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 ORIGINAL ARTICLE

Evaluation of an Advanced, Multimodal Skin Tone Correcting Serum in Participants With Mild-to-Severe Dyschromia and Hyperpigmentation

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ABSTRACT

Background: A new multimodal skin tone correcting serum formulated with *b.r.y.t.e.r.* (*b*rown, *r*ed, and *y*ellow tones with *e*nhanced *r*esurfacing) technology (EV-I) targets brown, red, and yellow dyschromia and acts through 5 pathways of melanin synthesis to reduce pigmentation, resurface and exfoliate skin, and improve overall skin tone.

Methods: A single-center, open-label, 12-week trial enrolled females with mild-to-severe dyschromia/hyperpigmentation. EV-I was applied twice daily for 12 weeks, with a subset of participants also applying a double-conjugated retinoid/AHA cream (AHARet) nightly. Pigmentation was graded using the Melasma Area and Severity Index (MASI) scale at baseline and at weeks 2, 4, 8, and 12. Skin dullness and texture were assessed using a 6-point grading scale. Erythema and dryness/flaking were assessed using a 4-point grading scale. Participant satisfaction and adverse events (AEs) were collected over 12 weeks.

Results: Sixty-five participants were enrolled (EV-I, n=40; EV-I/AHARet, n=25) with a mean age of 53 years; 78% of participants had Fitzpatrick skin types (FST) I-III, 22% were FST IV-VI. The majority of participants presented with moderate-to-severe dyschromia/hyperpigmentation. Significant percent improvements from baseline were demonstrated based on MASI scores at 12 weeks (EV-I, 42%, EV-I/AHARet, 47% [all, $P<.0001$]). Significant improvements from baseline were demonstrated in the appearance of skin texture (EV-I, 46%; EV-I/AHARet, 59% [all, $P<.0001$]) and dullness (EV-I, 47%; EV-I/AHARet, 59% [all, $P<.0001$]) at 12 weeks. No increases in erythema or dryness/flaking were observed.

Conclusions: A new multimodal skin tone correcting serum demonstrated significant improvements in MASI scores and in the appearance of skin texture and dullness. Significant improvements were also achieved in participants using both the skin tone correcting serum and double-conjugated retinoid/AHA cream. Participants reported high levels of satisfaction over 12 weeks.

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INTRODUCTION

Melanin provides pigmentation to skin, hair, and eyes and protects epidermal cells by absorbing harmful ultraviolet (UV) rays. Hyperpigmentation results from excess, cumulative melanin triggered by extrinsic aggressors such as UV radiation and pollution, and intrinsic factors including genetics, hormonal fluctuations, and imbalances that induce oxidative stress.[1-3]

Melanogenesis is a complex biochemical process that involves multiple pathways.[4] Among the primary cell signaling pathways that influence skin pigmentation are melanocyte activation, melanosome formation, melanin synthesis, and melanin transfer and removal.[4] Melanocyte activation and formation can be triggered by UV exposure, pregnancy, other hormonal fluctuations, inflammation, and aging. Sun exposure causes the body to increase production of melanin to defend against UV rays, increasing skin pigmentation. UV radiation produces free radicals, which, along with UV light, activate biological mechanisms that impact melanocytes.[5] In the presence of tyrosinase, a key enzymatic regulator of melanin production,[6] the amino acid L-tyrosine is converted to dopaquinone (DOPA), which is then transformed into either eumelanin (black-brown pigmented melanin) or pheomelanin (yellow-red pigmented melanin).[4,5]

Multiple modalities or agents are often required to manage hyperpigmentation sufficiently, and strategies always include routine, daily use of sunscreen and sun-protective measures. In an effort to address the multiple pathways involved in the development of melanin, recommended regimens often include the adjunctive use of several topical prescription and/or nonprescription products, including hydroquinone (HQ), retinoids, alpha-hydroxy acids (AHAs), and antioxidants.[7-13]

Prescription HQ has been the standard treatment for hyperpigmentation due to its ability to inhibit tyrosinase and reduce the conversion of DOPA to melanin.[14,15] However, due to its association with adverse events such as erythema, irritant or allergic contact dermatitis, and, in rare cases, ochronosis, use is limited to 3- to 4-month cycles, and its use is banned in some countries.[16]

A non-hydroquinone skin tone correcting formulation comprising *b.r.y.t.* (*b*rown, *r*ed, *y*ellow *t*ones) technology was developed to address 4 core pathways of pigmentation – melanocyte activation, melanosome formation, melanin synthesis, and melanin transfer.[17] The formulation was designed to interrupt the pigment cascade, correct redness and sallow skin, and improve skin texture.[17,18] Results from an initial clinical study in 52 participants who used this topical serum twice-daily demonstrated significant mean percent reductions from baseline in the appearance of dyschromia/hyperpigmentation after 12 weeks (-31%; *P*<.0001) based on a 6-point grading scale (0=None to 5=Severe), with a subset of participants combining use with a double-conjugated retinoid/alpha hydroxy acid cream (AHARet; PM only) demonstrating a 44% reduction (*P*<.0001) in the appearance of dyschromia/hyperpigmentation from baseline after 12 weeks.[17]

A new, advanced multimodal skin tone correcting serum formulated with *b.r.y.t.e.r.* technology (*b*rown, *r*ed and *y*ellow *t*ones with *e*nhanced *r*esurfacing) has been developed to uniformly improve the appearance of photodamaged skin by addressing persistent hyperpigmentation, redness, and yellow, sallow-looking skin with the incorporation of additional ingredients such as tranexamic acid, phenylethyl resorcinol, allyl pyrroloquinoline quinone (PQQ; antioxidant), acetyl glycyl beta-alanine (peptide), and a blend of alpha hydroxy acids (AHAs) comprising glycolic, lactic, and citric acids. This new formulation (EV-I) targets 5 key pathways of pigmentation: (1) melanocyte and (2) tyrosinase stimulation, (3) melanosome maturation, (4) melanosome transport, and (5) melanin removal or surface reduction.[18] The current study described herein evaluated the effectiveness and tolerability of this new, multimodal skin tone correcting serum in participants with mild-to-severe dyschromia/hyperpigmentation.

MATERIALS AND METHODS

This single-center, open-label trial was conducted under Institutional Review Board approval (Allendale Institutional Review Board, CT) in conjunction with Good Clinical Practice (cGCP) guidelines. A board-certified dermatologist recruited and enrolled healthy females, all of whom signed written informed consents prior to study participation.

The 12-week study enrolled female participants, aged 30 to 65 years, with mild (2) to severe (4) dyschromia/hyperpigmentation according to a 6-point grading scale (0=None to 5=Very Severe). Participants were deemed eligible for inclusion following a 2-week washout of alpha hydroxy acids (AHAs), beta hydroxy acids (BHAs), antioxidants, peptides, or nonprescription topical retinoids, and a 4-week washout of prescription topical products including tretinoin, hydroquinone, retinoids, corticosteroids, or medications for rosacea. Participants with severe lines/wrinkles, skin laxity, melasma, post-inflammatory hyperpigmentation (PIH), or scarring (acne or surgical) were excluded from study participation, as were participants with active or a history of atopic dermatitis or psoriasis, keloid scarring, or lupus erythematosus, or who were planning to become pregnant, were pregnant, or lactating. All participants were required to minimize UV exposure, apply the provided sunscreen daily, and wear sun-protective clothing.

Participants were instructed to apply the study product (EV-I) twice daily for 12 weeks (AM/PM) after cleansing their face, followed by a moisturizer (AM/PM) and sunscreen (AM). A subset of participants (n=25) also applied AHARet nightly for 12 weeks after applying EV-I.

All investigator assessments occurred at baseline and at weeks 2, 4, 8, and 12. Investigator evaluation of pigmentation was assessed using the Melasma Area and Severity Index (MASI) scale in which each area of involvement is assigned a numeric value of 0 (No Involvement) to 6 (90%-100% Involvement), resulting in a total MASI score range of 0 to 48.[19] The investigator also assessed skin dullness and texture/roughness using a 6-point grading scale (0=None to 5=Very Severe), and erythema and dryness/flaking using a 4-point grading scale (0=None to 3=Severe). In addition, participants completed self-assessment questionnaires at weeks 2, 4, 8, and 12. Adverse events (AEs) were collected throughout the study period.

RESULTS

Demographics

Sixty-five (65) participants were enrolled and completed the study. Participants were randomized to 2 groups, EV-I (n=40) and EV-I/AHARet (n=25, Table 1). Both groups were similar, with a mean age of 53 years, and the majority of females presented with moderate dyschromia/hyperpigmentation. Among the participants in the EV-I group, 93% were non-Hispanic, and 70% were Caucasian; 77% were FST I-III, 23% were FST IV-V. Similarly, 96% of participants in the EV-I/AHARet group were non-Hispanic, 76% were Caucasian, 80% were FST I-III, and 20% were FST IV-VI.

Efficacy

Significant mean percent reductions from baseline were demonstrated in MASI scores at 12 weeks in the EV-I group (-42%; *P*<.0001; Figure 1) and in the combination use group (EV-I/AHARet, -47%; *P*<.0001; Figure 2). A post-hoc analysis

TABLE 1.

Baseline Demographics				
Baseline Demographics	EV-I (n=40)		EV-I/AHARet (n=25)	
Mean Age (Range)	53 yrs (34 – 64)		53 yrs (38 – 65)	
Race	African American: 23%		African American: 20%	
	Caucasian: 70%		Caucasian: 76%	
	Other: 7%		Other: 4%	
Ethnicity	Hispanic: 7%		Hispanic: 4%	
	Non-Hispanic: 93%		Non-Hispanic: 96%	
Fitzpatrick Skin Type	FST I: 27%	FST IV: 3%	FST I: 20%	FST IV: 4%
	FST II: 45%	FST V: 20%	FST II: 56%	FST V: 12%
	FST III: 5%	FST VI: 0%	FST III: 4%	FST VI: 4%
Severity (Dyschromia)	Mild: 23%		Mild: 16%	
	Moderate: 70%		Moderate: 80%	
	Severe: 8%		Severe: 4%	

conducted in participants with FST IV-V (n=9) in the EV-I group demonstrated a 48% reduction from baseline in MASI scores at week 8 and a 68% reduction from baseline in MASI scores at week 12 (all, *P*<.05) with no observable increase in PIH. Participants in this group presented with either mild or moderate dyschromia/hyperpigmentation at baseline.

Significant mean improvements from baseline were demonstrated in both groups in the appearance of skin texture/roughness (EV-I, 46%; EV-I/AHARet, 59%) and skin dullness (EV-I, 47%; EV-I/AHARet, 59%) at 12 weeks (all, *P*<.0001; Figures 3, 4). No increases in erythema or dryness/flaking were observed in either group (Figures 5-8).

Participant Satisfaction

Participant satisfaction was high in both groups throughout the study, with most reporting that their skin tone was more even-looking (EV-I, 95%; EV-I/AHARet, 88%), looked brighter (EV-I, 98%; EV-I/AHARet, 96%), and the overall appearance of their skin improved (EV-I, 95%; EV-I/AHARet, 96%) at week 12.

At 4 weeks, 93% of participants in the EV-I group reported that their skin tone was more even-looking, 98% reported their skin looked brighter, and 93% reported the overall appearance of their skin improved. Ninety percent (90%) of participants reported that the brown/dark spots or patches on their skin were lighter in appearance after 12 weeks.

Ninety-two percent (92%) of participants in the EV-I/AHARet group reported that their dark spots were lighter in appearance and their skin tone looked more even and smoother at week 4. After 12 weeks, 96% of participants reported that their skin appeared brighter, less dull, and less discolored, 88% reported that the brown/dark spots or patches on their skin were lighter in appearance, and 100% reported feeling more confident in the appearance of their skin.

FIGURE 1. Mean percent reduction in MASI (EV-I Group, n=40).

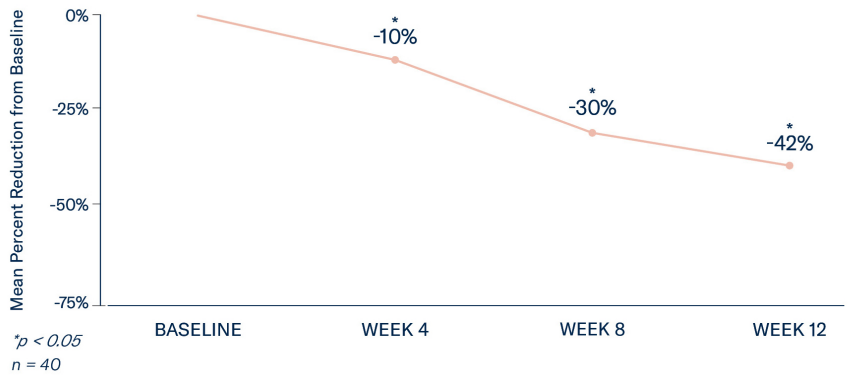


FIGURE 2. Mean percent reduction in MASI (EV-I/AHARet Group, n=25).

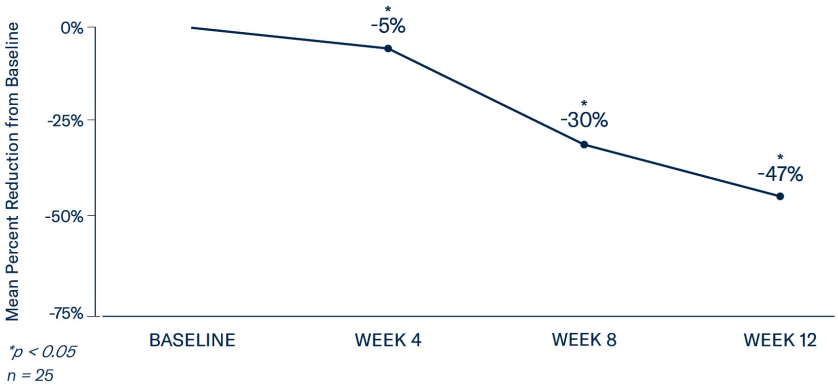


FIGURE 3. Mean percent improvement in the appearance of skin texture and skin dullness (EV-I Group, n=40).

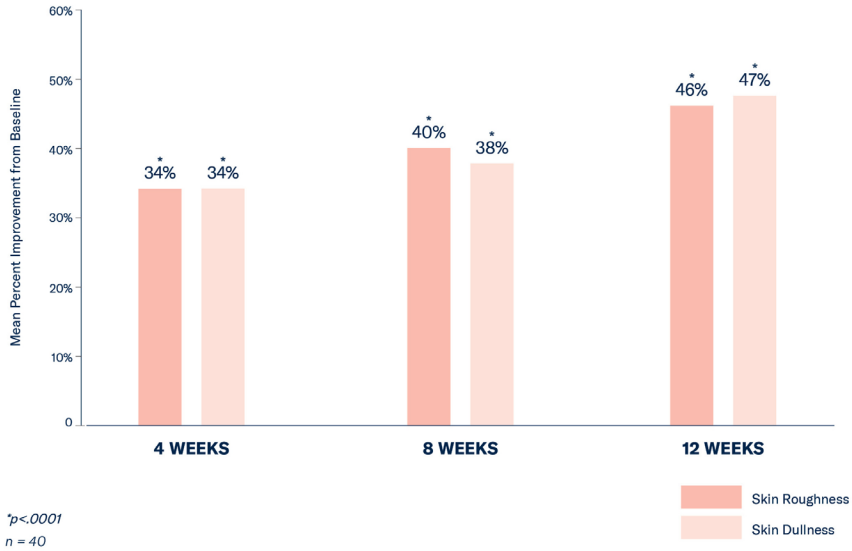


FIGURE 4. Mean percent improvement in the appearance of skin texture and skin dullness (EV-I/AHARet Group, n=25).

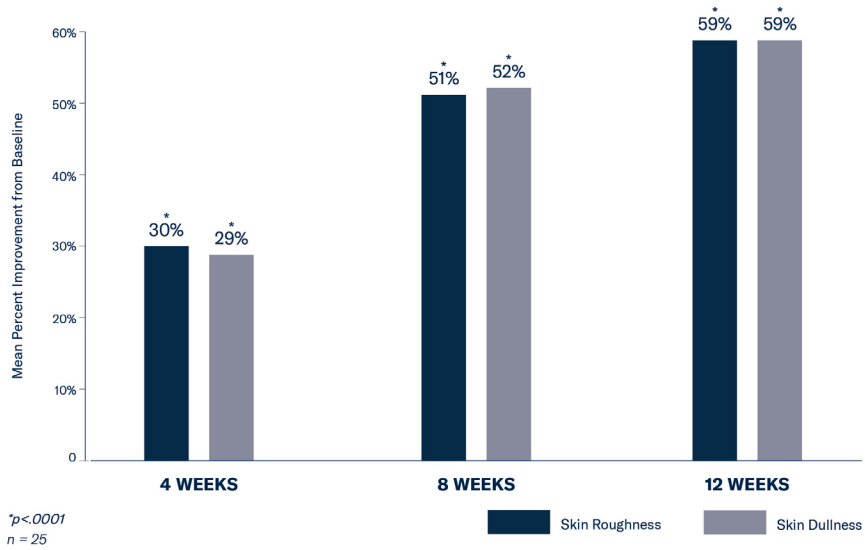
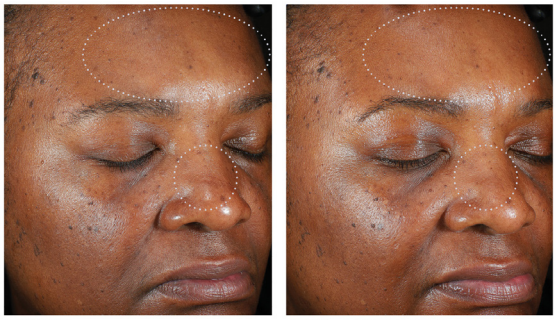
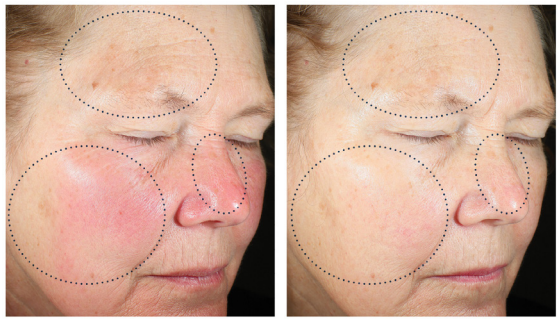


FIGURE 5. Visible improvements demonstrated after 12 weeks (EV-I Group).



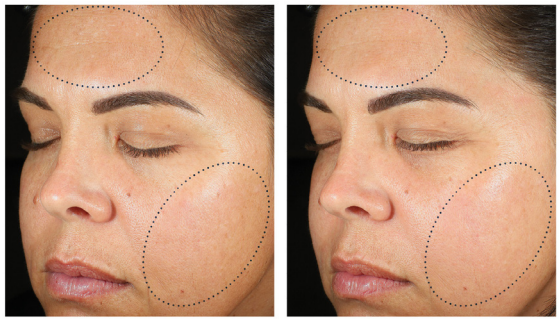
*Unretouched clinical photography on clean, product-free skin. **Image descriptions are based on average measurements of MASI from baseline at 12 weeks, separately assessed in patients using EV-I (n=40) and EV-I/AHARet (n=25).

FIGURE 6. Visible improvements demonstrated after 12 weeks (EV-I Group).



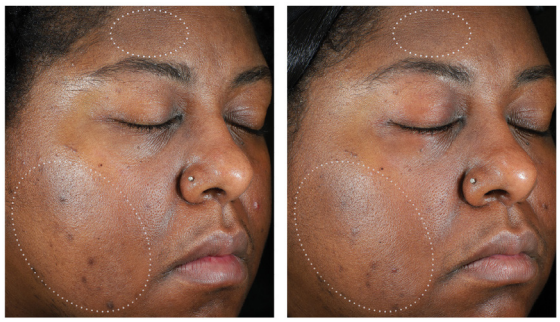
*Unretouched clinical photography on clean, product-free skin. **Image descriptions are based on average measurements of MASI from baseline at 12 weeks, separately assessed in patients using EV-I (n=40) and EV-I/AHARet (n=25).

FIGURE 7. Visible improvements demonstrated after 12 weeks (EV-I/AHARet Group).



*Unretouched clinical photography on clean, product-free skin. **Image descriptions are based on average measurements of MASI from baseline at 12 weeks, separately assessed in patients using EV-I (n=40) and EV-I/AHARet (n=25).

FIGURE 8. Visible improvements demonstrated after 12 weeks (EV-I/AHARet Group).



*Unretouched clinical photography on clean, product-free skin. **Image descriptions are based on average measurements of MASI from baseline at 12 weeks, separately assessed in patients using EV-I (n=40) and EV-I/AHARet (n=25).

DISCUSSION

The complex nature of melanogenesis and the diverse underlying etiologies make hyperpigmentation challenging to manage.[20] Treatment regimens often include the use of multiple topical agents, some of which may be irritating to the skin, impeding adherence, and influencing suboptimal outcomes.[13,21] In addition, treatment regimens involving multiple products can be costly and cumbersome for patients to manage, highlighting the need for tolerable, efficacious, and streamlined regimens to facilitate adherence and optimize results.

It is imperative that treatment strategies integrate sun-protective measures to minimize the consequences of sun exposure. In addition, numerous nonprescription topical ingredients have been shown to afford unique benefits in improving the appearance of hyperpigmented skin. The key ingredients in the formulation used in this study were selected owing to their specific benefits in addressing the 5 pathways of pigmentation (Table 2).[20,25-47] To facilitate a uniform, brighter skin tone, the active ingredients in EV-I help minimize the appearance of skin discoloration, brown patches and spots, and red, yellow, sallow-looking, and dull skin often caused by photodamage.

A subset of participants also applied AHARet cream in the evening. The intent of the study design was to ascertain incremental benefits associated with the combination use of the skin tone correcting serum and a double-conjugated retinoid/AHA cream. The unique structure of the AHARet molecule enables the gradual release of a retinoid and lactic acid to minimize irritation. Other ingredients contained in AHARet

TABLE 2.

Key Ingredients		
Category	**Ingredient**	**Properties**
b.r.y.t.e.r. Technology	Acetyl glycyl beta-alanine	Peptide that interferes with production and transport of melanosomes.[25]
	Aminopropyl ascorbyl phosphate	Water-soluble, stabilized form of vitamin C that inhibits tyrosinase.[20,26]
	AHA Blend (glycolic, lactic and citric acids)	Helps accelerate cell turnover and exfoliates surface pigmentation.
	Alpha-arbutin	Tyrosinase inhibitor that diminishes the appearance of unwanted pigmentation.[27]
	Glycyrrhiza glabra root extract/ licorice root extract	Isoflavone comprised of glabrinin that inhibits melanogenesis and brightens skin.[26,28]
	Niacinamide	Vitamin B3 derivative; protects the skin barrier, decreases hyperpigmentation, redness, and inflammation (PIH) by inhibiting melanosome transfer from melanocytes to keratinocytes.[29-31]
	Pancratium maritimum extract (sea daffodil)	Inhibits melanin synthesis and transfer, minimizing dark spots and evening skin tone appearance.[32]
	Phenylethyl resorcinol	Tyrosinase inhibitor derived from Scotch pine bark, known for its skin brightening properties.[33]
	Tranexamic acid (TXA)	Inhibits binding of plasminogen to keratinocytes and reduces the activity of melanocytes, inhibiting tyrosinase activity. Inhibits production of the inflammatory mediators, arachidonic acid and prostaglandin, which trigger melanogenesis. Improves barrier function permeability.[34,35]
	Ziziphus spina-christi leaf extract	Extract with antimicrobial properties and benefits. Reduces visible effects of glycation including skin yellowing and dullness.[36, 37]
	Blend of aloe, buddleja officinalis flower extract, ergothioneine, grape flower cell extract, and phloretin	A blend of botanical ingredients and extracts with known inflammatory and free radical protection properties.[38-40]
Additional Ingredients	Topical Allyl pyrroloquinoline quinone (TAP)	A redox cofactor shown to have protective effects against free radical damage in mitochondria; supports creation of mitochondrial energy necessary for renewal and repair processes of skin.[41-45]
	Superoxide Dismutase	Neutralizes superoxide radicals to mitigate oxidative damage.[46,47]
	Arginine	Amino acid that enhances antioxidant actions, stimulates collagenesis, protects the skin barrier and facilitates hydration.[41]
	Hydrolyzed sodium hyaluronate	Provides antioxidant support and hydration.[42]

include glycolic acid, niacinamide, ceramides, and peptides, all of which work together to support cellular turnover, hydration, and exfoliation.[48] The effectiveness and tolerability of AHARet applied each night has been studied alone and in combination with antioxidants and other products in a variety of skin types in participants with photodamaged skin, and has been shown to facilitate significant improvements in lines and wrinkles, skin texture, and skin tone, with mild, transient adverse events reported.[49,50]

In the current study, twice-daily application of EV-I, along with the use of sunscreen and a moisturizer, led to early and significant reductions from baseline in MASI scores, with significant reductions occurring among participants with darker skin tones. A post-hoc analysis in participants with FST IV–V noted a 68% significant reduction in hyperpigmentation based on the MASI scale at 12 weeks following twice-daily application of EV-I alone, with a noticeable decrease in PIH. Further, recognizing that UV damage and other extrinsic and intrinsic factors affect skin quality, this study demonstrated that use of EV-I alone or in combination with AHARet led to significant improvements in skin texture/roughness and dullness at 12 weeks without causing erythema or flaking. These beneficial results led the majority of participants to report being highly satisfied with the overall appearance of their skin after 12 weeks of use.

Due to the open-label nature of this study, a limitation of this study was the lack of a control comparison and a smaller sample size. The study was conducted during the Spring months in the southern part of the United States. While participants were provided with a mineral SPF50 sunscreen and were instructed and continually reminded to use the sunscreen along with other sun-protective measures, it is reasonable to assume that participants had encountered incremental exposures to UV, making this study representative of a real-world experience.

CONCLUSION

Twice-daily use of a multimodal skin tone correcting serum formulated with *b.r.y.t.e.r.* technology that targets key pathways involved in melanin production demonstrated significant reductions from baseline in MASI scores in participants with mild-to-severe dyschromia/hyperpigmentation after 12 weeks.

Significant reductions in MASI scores were demonstrated as early as week 4. A subset of participants with FST IV-V demonstrated significant reductions in dyschromia/hyperpigmentation at weeks 8 and 12. When combined with the use of a double-conjugated retinoid/AHA cream in the evening, additional and significant reductions from baseline were demonstrated in MASI scores in a subset of participants at week 4. Significant improvements in the appearance of skin texture and dullness occurred in both groups at 12 weeks. No increases in dryness/flaking or erythema were observed throughout the study. More than 90% of participants in both groups reported more even looking and brighter skin tone, and improvements in the overall appearance of their skin as early as week 4.

DISCLOSURES

Dr Draelos was a study investigator, and Ms Nelson was an employee of skinbetter science. This study was sponsored by skinbetter science, a Dermatological Beauty Brand of L'Oréal USA, Inc.

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