An Open-Label Study Assessing the Efficacy and Tolerability of a Skincare Regimen in Subjects of Different Ethnicities with Moderate-to-Severe Hyperpigmentation

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Abstract
Background: Hyperpigmentation is a common cosmetic concern that significantly impacts self-esteem. A skincare regimen has been developed to improve the appearance, tone, texture, and luminosity of subjects with facial hyperpigmentation (Even Up® Hyperpigmentation Regimen; Colorescience, Inc., Carlsbad, CA).

Aims: The objective of this open-label trial was to assess the efficacy and tolerability of this regimen for treating facial hyperpigmentation.

Patients/Methods: Subjects with moderate-to-severe facial hyperpigmentation (N = 33) were randomized to those not using prescription, advanced or physician-dispensed skin care products (Group A, n = 23) and those currently using prescription, advanced or physician-dispensed skincare products for facial hyperpigmentation (Group B, n = 10). Both groups were provided three skincare products comprising the hyperpigmentation regimen and instructions for use. Subjects were evaluated at baseline and Weeks 2, 4, 8 and 12.

Results: The overall median (range) baseline MASI score at baseline was 9.0 (2, 31), decreasing by 0.0 (−7, 0) points at Week 2 (p = 0.002), 0.6 (−8, 0) points at Week 4 (p < 0.0001), 1.5 (−16, 0) points by Week 8 (p < 0.0001) and 2.4 (−20, 0) points at Week 12 (p < 0.0001). At Week 12, the overall median improvement in MASI score was 26% and higher for Group B (32% vs. 22%). By Week 2, subjects reported lighter, less noticeable brown spots (76%), brighter, more luminous skin (88%), more even skin tone (67%), and healthier look and feel (85%). Improvements continued throughout the study. No adverse events were observed or reported.

Conclusions: This regimen addresses facial hyperpigmentation and protects skin against the damaging effects of ultraviolet and high energy visible light (HEV). It is safe to use on all skin types and tones.

KEYWORDS
Fitzpatrick skin types, hyperpigmentation, melasma, mineral sunscreen, solar lentigo
Hyperpigmentation is a common condition characterized by skin darkening due to the overproduction of the pigment melanin. It has many causes including excessive sun exposure (solar lentigo), changes in female hormones (melasma), acne (post-inflammatory hyperpigmentation), and certain medications (minocycline). Hyperpigmentation is a cosmetic concern that can have a significant impact on self-esteem and quality of life and is more prevalent among dark-skinned individuals although most skin types can be affected.

A skincare regimen has been developed to improve the appearance, skin tone, texture, and luminosity in those who struggle with hyperpigmentation (Even Up®). The regimen consists of three easy-to-use products, two of which contain the patented Lumira® complex (Table 1). The first product also contains Crystalilade®, a time-release peptide, glycerin and Phytomoist which is four times more hydrating than hyaluronic acid. This product diminishes the appearance of dark spots, age spots, and other discoloration for a more even-toned skin and luminous, youthful appearance. This product provides intense hydration and refines skin texture to reveal a naturally brighter, more radiant complexion (Test Product A, Even Up® Multi-Correction Serum).

The second product in the regimen also includes the patented Lumira® complex and using iron oxides, immediately corrects skin color and blurs brown spots for more even skin tone, and contains mineral sunscreens to protect against damage from ultraviolet A and B (UVA/UVB) and high energy visible (HEV) light (Test Product B, Even Up® Clinical Pigment Perfector® SPF 50). The third and final step provides additional environmental protection from factors that stimulate hyperpigmentation including UVA/UVB and HEV light and also protects against pollution and infrared radiation to prevent free radical formation, protecting against oxidative stress (Test Product C, Sunforgettable® Total Protection™ Brush-on Shield SPF 50).

The objective of this 12-week open-label clinical trial was to assess the efficacy and tolerability of this novel topical skin care regimen for women and men with moderate-to-severe facial hyperpigmentation.

## METHODS

### 2.1 Subjects

Adult subjects 25–60 years old, with Fitzpatrick skin types I–VI who were seeking treatment for moderate-to-severe uneven facial pigmentation were enrolled. Affected areas included the forehead, cheeks, nose, perioral area, and chin. Men who shaved regularly (at least three times weekly) with no beards were allowed to participate in this study. The study was open to subjects of all races and ethnicities including, but not limited to, Caucasian, African-American, Latino, Asian, Middle Eastern and East Indian.

Reasons for exclusion from study participation included active (flaring) skin diseases such as facial eczema or acne on the planned treatment area; facial plastic surgery or ablative laser resurfacing during the past year; non-ablative laser resurfacing, neurotoxins, and certain medications (minocycline).

### Test products and ingredients

| Test Product A (Even Up® Multi-Correction Serum) | Water/aqua/eau, glycerin, C13-15 alkane, Thermus thermophilus ferment, dimethyl isosorbide, triethylhexanoin, sorbitan stearate, polyglyceryl-2 disostearate, panthenol, triacetate, disodium laurimidopropionate tocopheryl phosphates, polyacrylate crosspolymer-6, Elaeis guineensis (palm) oil, Gossypium herbaceum (cotton) seed oil, aeryl/capric triglyceride, Bidens pilosa (hair beggarticks) extract, cethyl palmitate, Linum usitatissimum (linseed) seed oil, betaine, acetyl Rheum rhaponticum (rhubarb) root extract, Tremella fuciformis sporocarp (mushroom) extract, palmitoyl tetrapeptide-10, sorbityl laurate, polysorbate 80, t-buty alcohol, hydrogenated lecithin, tocopherol, potassium benzoate, potassium sorbate, citric acid, phenoxyethanol, benzoic acid, and dehydroacetic acid. |
|---|---|
| Test Product B (Even Up® Clinical Pigment Perfector® SPF 50) | Titanium dioxide 11.6%, zinc oxide 8.6% with cyclopentasiloxane, isostearyl steareate, dimethicone crosspolymer, Thermus thermophilus ferment, water/aqua/eau, dimethicone/vinyl dimethicone crosspolymer, disodium laurimidopropionate tocopheryl phosphates, panthenol triacetate, acetyl Rheum rhaponticum (rhubarb) root extract, Bidens pilosa (hair beggarticks) extract, Elaeis guineensis (palm) oil, Gossypium herbaceum (cotton) seed oil, Linum usitatissimum (linseed) seed oil, tocopherol, dimethiconol, Citrus paradisi (grapefruit) seed extract, glycerin, dimethicone, Fusanus spicatus wood oil, Vanilla planifolia fruit extract, ascorbic acid, caprylic/capric triglyceride, pentylene glycol, triethoxycaprylylsilane, acrylates/C12-22 alkyl methacrylate copolymer, phenoxyethanol, benzoic acid, dehydroacetic acid, potassium sorbate, farnesol and iron oxides (CI 77491, CI 77492, CI 77499). |
| Test Product C (Sunforgettable® Total Protection Brush-on Shield SPF 50) | Titanium dioxide 22.5%, zinc oxide 22.5% with mica, dimethicone/vinyl dimethicone crosspolymer, dimethiconol/proplisilsequioxane/silicate crosspolymer, Lycoptodium clavatum (club moss) extract, sodium hyaluronate, Imperata cylindrica (cogongrass) root extract, glycerin, water, Caesalpinia spinosa (tara) fruit pod extract, Vitis vinifera (grape) seed extract, Camellia sinensis leaf extract, Quercus robur (oak) wood extract, Helianthus annuus (sunflower) sprout extract, maltodextrin, methicone, triethoxycaprylylsilane, laureth-4, sodium benzoate, potassium sorbate, chromium oxide greens (CI 77288), and iron oxides (CI77491, CI 77492, CI 77499). |
or dermal fillers during the previous 3 months; superficial resurfacing treatment (chemical peels, microdermabrasion, micro-needling); neurotoxin or dermal fillers during the previous 6 weeks; allergy to any of the ingredients include in the test products; presence of an autoimmune disease; pregnancy or planned pregnancy or planned changes their oral contraceptive routine.

Enrolled subjects expressed their willingness to limit their sun exposure, including traveling to hot/sunny places in which would increase daily sun exposure compared to their home; limit outdoor activities such as hiking, running, or swimming beyond their normal routine; and avoid facial makeup tattoos including but not limited to eyebrows, eyeliner, lips or lash extensions during the 12-week study.

Subjects were divided into two groups. Subjects in Group A presented with moderate-to-severe facial hyperpigmentation and were not using any prescription or advanced or physician dispensed skincare product containing ingredients known to affect hyperpigmentation, such as vitamin A derivatives, hydroquinone, resorcinol or tranexamic acid.

Subjects in Group B were currently using advanced skin care products to address their uneven facial hyperpigmentation using topical prescription products including hydroquinone and non-hydroquinone products, retinoic acids and/or antioxidants alone or in combination, for at least 3 months and they continued using these products during the study.

2.2 | Procedures

Subjects in Group A were provided with the skincare product regimen to be used as follows: each morning, each subject washed their face with a nonmedicated cleanser provided or approved by the study sponsor. Immediately after cleansing, subjects applied 2–3 pumps of Test Product A followed by a nonmedicated moisturizing lotion, as needed. One pump of Test Product B was then applied to the entire face. Test Product C was reapplied at least three times during the day or every 2 h. Every evening, each subject washed their face using a nonmedicated cleanser to remove makeup and daily debris. Immediately after cleansing, subjects applied 2–3 pumps of Test Product A followed by their nonmedicated moisturizer.

Subjects in Group B were provided with skincare regimen study products to be used as follows: each morning, subjects washed their faces using their usual facial cleanser. Immediately after cleansing, they applied their topical prescription and/or physician dispensed products for treating hyperpigmentation, with the addition of 2–3 pumps of the Test Product A, followed by a nonmedicated moisturizer lotion, as needed, and one pump of Test Product B. Test product C was applied at least three times throughout the day or every 2 h. Every evening, subjects washed their faces using their usual facial cleanser to remove makeup and daily debris. Immediately afterwards. Subjects applied their prescription and or physician dispensed products for treating facial hyperpigmentation with the addition of 2–3 pumps of Test Product A and their nonmedicated moisturizer lotion.

2.3 | Study Assessments

Subjects were evaluated at baseline and Weeks 2, 4, 8 and 12. Subjects were to wash their face and remove any makeup at least 30 min prior to each scheduled visit. Subjects refrained from any exercise activities, hot or spicy foods or beverages, smoking, or sun exposure for at least 1 h prior to each study visit and acclimated to ambient temperature and humidity conditions of the study site for at least 15 min prior to evaluation procedures.

The Melasma Area and Severity Index (MASI) score was determined at baseline and each visit as described elsewhere. MASI scores were calculated by investigator assessment of area of involvement, darkness and homogeneity of the total face. Facial areas were forehead (30%), right malar region (30%), left malar region (30%) and chin (10%). The area of involvement in each facial area was given a numeric value of 0 to 6 (0, no involvement; 1, <10%; 2, 10%–29%; 3, 30%–49%; 4, 50%–69%; 5, 70%–89%; 6, 90%–100%). Darkness and homogeneity were rated on a scale from 0 to 4 (0, absent; 1, slight; 2, mild; 3, marked; 4, maximum). MASI scores are calculated by adding the sum of the severity ratings for darkness and homogeneity, multiplied by the value of the area of involvement, for each of the four facial areas, resulting in a total score from 0 to 48.

Facial cutaneous tolerability was evaluated by assessing the signs and symptoms of objective and subjective irritation on the face at baseline and Weeks 2, 4, 8 and 12. Objective irritation was clinically graded by the investigator, with an emphasis on erythema, edema, dryness, scaling, stinging, and burning at each visit.

- Erythema: 0, No erythema of the treatment area; 1, Mild. Slight, but definite redness of the treatment area; 2, Moderate. Definite redness of the treatment area; 3, Severe. Marked redness of the treatment area.
- Edema: 0, No edema/swelling of the treatment area; 1, Mild. Slight, but definite edema of the treatment area; 2, Moderate. Definite edema of the treatment area; 3, Severe. Marked edema of the treatment area.
- Dryness: 0, No dryness of the treatment area; 1, Mild. Slight but definite dryness of the treatment area; 2, Moderate. Definite dryness of the treatment area; 3, Severe. Marked dryness of the treatment area.
- Scaling: 0, No scaling of the treatment area; 1, Mild. Barely perceptible, fine scales in limited areas of the treatment area; 2, Moderate. Fine scaling generalized to all areas of the treatment area; 3, Severe scaling and peeling of skin over all areas of the treatment area.
- Burning: 0, No burning of the treatment area; 1, Mild. Slight burning sensation of the treatment area; not really bothersome; 2, Moderate. Definite warm, burning of the treatment area that is somewhat bothersome; 3, Severe. Hot burning sensation of the treatment area that causes definite discomfort and may interrupt daily activities and/or sleep.
- Stinging: 0, No stinging of the treatment area; 1, Mild. Slight stinging sensation of the treatment area; not really bothersome;
2. Moderate. Definite stinging of the treatment area that is somewhat bothersome; 3. Severe. Marked stinging sensation of the treatment area that causes definite discomfort and may interrupt daily activities and/or sleep.

Digital images were obtained at baseline and Weeks 2, 4, 8 and 12 (VISIA® CR Imaging System; Canfield Scientific, Fairfield, NJ). Three images were obtained of each subject’s face (left, center, and right views) under standard bright visible, standard visible, and standard raking under cross-polarized and parallel-polarized lighting conditions. Clinic personnel ensured that each subject had a clean face, no jewelry in the areas to be photographed, used a headband to keep hair away from the face and a black matte cloth to drape over their clothing. Subjects were instructed to adopt neutral, non-smiling expressions with their eyes gently closed and chin softly positioned over a chin-rest.

The investigator assessed changes in subject appearance of fine lines, wrinkles, smoothness (tactile), mottled hyperpigmentation, and firmness/laxity using a 5-point Global Improvement Scale: 0, worse; 1, no improvement; 2, mild improvement (25% overall improvement); 3, moderate improvement (50% overall improvement); or 4, marked improvement (75% overall improvement) at Weeks 2, 4, 8 and 12. All assessments were made by the same investigator to maintain consistent results.

Both subjects and Investigator complete self-assessment questionnaires at Weeks 2, 4, 8, and 12 by responding whether that Agree or Disagree with a series of questions about their treatment results and treatment experience.

2.4 | Ethics

Written informed consent conforming to Title 21 Code of Federal Regulations 50.25 was obtained from each subject prior to participating in any study-related activities. This protocol and related materials were approved by a commercial institutional review board (Aspire IRB; Santee, CA). Each subject agreed to permit the use of unblinded images for scientific publication.

2.5 | Statistical Analysis

Statistical analyses were performed using commercial software (SPSS® Statistics for Windows, Version 27.0; IBM® Corporation, Armonk, NY). Frequencies, means, standard deviations, and medians were calculated to summarize subject demographics and survey data collected from subjects and the Investigator. The 33 enrolled subjects were sufficient to detect significant changes over time and between groups. Chi-square tests (or Fisher’s exact tests for small sample sizes, when appropriate) were used to compare responses between subject Groups A and B. Two-tailed tests were used with significance established at $p < 0.05$.

| TABLE 2 | Subject demographics and baseline characteristics |
|---------|--------------------------------------------------|
|         | Group A (n = 23) | Group B (n = 10) | p-Value |
| Mean Age, years (SD) | 45.7 (10.5) | 47.7 (5.4) | 0.466 |
| Median Age, years (min, max) | 46.0 (22, 59) | 47.5 (40, 55) |
| Fitzpatrick Skin Type, n (%) | | | |
| II | 6 (21.1) | 2 (20.0) | 0.114 |
| III | 8 (34.8) | 0 |
| IV | 6 (26.1) | 7 (70.0) |
| V | 2 (8.7) | 1 (10.0) |
| VI | 1 (4.3) | 0 |

2.6 | Safety

Safety assessments were based on reports of adverse events and visual examination of the facial treatment area by the investigator.

3 | RESULTS

Male and female subjects (N = 33) were randomized to Group A (n = 23) and Group B (n = 10) and all subjects completed the trial. Demographics and baseline characteristics are summarized in Table 2.

3.1 | Investigator Efficacy Results

The overall median (range) baseline MASI score at baseline was 9.0 (2, 31), decreasing by 0.0 (2, 30) points at Week 2 ($p = 0.002$), 0.6 (−8, 0) points at Week 4 ($p < 0.0001$), 1.5 (−16, 0) points by Week 8 ($p < 0.0001$) and 2.4 (−20, 0) points at Week 12 ($p < 0.0001$). At Week 12, the overall median improvement in MASI score was 26% and higher for Group B (32% vs 22%).

As early as Week 2, the Investigator reported most subjects had lighter brown spots that were less noticeable (76%), the skin of nearly all subjects appeared more even in tone, was brighter, more luminous and looked younger (97%). Nearly all had overall improvements in skin appearance (97%), and the skin of all subjects looked and felt healthier, was more hydrated/less dry and had a smoother/softer/less rough texture (100%). By Week 12, the Investigator reported improvements for all subjects (100%). These included incremental improvements among subjects in Group B subjects in addition to their existing advanced skincare routine (Table 3).

At Week 12, the investigator reported 64% of all subjects had mild-marked Global Improvement in skin quality and appearance (Table 4). Fewer subjects in Group B reported worsening or no change in skin quality or appearance. The change in hyperpigmentation is apparent in several representative subjects (Figures 1-5).
### 3.2 Subject Efficacy Results

As early as Week 2, most subjects reported that the skincare regimen made their brown spots lighter and less noticeable (76%), made their skin brighter and more luminous (88%) with more even skin tone (67%), made their skin look and feel healthier (85%), made their skin look younger (57.6%), made their skin feel more hydrated/less dry (85%), that the skincare regimen made their skin texture smoother/softer (76%), improved the overall appearance of their skin (79%) and were more confident about their overall skin appearance (70%). These measures had improved substantially by Week 12 (Table 5). Improvements in skin quality and appearance were generally greater among subjects in Group B.

### 3.3 Safety

No adverse events were observed or reported for any subjects at any time points during the study. Overall, the regimen was...
**FIGURE 1** Group A Subject. This was a 33-year-old subject with Fitzpatrick Skin Type IV. Her MASI Score was 11.4 at Baseline (left), 11.6 at Week 4 (center) and 8.4 at Week 12 (right), a 26.0% improvement.

**FIGURE 2** Group A Subject. This was a 56-year-old subject with Fitzpatrick Skin Type IV. Her MASI Score was 24.0 at Baseline (left), 23.9 at Week 4 (center) and 11.7 at Week 12 (right), a 51.0% improvement.
well-tolerated. This hyperpigmentation regimen was safe to use on all skin types and skin tones.

4 | DISCUSSION

The objective of this trial was to assess the efficacy and tolerability of a novel skincare regimen for subjects with moderate-to-severe facial hyperpigmentation including several subjects with Fitzpatrick Skin Types IV, V and VI. Based on the Investigator Global Improvement scale, improvement was noted as early as 2 weeks with continued improvement throughout the 12-week trial. Improvements were somewhat greater among Group B subjects. Similarly, the Investigator Efficacy Questionnaire results showed substantial improvements at 2 weeks, reaching nearly 100% for all responses at 8 weeks and 100% at 12 weeks.

The Subject Efficacy Questionnaire also showed steady improvement throughout the trial as 100% of subjects reported their skin looked brighter and more luminous at 8 weeks and 100% were more confident about skin appearance at 12 weeks.

Numerous therapies have been developed for the treatment of facial hyperpigmentation. Commonly used topical treatments

FIGURE 3 Group A Subject. This was a 42-year-old subject with Fitzpatrick Skin Type III. Her MASI score was 12.6 at baseline (top row), 9.3 at Week 4, and 3.9 a Week 12 (bottom row), a 69.0% improvement

FIGURE 4 Group B Subject. This was a 54-year-old subject with Fitzpatrick Skin Type IV. Her MASI Score was 10.8 at Baseline (left), 10.8 at Week 4 (center) and 6.0 at Week 12 (right), a 44.4% improvement
include hydroquinone\textsuperscript{17,18} and tretinoin/retinoic acid.\textsuperscript{19,20} In one study, there was an improvement in facial post-inflamatory hyperpigmentation after 4 weeks of treatment with isotretinoin, reaching 40\% lightening after 40 weeks.\textsuperscript{21} In a similar study, there was a 32\% improvement MASI score among subjects with melasma treated with tretinoin for 40 weeks.\textsuperscript{16} These results compare favorably with decreased brown spots and less noticeable skin discoloration and 12-week improvement in MASI scores in the present study. Additional improvement in hyperpigmentation related to photodamaged skin and melasma with tretinoin is slow, requiring 6–10 months of treatment.\textsuperscript{19,20,22,23} Treatment with topical tretinoin is often associated with mild-to-moderate skin reactions.\textsuperscript{22,24}

Hydroquinone has long been considered the gold-standard for skin lightening\textsuperscript{17,18}; however, its safety has recently been questioned.\textsuperscript{25} Due to numerous reports of ochronosis, a blue-black skin pigmentation\textsuperscript{26} and other safety issues related to the use of topical hydroxyquinone products,\textsuperscript{27–29} the Food and Drug Administration proposed a rule in 2006 that classified OTC skin bleaching drug products including hydroquinone as Category II, not generally recognized as safe and effective (GRASE).\textsuperscript{30} The rule was finalized as a result of the OTC reform bill in 2020 as part of the Coronavirus Aid, Relief, and Economic Security Act (CARES) Act passed by Congress. Perhaps partly for this reason, there has been an increased interest in products that can address skin brightening and the appearance of brown spots without hydroquinone.\textsuperscript{31–34}

This skin care regimen employs a unique approach to addressing hyperpigmentation, providing rapid improvement in appearance while protecting against further melanogenesis.\textsuperscript{35} The morning/evening Product A incorporates the proprietary Lumira™ complex which addresses each of the four phases of the melanin pathway together with the ingredient Crystalide™, a novel time-release peptide that improves cellular renewal, increases and maintains moisturization and visibly improves skin luminosity. The three-in-one morning Product B is also formulated with Lumira™ plus all-mineral SPF 50 sunblocks which attenuate environmental injury while the brush-on, triple-coated all-mineral SPF 50 powder provides added skin protection throughout the day.

In this study, the skin care regimen demonstrated a 26\% MASI score improvement after 12 weeks for subjects with Fitzpatrick Skin Types II–VI who presented with moderate-to-severe hyperpigmentation. Unlike other studies of similar skin care products, improvement in the appearance of brown spots (75.8\%), even skin tone (66.7\%), texture (75.8\%) and radiance (87.9\%) were reported as early as 2 weeks based on subject and investigator assessments for all subjects.

Importantly, this novel skincare regimen provided incremental improvement among subjects currently being treated for facial hyperpigmentation (Group B). These treatments included hydroquinone and retinoic acid, alone or in combination with each other or other physician-dispensed advanced skin care products. These results suggest that the addition of a novel regimen that includes both treatment products and novel mineral sun protection may provide meaningful additional benefits to patients that are already on a hyperpigmentation regimen.

Other treatments for hyperpigmentation are minimally-invasive, office-based procedures such as chemical peels,\textsuperscript{36} microneedling,\textsuperscript{37} lasers\textsuperscript{38–40} and intense pulsed light,\textsuperscript{41} alone or in combination. While effective, these techniques may require multiple treatment sessions in a clinic or office setting and can be associated with periods of downtime. Care must be taken when treating darker-skinned patients as these resurfacing treatments can also worsen some kinds of hyperpigmentation.\textsuperscript{10,42}
Regardless of the treatment used for addressing hyperpigmentary conditions, the use of an effective sunscreen is an essential part of therapy to prevent the relapse of pigmentary changes. The Test Products B and C used in this study contain only mineral active ingredients titanium dioxide and zinc oxide providing SPF 50 protection against UVA and UVB radiation. The addition of iron oxides provides additional protection against HEV light. In addition to preventing unwanted pigment changes, these sunscreens help protect against other damaging effects of UV radiation including skin atrophy, skin laxity, rhytids, loss of elasticity and resilience, and DNA damage leading to skin cancers.

A limitation to the study was the inability to control for the amount of sun exposure experienced by each subject. Subjects with occupational sun exposure should be encouraged to wear hats and protective clothing. The investigator was not blinded to treatments.

5 | CONCLUSION

Following the daily use of this novel skin care regimen, subjects achieved improvements after 2 weeks, ultimately reaching a 26% improvement MASI in scores after 12 weeks. Subjects currently receiving topical treatment for facial hyperpigmentation achieved incremental improvements. This hyperpigmentation treatment regimen was safe to use on all skin types and tones and provides novel ingredients to address the appearance of facial hyperpigmentation and provides skin protection against the damaging effects of ultraviolet and high energy visible radiation.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

ETHICAL STATEMENT

Written informed consent conforming to Title 21 Code of Federal Regulations 50.25 was obtained from each subject prior to

| TABLE 5 (Continued) |
|---|
| TABLE 5 Subject efficacy questionnaire |
| Positive responses, n (%) | Group A (n = 23) | Group B (n = 10) | p-Value |
| **Brown spots are lighter?** | | | |
| Week 2 | 18 (73.8) | 7 (70.0) | 0.673 |
| Week 4 | 21 (91.3) | 10 (100.0) | 1.000 |
| Week 8 | 22 (95.7) | 10 (100.0) | 1.000 |
| Week 12 | 21 (91.3) | 9 (90.0) | 1.000 |
| **Skin discoloration less noticeable?** | | | |
| Week 2 | 17 (73.9) | 8 (80.0) | 1.000 |
| Week 4 | 21 (91.3) | 10 (100.0) | 1.000 |
| Week 8 | 21 (91.3) | 9 (90.0) | 1.000 |
| Week 12 | 22 (95.7) | 9 (90.0) | 0.521 |
| **Skin looks brighter and more luminous?** | | | |
| Week 2 | 20 (87.0) | 9 (90.0) | 1.000 |
| Week 4 | 21 (91.3) | 10 (100.0) | 1.000 |
| Week 8 | 23 (100.0) | 10 (100.0) | * |
| Week 12 | 23 (100.0) | 10 (100.0) | * |
| **Skin tone is more even?** | | | |
| Week 2 | 14 (60.9) | 8 (80.0) | 0.430 |
| Week 4 | 20 (87.0) | 10 (100.0) | 0.536 |
| Week 8 | 20 (87.0) | 10 (100.0) | 0.536 |
| Week 12 | 22 (97.7) | 9 (90.0) | 0.521 |
| **Skin looks and feels healthier?** | | | |
| Week 2 | 19 (82.6) | 9 (90.0) | 1.000 |
| Week 4 | 20 (87.0) | 10 (100.0) | 0.536 |
| Week 8 | 21 (91.3) | 10 (100.0) | 1.000 |
| Week 12 | 21 (91.3) | 10 (100.0) | 1.000 |
| **Skin looks younger?** | | | |
| Week 2 | 12 (52.2) | 7 (70.0) | 0.455 |
| Week 4 | 16 (69.4) | 9 (90.0) | 0.217 |
| Week 8 | 15 (65.2) | 10 (100.0) | 0.071 |
| Week 12 | 18 (73.8) | 9 (90.0) | 0.640 |
| **Skin looks more hydrated/less dry?** | | | |
| Week 2 | 19 (82.6) | 9 (90.0) | 1.000 |
| Week 4 | 19 (82.6) | 10 (100.0) | 0.289 |
| Week 8 | 20 (87.0) | 10 (100.0) | 0.536 |
| Week 12 | 21 (91.3) | 10 (100.0) | 1.000 |
| **Skin texture is smoother/less rough?** | | | |
| Week 2 | 16 (69.4) | 9 (90.0) | 0.382 |
| Week 4 | 22 (95.7) | 9 (90.0) | 0.521 |
| Week 8 | 17 (73.9) | 10 (100.0) | 0.145 |
| Week 12 | 21 (91.3) | 10 (100.0) | 1.000 |
| **Overall skin appearance is improved?** | | | |
| Week 2 | 17 (73.9) | 9 (90.0) | 0.397 |
| Week 4 | 21 (91.3) | 10 (100.0) | 1.000 |
| Week 8 | 22 (95.7) | 9 (90.0) | 0.521 |
| Week 12 | 23 (100.0) | 9 (90.0) | 0.303 |

* p-Value not calculated because scores were constant.
participating in any study-related activities. This protocol and related materials were approved by a commercial institutional review board (Aspire IRB; Santee, CA). Each subject agreed to permit the use of unblinded images for scientific publication.

DATA AVAILABILITY STATEMENT
There are no additional unpublished data associated with this study.

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