 

# In Vitro and In Vivo Efficacy and Tolerability of a Non-Hydroquinone, Multi-Action Skin Tone Correcting Cream

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## ABSTRACT

**Background:** Pigmentation disorders are therapeutically challenging to treat, requiring complicated regimens.
**Objectives:** Alternatives to hydroquinone (HQ) are desired. We evaluated the efficacy and tolerability of a non-HQ multi-action skin tone corrector (ETCS) developed to inhibit melanin production and improve skin quality.
**Design and Methods:** Twice-daily use of ETCS and ETCS + AHA-Ret, a retinoid-based alpha hydroxy acid cream, was evaluated in subjects with mild to severe dyschromia. Digital images were obtained at baseline, 4, 8, and 12 weeks and included assessment of dyschromia, erythema, fine lines/wrinkles, pores, texture, and global improvement. Melanin Index (MI) measurements were obtained at baseline, 4, 8, and 12 weeks. Subject self-assessments were obtained over the course of the study. Adverse Events (AEs) were collected throughout the study. An extension study evaluated use over 16-weeks.
**Results:** Significant mean reductions from baseline occurred in dyschromia for ETCS (n=42) and ETCS + AHA-Ret (n=10) over 12 weeks ($P<0.0001$, each). Significant mean reductions from baseline in MI were achieved in both groups at every timepoint (ETCS: $P<0.0001$; ETCS + AHA-Ret: $P<0.02$, 4 weeks; $P<0.0001$, 8 and 12 weeks). Substantial improvements were demonstrated in global improvement, fine lines/wrinkles, erythema, pores, and texture at 12 weeks. Reductions from baseline occurred in dyschromia and MI ($P<0.0001$, each) at 16 weeks. High levels of subject satisfaction were reported with nearly all subjects reporting reduced appearance of uneven skin tone/discoloration and lightened darker patches, and improvement in overall skin tone. Mild, transient AEs were reported with no discontinuations due to an AE.
**Conclusions:** Twice daily use of ETCS led to early, significant reductions in dyschromia and melanin index. Combination use with a retinoid-based, AHA cream in the evening demonstrated enhanced reductions. ETCS effectively reduced hyperpigmentation, improved overall skin appearance, and was highly tolerable.

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## INTRODUCTION

Dyschromia caused by photodamage is a common cosmetic concern, with more than 5.5 million patients having a sole diagnosis of dyschromia or hyperpigmentation.[1] Often a chief complaint reported to dermatologists by women with skin of color,[2] facial hyperpigmentation can have a substantial negative psychosocial impact on self-esteem and quality of life[1-3] and is challenging to treat.

The initiation and extent of pigmentation may be influenced by intrinsic (age, ethnicity, hormonal changes) and extrinsic (stress, inflammation, UV exposure) factors.[4] Epidermal melanin content is significantly greater (up to 2-fold) in chronically, photo-exposed vs. photo-protected skin, regardless of skin color.[5] Disruption or deregulation of production of melanin leads to skin pigmentary disorders.[6,7] A greater understanding of the pathophysiology of pigmentation has led to the development of treatments targeting the underlying pathways involved in melanogenesis.

Melanogenesis or melanin production is based on a complex biochemical process that involves multiple pathways.[8] The core cell signaling pathways that affect skin pigmentation include melanocyte activation, melanosome formation, melanin synthesis, melanin transfer, and melanin removal.[8] Melanocyte activation can be triggered by UV exposure, inflammation, pregnancy, and aging. Melanin production results from tyrosinase-mediated synthesis of melanin. Tyrosinase is a key enzymatic regulator of melanin production.[9] L-Tyrosine, in the presence of tyrosinase, is converted to dopaquinone (DOPA) and then to either eumelanin (black-brown melanin) or pheomelanin (yellow-red melanin).

Disorders of hyperpigmentation include melasma, dyschromia, post-inflammatory hyperpigmentation (PIH), and solar lentigines.[7,10,11] Hyperpigmentation manifests as patches of uneven skin color and is most frequently caused by UV exposure. Successful treatment of hyperpigmentation often requires multiple

modalities in addition to rigorous sun protection and avoidance.[12] Topical therapies are a consistent and core component of treatment strategies; when needed, additional interventions may include lights and lasers, chemical peels, and systemic approaches, as well as a combination of treatments.[11] Optimal treatment approaches reduce hyperpigmentation without causing hypopigmentation or irritation.[13]

Hydroquinone (HQ) has been the standard treatment for hyperpigmentation for more than 50 years and exerts its effect on melanin primarily by inhibiting activation of melanocytes.[14,15] HQ inhibits tyrosinase, reducing conversion of DOPA to melanin; studies have shown that HQ has melanocyte-specific cell toxicity.[16] Potential side effects of HQ include erythema, irritant and allergic contact dermatitis and in rare cases, ochronosis. Given the concerns regarding side effects, HQ has been banned in some countries. There is a global need for effective, tolerable skin lightening agents.

In an effort to address safety concerns and provide alternatives for patients, a new, non-HQ, non-retinol, multi-action skin tone correcting cream (ETCS) has been developed to comprehensively target and inhibit melanin production throughout the cell signaling pathways that affect skin pigmentation without the accompanying adverse effects of melanocyte toxicity.[8] ETCS was developed based on a balanced ratio of ingredients designed to address multiple concerns in the overall appearance of skin, including visibly reducing brown patches associated with hyperpigmentation, reducing redness and age-related yellowing of skin tone, and brightening and evening skin tone while supporting the overall quality of skin across a variety of skin types.

An initial study was conducted to quantify melanin and the effects of ETCS relative to 4% hydroquinone (HQ) following 14-days of topical exposure in a reconstructed skin model consisting of human-derived keratinocytes and melanocytes from African American donor cells. Initial pre-toxicity screening revealed that 4% HQ at the standard amount tested in this model, 10µL, resulted in <90% viability of the donor cell model. Consequently, it was determined that 2µL was the maximum tolerable amount of 4% HQ that did not result in toxicity to the skin model. In an effort to make relative comparisons, ETCS tissue samples were topically treated with the lower adjusted amount (2µL) as well as the standard amount (10µL), as viability of the skin model was not an issue using the standard amount of ETCS. ETCS demonstrated 55% (10 µL) and 22% (2µL) reductions in melanin versus negative control ($P$<0.05). Reduction in melanin with 4% HQ (2 µL) was 17% versus negative control ($P$<0.05).

Following initial testing, we clinically evaluated twice daily use of this formulation. Additionally, we postulated that a regimen that included use of a potent, non-irritating retinoid/alpha hydroxy acid cream (AHA-Ret) in the evening would further reduce pigmentation and contribute to additional improvements in the quality of skin tone and texture.[17]

**Study Objectives**

This open-label trial conducted across two dermatology research practices evaluated the efficacy and tolerability of twice-daily use of ETCS over 12 weeks in subjects with mild to severe facial dyschromia or hyperpigmentation. Additionally, efficacy and tolerability of ETCS in combination with AHA-Ret was evaluated in a separate group of subjects.

**Study Design**

*Study Population*

Women, 30 to 65 years of age, were eligible to participate in the study if they exhibited evidence of mild to severe dyschromia or hyperpigmentation, had no known medical conditions that may interfere with study participation, and agreed to minimize sun exposure, including the consistent use of sunscreen when outdoors and total avoidance of tanning beds. Exclusion criteria included any dermatologic disorder that may interfere with evaluation of facial skin (i.e. severe acne vulgaris, any active inflammatory skin condition), pregnant or lactating women, hypersensitivity to any of the ingredients contained in the study products, current or prior use of any cosmetic skin care product that, in the investigator's opinion, may interfere with the study including prescription products such as HQ and retinoids (12-week wash-out period) and non-prescription products (up to 4-week wash-out period).

*Study Product(s)*

The study product was provided in identical individual containers labelled only with lot and batch numbers. Additionally, AHA-Ret was provided for use in the evening (Treatment Group 2). A basic, gentle, commercially available cleanser, moisturizer (as needed), and a sunscreen (SPF 50) were also supplied.

*Study Procedures*

Subjects at each site were randomly assigned to ETCS only (Treatment Group 1) or ETCS + AHA-Ret (Treatment Group 2). ETCS was applied twice daily to clean skin, with subjects in Treatment Group 2 applying ETCS (AM/PM) and AHA-Ret (PM only, following ETCS) for a period of 12 weeks.

Digital images of subjects were obtained at baseline, 4, 8, and 12 weeks (VISIA® CR, Canfield Scientific, Inc., NJ) on clean, washed skin. Evaluations occurred at each timepoint and assessed changes in five categories using a 6-point grading scale (0=None, 1=Minimal, 2=Mild, 3=Moderate, 4=Moderately Severe, 5=Severe) for dyschromia, erythema, fine lines/wrinkles, pore size, and skin texture. Global improvement was assessed using a 5-point grading scale (0=None, 1=Minimal Im-

provement, 2=Mild Improvement, 3=Moderate Improvement, 4=Marked Improvement) at 4, 8, and 12 weeks.

Melanin index measurements were obtained at baseline, 4, 8, and 12 weeks (Mexameter® MX 18, Courage+Khazaka Electronic GmbH, Germany). Standardized measurements were based on an average of 3 measurements obtained from the same location of a hyperpigmented area (an easily identifiable location or "spot"). Subjects completed a 21-question self-assessment at baseline, 4, 8, and 12 weeks. Evaluation of tolerability and collection of Adverse Events (AEs) occurred throughout the study period.

All methods and procedures were identical in an optional 4-week extension study conducted through week 16.

### Statistical Analysis

Endpoints were analyzed as mean least squares (LS) improvement and mean LS percent improvement from baseline to each timepoint. Global Improvement was analyzed based on the observed values.

Mean percent improvement over time was based on the adjusted means (LS Means). Adjusted means were calculated using a general linear model, considering individual values at baseline for each variable.

## RESULTS

### Subject Demographics and Disposition

A total of 52 subjects completed the study. Three subjects withdrew from the study and one subject was lost to follow-up. There were no significant differences between the two treatment groups. The majority of subjects in each treatment group presented with moderate dyschromia. Skin types I–V were represented in the study. All subjects continued using the product(s) through week 16.

*Treatment Group 1 (ETCS, n=42)*

Twice daily application of ETCS demonstrated significant mean percent reductions from baseline in dyschromia at all timepoints (13% at 4 weeks, 24% at 8 weeks, and 31% at 12 weeks; *P*<0.0001, each) (Figure 1). Approximately half of the subjects (48%) achieved at least a ≥1-grade improvement in the appearance of dyschromia as early as 4 weeks. Significant mean percent reductions from baseline in melanin index were demonstrated in subjects at all timepoints (*P*<0.0001, each; Figure 2), with 7%, 12%, and 16% mean reductions from baseline at 4, 8, and 12 weeks, respectively. Additional parameters measured resulted in significant mean percent improvements from baseline in subjects at 12 weeks in the appearance of fine lines/wrinkles, pore size, and skin texture (Table 1; Figures 3 and 4). Subjects also experienced significant mean improvements in global improvement at 12 weeks (*P*<0.0001).

At 16 weeks, subjects achieved significant mean percent reductions from baseline in dyschromia (37%; *P*<0.0001) and melanin index (19%; *P*<0.0001). Significant mean improvements from baseline were also visibly demonstrated in subjects for erythema (28%; *P*<0.006), skin texture (29%; *P*<0.0001), fine lines/wrinkles (15%; *P*=0.0002) and pore size (16%; *P*=0.003).

**TABLE 1.**

| Mean (LS) Percent Improvement from Baseline at 12 Weeks | | | | |
|---|---|---|---|---|
| | ETCS % (SE), n=42 | *P*-value | ETCS + AHA-Ret % (SE), n=10 | *P*-value |
| Skin Texture | -27.25 (4.49) | <0.0001 | -35.70 (9.25) | 0.0003 |
| Erythema | -18.50 (11.16) | NS | -46.37 (23.18) | NS |
| Fine Lines/ Wrinkles | -14.10 (3.51) | 0.0002 | -20.61 (7.20) | 0.0062 |
| Pore Size | -12.54 (5.06) | 0.0166 | -10.65 (10.73) | NS |

**FIGURE 1.** Percent Reduction in Dyschromia: Treatment Group 1.

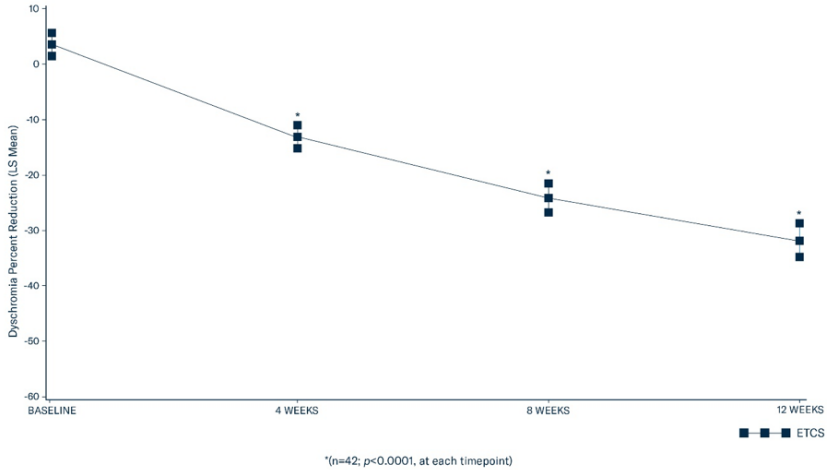
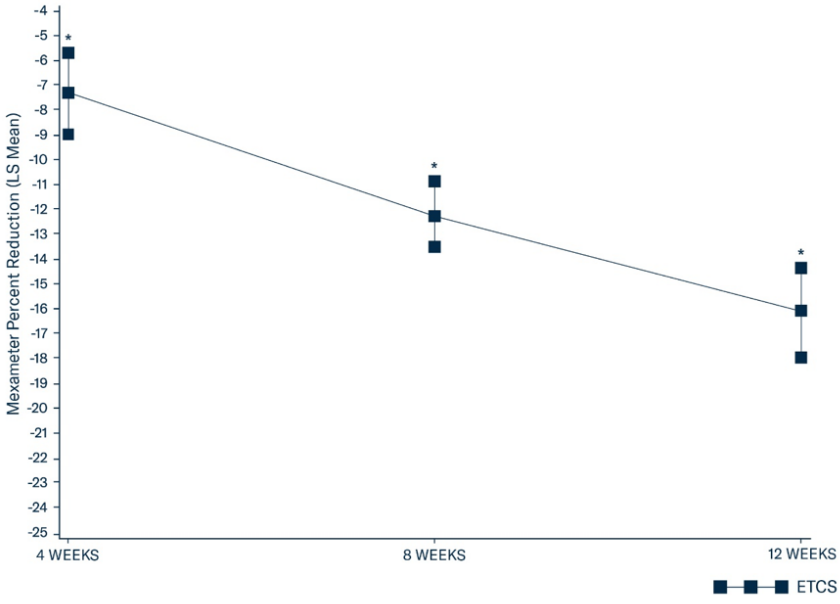


**FIGURE 2.** Percent Reduction in Melanin Index: Treatment Group 1.

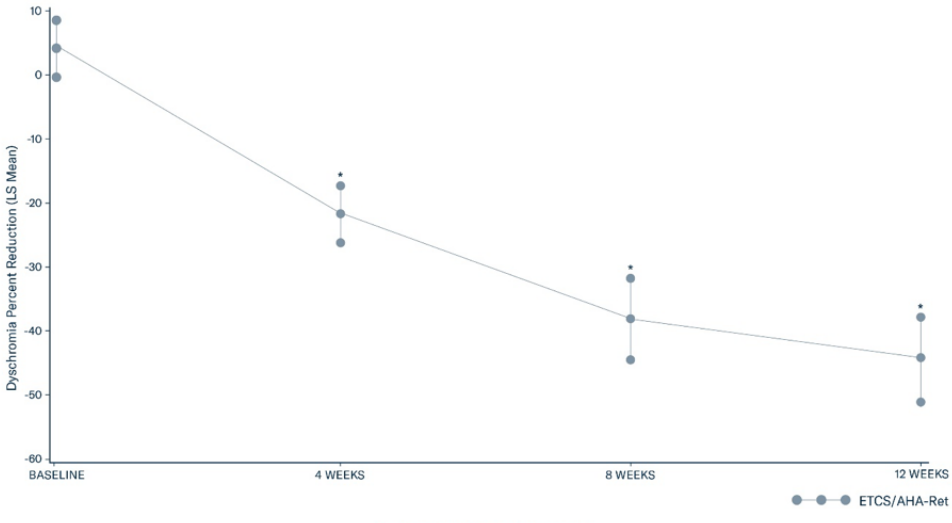



*(n=42; $p<0.0001$, at each timepoint)

**FIGURE 3.** Improvement from Baseline at 12 Weeks.

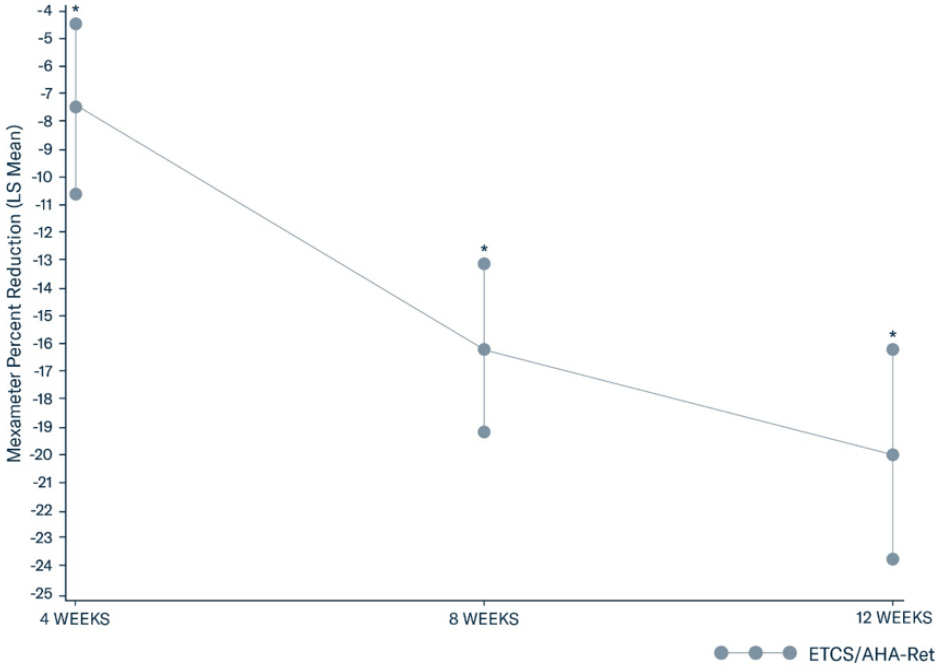

**FIGURE 4.** Improvement from Baseline at 12 Weeks.


**FIGURE 5.** Percent Reduction in Dyschromia: Treatment Group 2.




*(n=10; $p<0.0001$, at each timepoint)

**FIGURE 6.** Percent Reduction in Melanin Index: Treatment Group 2.




*(n=10; $p<0.02$, 4 weeks; $p<0.0001$, 8 and 12 weeks)

**FIGURE 7.** Improvement from Baseline at 12 Weeks (Combination Treatment).


*Treatment Group 2 (ETCS + AHA-Ret, n=10)*

Subjects using combination treatment of ETCS + AHA-Ret demonstrated significant mean percent reductions from baseline for dyschromia at all timepoints (*P*<0.0001, each) with 21%, 38% and 44% reductions occurring at 4, 8, and 12 weeks, respectively (Figure 5). More than half of the subjects (55%) achieved at least a ≥1-grade improvement in dyschromia at 4 weeks. Significant mean percent reductions from baseline for melanin index were achieved in subjects at all timepoints (week 4, *P*<0.02; weeks 8 and 12, *P*<0.0001; Figure 6), with 8%, 16%, and 20% mean reductions from baseline at 4, 8, and 12 weeks, respectively. Subjects also achieved significant mean percent improvements at 12 weeks in the appearance of fine lines/wrinkles, skin texture, and global improvement (Table 1; Figure 7).

At 16 weeks, subjects demonstrated significant mean percent reductions from baseline for dyschromia (52%, *P*<0.0001) and melanin index (24%; *P*<0.0001) with combination use of ETCS + AHA-Ret. Significant mean improvements from baseline were also demonstrated at 16 weeks in subjects in the appearance of erythema (52%; *P*<0.02), skin texture (34%; *P*<0.0017), and fine lines/wrinkles (29%; *P*=0.016).

*Subject Self-Assessments*

High levels of satisfaction were reported by subjects in both treatment groups. At 12 weeks, nearly all subjects reported improved overall appearance of skin (98%), reduced appearance of uneven skin tone/discoloration (96%), lightened darker patches (96%), improved evenness of skin (96%), and improved overall skin tone (98%). Only 20% of subjects reported bright skin tone at the start of study, which increased to 62% after 12 weeks.

*Tolerability*

Treatments were well-tolerated with only mild, transient AEs reported. Two AEs occurred in subjects in the combination treatment group. AEs included blemishes (n=3), redness (n=3), irritation (n=1), dryness (n=1), oiliness (n=1) and tingling (n=1). No subject discontinued use of the study products or dropped out of the study owing to an AE.

## DISCUSSION

Cutaneous hyperpigmentation is among the most common complaints in dermatology offices and is one of the more difficult conditions to treat, as many regimens are often complicated and may include the use of up to 6 topical agents in addition to other treatment modalities. Furthermore, products may be highly irritating.[18] Historically, hyperpigmentation has been managed with topical formulations that include 4% hydroquinone; while often effective,[19] concerns regarding irritation and long-term use have led to the development of non-HQ-containing formulations.

In an effort to inhibit melanin production at the multiple pathways involved in skin pigmentation, currently available prescription and nonprescription products often include the use of several topical agents including the adjunctive use of retinoids, AHAs, moisturizers and/or hydrating serums to enhance overall efficacy and minimize adverse effects.[3,14,18,19,20-28] This system-based approach requires consumers purchase and use multiple products in order to achieve optimal results. This not only necessitates adherence to complicated regimens, but these regimens can also be quite costly. ETCS was developed to address the need for an efficacious, streamlined approach to the treatment of hyperpigmentation and other concerns associated with photodamage skin, such as redness and age-related yellowing of the skin, skin tone, and fine lines and wrinkles. The synergistic blend of ingredients contained in ETCS were identified to comprehensively inhibit melanin by addressing the primary pathways of melanin production and improve the overall quality of skin (Table 2). For example, in addition to inhibiting ROS and melanin production at several levels, Diglucosyl Gallic Acid brightens skin tone and reduces the appearance of redness. Derived from the Australian Kakadu plum, Terminalia Ferdinandiana is a potent form of vitamin C that reduces oxidative stress in the skin, brightens skin, and also enhances collagen and hyaluronic acid, thus contributing to improvements in tone, evenness, redness, and wrinkles.

ETCS effected early, significant reductions from baseline in the appearance of dyschromia based on expert and biometric assessments. Hyperpigmentation is often accompanied by other concerns associated with cumulative sun and environmental exposures, including changes to skin texture, color, and the development of fine lines and wrinkles. In addition to brightening and evening skin tone, visible improvements in skin texture, erythema, fine lines/wrinkles, and pore size were observed leading to enhanced global appearance in the quality of skin as a result of the multi-functional properties of its ingredients. Importantly, efficacy outcomes mirrored subject satisfaction, with subjects reporting high levels of satisfaction in improvements in overall appearance, evenness, brightness, tone, lightening of dark patches, and discoloration of skin. Progressive improvements were observed with continued use through week 16 in all categories measured.

**TABLE 2.**

| KEY INGREDIENTS | MELANIN PRODUCTION PATHWAYS | | | |
|---|---|---|---|---|
| | Activation | Development | Production | Transfer |
| **Diglucosyl Gallic Acid** Bioactivated melanoregulator and free-radical scavenger | ✓ | ✓ | | ✓ |
| **Hexylresorcinol** Tyrosinase inhibitor | | ✓ | | |
| **Acetyl Glycl Beta-Alanine** Multi-functional peptide that targets transcription and interferes with transport | ✓ | | ✓ | ✓ |
| **Alpha-Arbutin** Tyrosinase inhibitor | | ✓ | | |
| **Artemisia Capillaris Flower Extract** Reduces melanin transfer to keratinocytes | | | | ✓ |
| **Terminalia Ferdinandiana Fruit Extract** Potent source of Vitamin C and free-radical scavenger | | ✓ | | |
| **Pancreatium Maritimum Extract** Reduces melanin transfer to keratinocytes | ✓ | | | ✓ |
| **Arginine PCA** Amino acid complex that targets glycation and age-related yellowing of the skin | | | | |
| + **Ceramides, Linolenic and Linoleic Acids** | | | | |

Despite the small sample size, the addition of AHA-Ret each night resulted in statistically significant improvements in dyschromia and melanin index, along with substantial improvements in the appearance of erythema, fine lines/wrinkles, and skin texture. The advantage of combination treatment increased over time, without adverse effects.

AHA-Ret is a double-conjugated retinoid/AHA-based cream that combines a potent retinoid and lactic acid into one molecule via double conjugation. Double bonds joining the two molecules are naturally broken in the skin through hydrolysis, gradually releasing the retinoid and lactic acid into the skin, maximizing efficacy and minimizing potential irritation. AHA-Ret also contains glycolic acid to support exfoliation of skin which is vital in the removal of melanin from the epidermis, as well as ingredients that help soothe, hydrate, protect and rejuvenate skin.[17]

Differences in sample size between the treatment groups, severity and ethnicity limited the ability to draw comparisons between the two treatment groups.

## CONCLUSIONS

A new, non-hydroquinone skin tone correcting cream demonstrated early, clinically significant reductions in dyschromia and melanin index in subjects with photodamaged skin. Combination use with a retinoid-based AHA cream led to enhanced visible reductions in hyperpigmentation and improvements in

the overall quality of skin. This new, non-hydroquinone skin tone correcting cream represents an effective, non-irritating treatment option for patients with photodamage seeking to reduce the appearance of hyperpigmentation and improve the overall quality of their skin.

## DISCLOSURES

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