, intent to treat.

Table 1

Demographics and Baseline Characteristics of Efficacy-Valid Participants

	Tre-A (n=122)	Tre-B (n=125)	Vehicle (n=135)
Gender, n (%)			
Male	20 (16)	17 (14)	19 (14)
Female	102 (84)	108 (86)	116 (86)
Age, y			
Mean	60.8	61.0	61.1
Range	40–75	41–75	40–75
Race, n (%)			
Caucasian	122 (100)	125 (100)	135 (100)
Fine wrinkling, n (%)[a]			
2–3 (mild)	15 (12)	17 (14)	24 (18)
4–5 (moderate)	30 (25)	33 (26)	30 (22)
6–7 (moderate/severe)	77 (63)	75 (60)	81 (60)
Mottled hyperpigmentation, n (%)[a]			
2–3 (mild)	68 (56)	69 (55)	74 (55)
4–5 (moderate)	50 (41)	51 (41)	56 (41)
6–7 (moderate/severe)	4 (3)	5 (4)	5 (4)
Irritation, n (%)[b]			
0 (none)	59 (48)	67 (54)	73 (54)
1 (minimal)	57 (47)	51 (41)	58 (43)
2 (mild)	6 (5)	7 (6)	4 (3)

Abbreviations: Tre-A, tretinoin emollient cream 0.05% (Refissa); Tre-B, tretinoin emollient cream 0.05% (Renova).
[a]Measured on a scale of 0 to 9 (0=no damage; 8–9=severe).
[b]Measured on a scale of 0 to 4 (0=none; 4=severe).

TABLE 2

Percentage Improvement and Bioequivalence Analysis of Fine Wrinkling and Mottled Hyperpigmentation for Efficacy-Valid Participants[a]

	Tre-A, n (%) (n=122)	Tre-B, n (%) (n=125)	Difference in Success Rates	90% Confidence Limits	Equivalent
Improvement in fine wrinkling	86 (70.5)	93 (74.4)	−3.9%	−14.1%, −6.2%	Yes
Improvement in mottled hyperpigmentation	101 (82.8)	110 (88.0)	−5.2%	−13.4%, 3.0%	Yes

Abbreviations: Tre-A, tretinoin emollient cream 0.05% (Refissa); Tre-B, tretinoin emollient cream 0.05% (Renova).
[a]Improvement was defined as a change from baseline of 1 or more points by week 24.

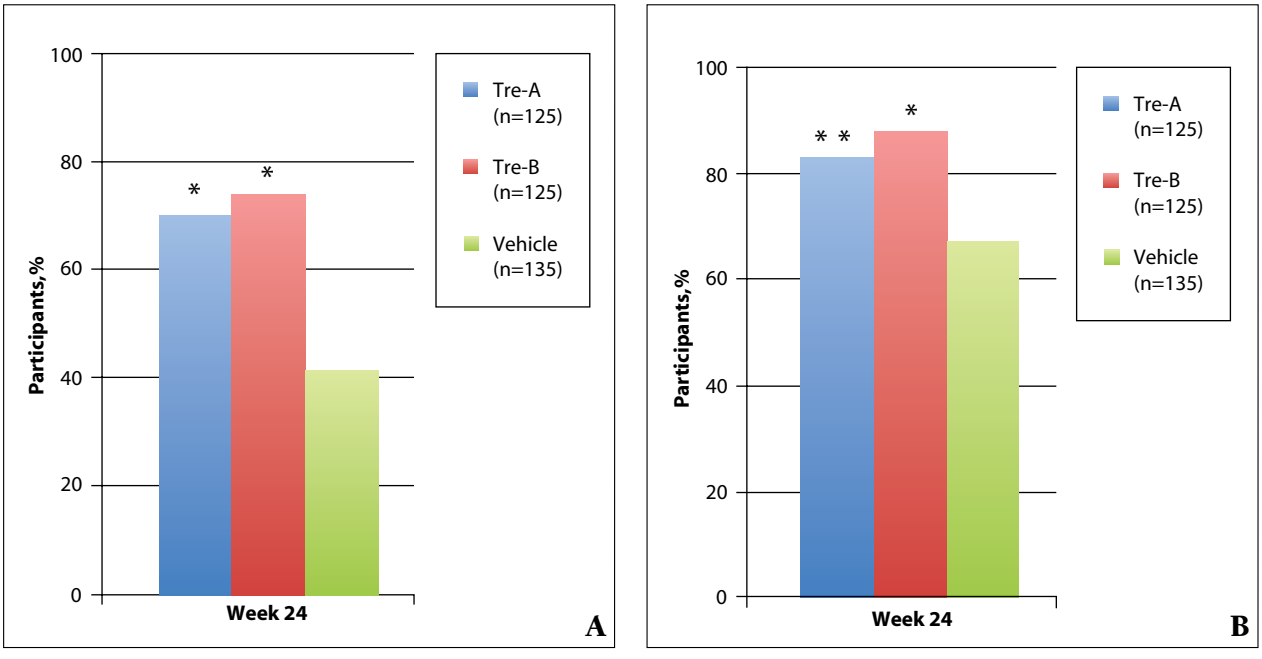

Figure 2. Improvement in fine wrinkling (A) and mottled hyperpigmentation (B) at week 24 (active treatment vs vehicle [intent-to-treat participants, minus those participants not reported]). Tre-A indicates tretinoin emollient cream 0.05% (Refissa); Tre-B, tretinoin emollient cream 0.05% (Renova); asterisk, $P<.001$ vs vehicle; double asterisk, $P\leq.002$ vs vehicle. There were no statistically significant differences between tre-A and tre-B.

24 weeks of tre-A treatment compared to 78% (98/125) treated with tre-B and 48% (65/135) treated with vehicle (Table 3). There was no statistical difference between the 2 active groups.

Cutaneous Tolerability and Safety

Mean irritation scores are shown in Table 4. There was a significant overall treatment effect at weeks 4, 12, and 24 ($P<.001$); the mean scores of the active treatments were significantly higher than vehicle ($P\leq.006$).

At baseline, the mean irritation scores were 0.58, 0.54, and 0.49 for tre-A, tre-B, and vehicle, respectively. The most irritation was noted at week 4, with mean irritation scores of 0.93 for tre-A and 1.03 for tre-B ($P=.093$ vs tre-A) and 0.61 for vehicle. At week 24, irritation levels returned to or below baseline with the exception of tre-B.

TABLE 3

Participant Self-assessment (ITT Population)[a]

	Tre-A	Tre-B	Vehicle
No. of participants	135	136	141
Not reported	10	11	6
Worse, n (%)	1 (1)	4 (3)	4 (3)
Same, n (%)	38 (30)	23 (18)	66 (49)
Somewhat improved, n (%)	63 (50)	70 (56)	54 (40)
Much improved, n (%)	23 (18)	28 (22)	11 (8)
Mean (SD)[b]	2.86 (0.71)	2.98 (0.73)	2.53 (0.69)

Abbreviations: ITT, intent to treat; Tre-A, tretinoin emollient cream 0.05% (Refissa); Tre-B, tretinoin emollient cream 0.05% (Renova); SD, standard deviation.
[a]Participant self-assessment measured on a scale of 1 to 4 (1=worse; 4=much improved).
[b]The mean comes from assigning a numerical value to each group and averaging the groups to compare. There was no statistical difference comparing the 2 active groups.

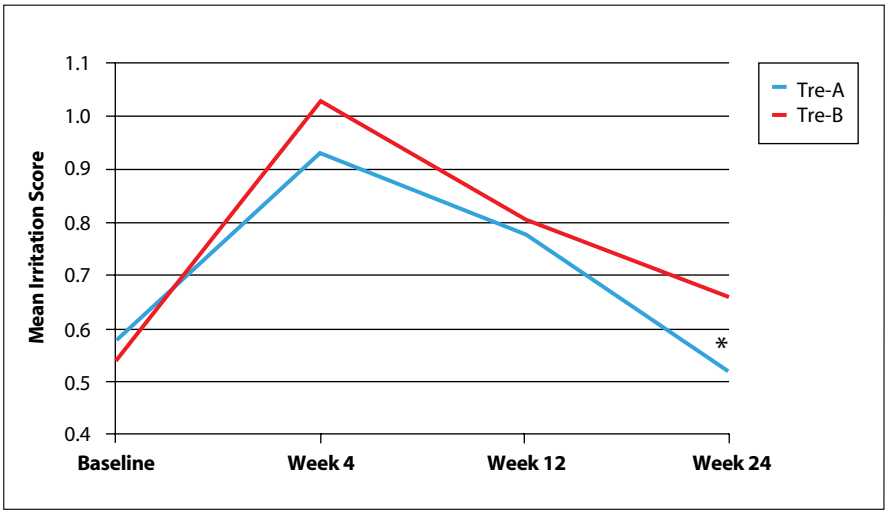

Figure 3. Mean skin irritation (0–24 weeks) comparison between active treatments. Tre-A indicates tretinoin emollient cream 0.05% (Refissa); Tre-B, tretinoin emollient cream 0.05% (Renova); asterisk, $P=.040$.

The mean irritation score with tre-B (0.66) was significantly greater than tre-A (0.52)($P=.040$)(Figure 3; Table 4).

A total of 318 adverse events (AEs) were reported in 41% (55/135) of participants with tre-A, 38% (51/136) with tre-B, and 45% (63/141) with vehicle. There was no significant difference between treatment groups. Most AEs (94% [300/318]) were considered mild or moderate in nature, and the overwhelming majority of AEs

Table 4

Skin Irritation at Each Evaluation (ITT Population)[a]

	Tre-A (n=135)	Tre-B (n=136)	Vehicle (n=141)
Baseline			
None, n (%)	65 (48)	70 (51)	77 (55)
Minimal, n (%)	62 (46)	58 (43)	59 (42)
Mild, n (%)	8 (6)	8 (6)	5 (4)
Mean (SD)	0.58 (0.60)	0.54 (0.61)	0.49 (0.57)
Week 4			
None, n (%)	22 (16)	12 (9)	59 (42)
Minimal, n (%)	100 (75)	107 (80)	78 (55)
Mild, n (%)	12 (9)	14 (10)	4 (3)
Moderate, n (%)	0 (0)	1 (1)	0 (0)
Mean (SD)	0.93 (0.50)	1.03 (0.47)	0.61 (0.54)
Week 24			
None, n (%)	62 (50)	46 (37)	91 (67)
Minimal, n (%)	61 (49)	76 (61)	42 (31)
Mild, n (%)	2 (2)	3 (2)	2 (1)
Mean (SD)	0.52 (0.53)	0.66 (0.53)	0.34 (0.51)

Abbreviations: ITT, intent to treat; Tre-A, tretinoin emollient cream 0.05% (Refissa); Tre-B, tretinoin emollient cream 0.05% (Renova); SD, standard deviation.
[a]Measured on a scale of 0 to 4 (0=none; 4=severe).

(97% [308/318]) were not considered drug related. There were 14 serious AEs reported during the study; none were related to study drug and they were equally distributed across treatment groups.

COMMENT

This study demonstrated efficacy and safety bioequivalence between 2 tretinoin emollient cream 0.05% formulations. Bioequivalence was demonstrated for both

improvements in fine wrinkling and mottled hyperpigmentation at week 24. Both active treatments were significantly superior to vehicle. In addition, the participant self-assessment showed a significant positive correlation to the sum of improvement scores for fine wrinkling and mottled hyperpigmentation.

The study drugs were well tolerated. Skin irritation scores and AE profiles did not reveal any unexpected or unusual results. In prior studies, retinoid therapy has been associated with irritation, exfoliation, dryness, and scaling, especially during the first 3 to 4 weeks of treatment.[12] Our study revealed increased skin irritation at week 4 with the active treatments, which was consistent with prior studies. By week 24 of the study, however, irritation scores had returned to baseline levels and were significantly lower with the newer tretinoin emollient cream 0.05% formulation (tre-A).

Postapproval, both the fragrance and quaternium-15, a preservative that converts to formaldehyde, were removed from the formulation to reduce the already low incidence of contact dermatitis.

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