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Clinical Experience With a Unique Multimodal Skin Brightener for Facial Hyperpigmentation

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ABSTRACT

Background and Objective: Skin lightening preparations are used by people all over the world for a diverse range of dermatologic indications. Hydroquinone (HQ) is the gold standard and remains the only prescription product available in the United States for the treatment of generalized facial hyperpigmentation. Irritation and the risk of exogenous ochronosis are the main adverse effects for concern. Therefore, there has been a constant search for new treatment alternatives. Understanding the molecular mechanisms involved in pigmentation has resulted in the development of a series of formulations that utilize a multimodal treatment approach. These proprietary formulas combine skin lightening agents that act via different mechanisms of action. The actives included 4-ethoxybenzaldehyde (anti-inflammatory and prostaglandin E_2 suppressor), licorice extract (tyrosinase inhibitor), tetrahexyldecyl ascorbate (antioxidant), niacinamide (melanosome transport inhibitor), ethyl linoleate (tyrosinase inhibitor; enhances turnover of epidermis), hexylresorcinol (tyrosinase inhibitor), and retinol (tyrosinase transcription inhibitor; enhances turnover of epidermis).

Methods: Select formulations were tested in several studies using the MelanoDerm™ Skin Model (MatTek Corporation, Ashland, MA) to assess the ability of the product to reduce melanin production and distribution. A single-center, double-blind comparison clinical study of 18 subjects was conducted to evaluate the efficacy of the product in reducing ultraviolet-induced hyperpigmentation. Test sites were irradiated with 1.0, 1.5, 2.0, and 2.5 minimal erythema doses. After 5 days, to allow for pigmentation development, the product or 4% HQ cream was applied to the respective test sites, once daily for 4 weeks. Chroma Meter measurements (L* brightness) and standardized digital photographs were taken of the test sites twice a week.

Results: The test product resulted in greater reduction in melanin as measured by melanin content and histological staining compared with the positive control in the MelanoDerm Skin Model. The product also demonstrated statistically significant reductions in pigmentation compared with baseline (all $P \leq .0001$) at the end of the clinical study, and produced greater increases in L*, compared with 4% HQ. Results from these studies indicate that a product designed to affect multiple pathways of melanogenesis and melanin distribution may provide an additional treatment option beyond HQ for hyperpigmentation.

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INTRODUCTION

Hyperpigmentation disorders pose a real treatment challenge for patients all over the world. The number of people seeking treatments to alleviate the psychological distress associated with facial hyperpigmentation continues to grow rapidly. Currently, 4% hydroquinone (HQ) remains the gold standard of topical treatments and is the only prescription product available in the United States for the treatment of generalized facial hyperpigmentation. Hydroquinone has been used as a skin lightener for more than 50 years, and multiple clinical studies have documented its efficacy in various formulations.[1-5] However, regulatory agencies have recently begun questioning the safety of this drug.[6,7] Adverse effects, including skin irritation, contact dermatitis, and exogenous ochronosis, may occur with use of this compound. The US Food and Drug Administration (FDA) has initiated long-term studies to better understand the safety of topical HQ but has not made a final determination.[8] Many user interest groups have taken the position that products containing HQ should not be used due to potential safety concerns, and both physicians and patients are now asking about product options that are free of HQ or its derivatives such as α-arbutin. As a result, there exists a large and growing market for alternative products that effectively lighten the skin.

The first objective of this study was to develop a HQ-free, arbutin-free formulation that addresses all major known biochemical pathways of skin pigmentation regulation. The second objective of this study was to determine the efficacy of such a composition using the most advanced techniques available that closely mimics the natural depigmenting effects in skin.

The control of pigmentation can be achieved by combining 4 groups of biochemical approaches summarized in Table 1: (1) prevent stimulation of melanocytes by minimizing the effect of ultraviolet (UV) exposure and activation via keratinocytes; (2) inhibit activity or decrease the levels of tyrosinase, the key enzyme responsible for the synthesis of melanin; (3) inhibit transfer of mel-

anin-containing melanosomes from melanocytes to keratinocytes; and (4) enhance removal and exfoliation of melanin-containing keratinocytes from the epidermis. An ideal skin lightening formulation would include a combination of agents that act on different stages in the melanogenesis and melanin distribution pathways.

In addition to conceptualizing an ideal pigment-reducing combination, it is equally important to employ clinically relevant assessment techniques to ensure that the selected formulations are efficacious when used in human subjects. Inhibition of mushroom tyrosinase is an in vitro chemical reaction that has been extensively used to screen the skin lightening benefits of many ingredients, but very few show benefits in controlled clinical studies.[9] Inhibition of melanin production in cultures of human or mouse melanocytes is also used to demonstrate the ability of ingredients to reduce melanin production. While more relevant than in vitro tyrosinase inhibition, this technique does not account for the critical role of keratinocytes in the stimulation of melanogenesis or the process of melanin distribution. Assessments such as these are not clinically relevant and often lead to inflated claims of product activity.

In this study, we first used a 3-dimensional tissue construct of human skin comprising live human keratinocytes and melanocytes to assess the ability of various formulations to reduce melanin production and transfer. This assessment technique closely resembles the physiology of melanin production and distribution in human skin, making the results clinically relevant. The activity of selected formulations was confirmed by measuring their ability to reduce UV-induced skin pigmentation in human volunteers. This clinical assessment of activity was used to finalize the composition of the skin brightener formulation.

"The first objective of this study was to develop a hydroquinone-free, arbutin-free formulation that addresses all major known biochemical pathways of skin pigmentation regulation."

MATERIALS AND METHODS

Skin Brightening Compositions

Skin brightening formulations were selected based on an understanding of the pathway for melanogenesis and employing a combination of ingredients that intervene with differing components of this pathway. Table 1 shows the composition of the skin brightener (Lytera™ Skin Brightening Complex; SkinMedica®, Inc., Carlsbad, CA) used in this study. Appropriate negative (no treatment) and positive (Hydroquinone USP, 4% Skin Bleaching Cream; Stiefel Laboratories, Inc., Coral Gables, FL) controls were used in each study to ensure the validation of experiments.

TABLE 1.

Critical Pathways Affecting Melanin Production and Distribution With Ingredients Influencing the Pathways

Pathway	Ingredients	Ref
Reduce Melanocyte Activation		
Free-radical scavenger	Tetrahexyldecyl ascorbate	17
Inflammatory cytokines suppression	4-Ethoxybenzaldehyde	18
Reduce Melanin Synthesis by Limiting Tyrosinase Availability		
Tyrosinase transcription inhibition	Retinol	19
Tyrosinase degradation	Linoleic acid	20
Competitive tyrosinase inhibition	Glabridin	21
Competitive tyrosinase inhibition	Hexylresorcinol	22
Reduce Melanin Transfer to Keratinocytes		
Melanocytic dendrite suppression	Niacinamide	15
	4-Ethoxybenzaldehyde	18
Remove Epidermal Melanin		
Keratinocyte-turnover accelerator	Retinol	23

Reduction of Melanogenesis and Melanin Distribution in Human Skin Equivalents

Evaluation of melanogenesis and melanin distribution was performed in a 3-dimensional model of human skin, MelanoDerm™ tissues (MEL-300B; MatTek Corporation, Ashland, MA). MelanoDerm tissue consists of normal, human-derived epidermal keratinocytes and melanocytes that have been co-cultured to form a multilayered, highly differentiated model of the human epidermis. The melanocytes within this model undergo melanogenesis, leading to a basal level of melanin accumulation within the tissues over time, which can be influenced by test materials that can alter the melanin synthesis and distribution. The tissue has a functional stratum corneum, allowing direct application of complex formulations to the surface of the MelanoDerm tissue. The end points were measurements of melanin content and visual and histological assessment of melanin distribution.

The tissues were treated with 15 µL of formulations or with 25 µL of negative (deionized water) controls every other day during this period. Tissues were extracted in this period at specific days and fixed for histological imaging or for melanin quantification. For histological imaging, tissues were fixed for 3 hours in HistoChoice® (Amresco LLC, Solon, OH) dehydrated with increasing concentration of ethanol, and embedded in paraffin; and 5 µm sections were obtained for microscopy. The sections were stained with Fontana-Masson staining (American Master*Tech Scientific, Inc., Lodi, CA) and imaged under a microscope for histology. For melanin quantification, tissues were analyzed us-

ing Solvable™ (PerkinElmer Inc, MA, USA), incubated at 60˚C overnight, and centrifuged to isolate solubilized melanin. The supernatant was then analyzed for the amount of melanin by UV absorbance at 490 nm. The standards were treated with the similar protocol as samples, and the amount of melanin in samples was determined from the standard curve. Standard photographs of the treated tissues were taken at day 14 to view the visible changes in pigmentation.

Reduction of UV-Induced Skin Pigmentation in Humans

In full conformance with FDA guidelines, written informed consent, a confidentiality/photography release agreement, and an HIPAA disclosure agreement were obtained from each subject prior to enrollment in the study.

Subjects were examined on the back for evenness of skin tone (a Fitzpatrick skin type of III) and the absence of any skin irregularities that would interfere with the assessment of pigmentation. Each subject's natural/inherent minimal erythema dose (MED) of UV exposure was determined on unprotected skin sites on the lower back. UV radiation was supplied by a solar simulator (Model 16S, Solar UV Simulator; Solar Light Co, Philadelphia, PA) with a 150-watt xenon arc lamp and appropriate filters.

Multiple test sites (3.0 cm x 5.0 cm) were designated on each subject's lower back and assigned to skin brightener, 4% HQ, or a no-treatment control per a predetermined randomization scheme. Each test site was exposed to UV radiation in doses of 1.0, 1.5, 2.0, and 2.5 times the previously determined MED. Each irradiated spot resulted in a 1.0 cm diameter area of erythema on the skin. Subjects rested for 5 days to allow pigmentation to develop at the irradiated sites. Treatment started on day 8 and continued through day 36, Monday to Saturday every week. On days 8 to 13, 15 to 20, 22 to 27, and 29 to 34, approximately 30 µL of each of the assigned test materials was applied to the test sites using an open application technique. The control site remained untreated.

Prior to treatment, the study sites were photographed under standardized conditions and each spot was evaluated with a digital Chroma Meter (CR-400; Minolta, Tokyo, Japan) to assess changes in skin color using CIE L*a*b* (CIELAB) color space.[10] This color model describes all the colors visible to the human eye. The L* component of CIELAB color space closely matches human perception of lightness with a value of 0 for black and 100 for diffuse white.

RESULTS

Suppression of Melanin Production

Two independent experiments were conducted to evaluate the effect of the skin brightener on melanin production in Melano-Derm tissue. Figure 1 shows that the product reduced the level of melanin significantly below the control, and the results are reproducible. Low-magnification inset photographs above each bar show a reduction in pigmentation in product-treated tissue as compared to untreated tissue. High-magnification (100X) inset photographs further show a reduction in the number of melanocytes in the tissue correlating with the reduction in visible pigmentation.

FIGURE 1. Product significantly reduces melanin levels in MelanoDerm model compared with control. Insets show photograph and photomicrographs of the tissue showing overall pigmentation and melanocytes.

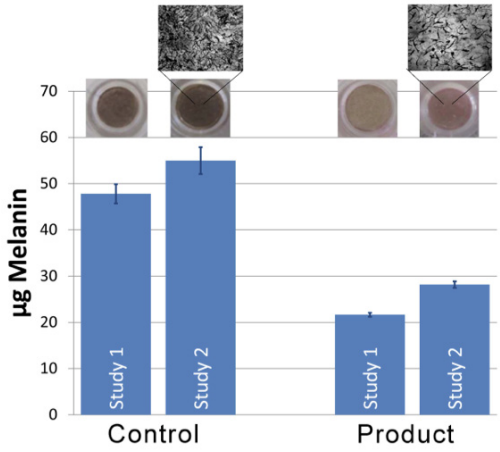
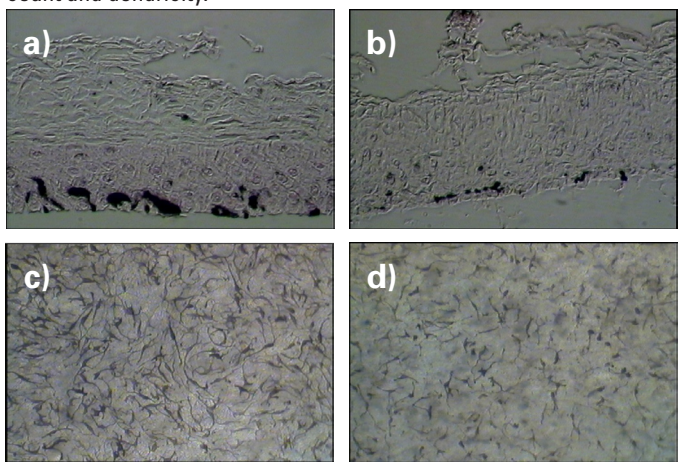


FIGURE 2. Histological cross section of a Fontana-Masson–stained Melano-Derm tissue from **a)** untreated and **b)** product-treated samples shows a reduction in the number of melanocytes with product. High-resolution photographs of the tissue surface for **c)** untreated and **d)** product-treated samples show a reduction in melanocytes count and dendricity.



In another study, skin brightener–treated MelanoDerm tissues were assessed for structural changes. Histological images of the tissue cross sections after Fontana-Masson staining show that tissue treated with skin brightener (Figure 2b) contain a reduced number of melanocytes in the basal cell layer compared with untreated tissue (Figure 2a). Microscopic images of the intact tissue show a reduction in the number of pigmented melanocytes as well as a reduction in melanocyte dendricity for skin brightener–treated tissue (Figure 2d) compared with untreated controls (Figure 2c).

FIGURE 3. Increase in L* values for untreated sites and sites treated with product or 4% hydroquinone over time at 3 different levels of initial ultraviolet exposure. Higher L* value indicates greater skin brightness. MED, minimal erythema doses.

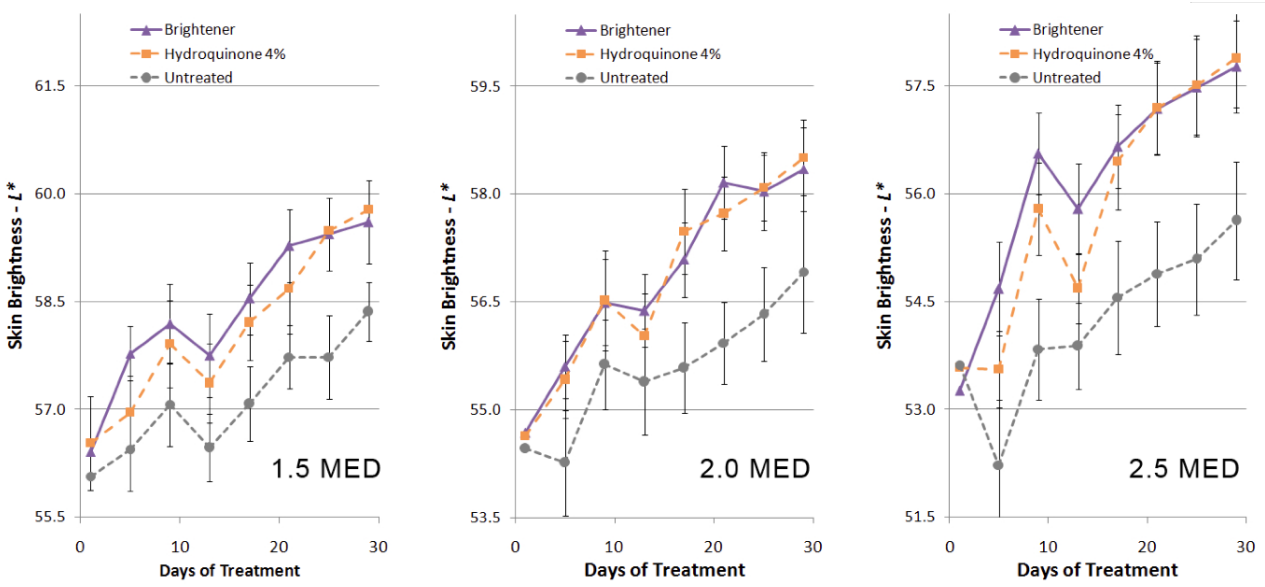


TABLE 2.

Summary of Demographic Information		
		All Subjects (n=18)
Age (years)	Mean age ± standard deviation	43.40 ± 10.1
	Minimum age	23.7
	Maximum age	58.2
Ethnicity	Asian-Indian n (%)	1 (5.6%)
	Asian-Vietnamese n (%)	1 (5.6%)
	Caucasian n (%)	10 (55.6%)
	Caucasian/Hispanic-Mexican n (%)	1 (5.6%)
	Hispanic-Mexican n (%)	4 (22.2%)
	Hispanic-Nicaraguan n (%)	1 (5.6%)
Gender	Female n (%)	13 (72.2%)
	Male n (%)	5 (27.8%)

Reduction of UV-Induced Skin Pigmentation in Humans

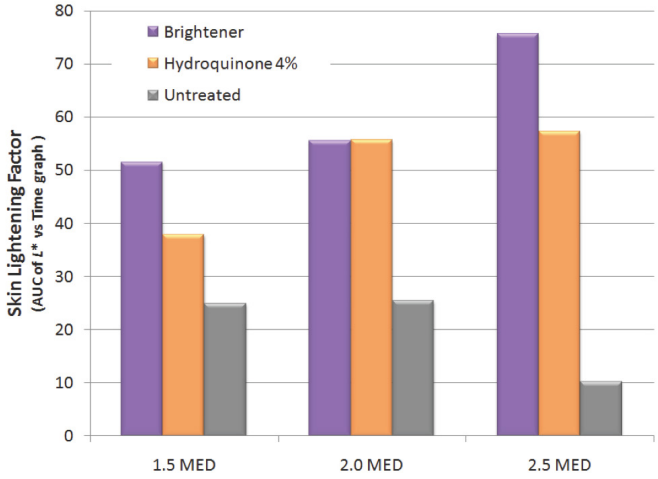
A total of 18 subjects with a Fitzpatrick skin type of III completed the study. Table 2 contains a summary of the demographic information for all subjects. Reduction in UV-induced melanin in subjects was evaluated by measurement of skin brightness using the parameter L* from the CIELAB color space of treatment site photographs. Figure 3 shows the L* values from the day of the treatment to the end of study for sites treated with the skin brightener, a 4% HQ cream, and untreated sites at 3 different UV doses. Initial L* values correlate well with the UV exposure, with lower UV doses producing less pigmentation, resulting in higher L* values than were seen following the higher UV doses. Change in L* for untreated sites represents skin's natural de-tanning process. Sites treated with brightener and 4% HQ show statistically similar increase in skin brightness. Both products produced statistically greater increases in brightness than untreated control, and the magnitude of change was greater with higher initial pigmentation. Overall skin lightening factor was calculated from area under the L* vs Time curve for each product at different UV doses, as described earlier.[11] Figure 4 shows that the skin lightening factor for the skin brightener and 4% HQ are comparable and greater than that for the untreated site.

DISCUSSION

Control of hyperpigmentation remains one of the most sought-after beauty treatments in the world. It is a cosmetically important condition that can arise from a variety of sources, including UV exposure, skin disorders such as melasma, photosensitizing agents, and other factors such as aging, liver disease, and pregnancy. Hydroquinone has been used successfully in the treatment of facial hyperpigmentation for many decades, but continued interest in reducing HQ usage has stimulated research into alternative skin lightening preparations. By taking a multimodal treatment approach, novel formulations were developed to include multiple agents that target various molecular mechanisms involved in the pigmentation pathway.

In vitro human-skin substitutes and in vivo clinical models are excellent tools for the optimization of ingredient concentrations and formulation variables. Using these models enhances ingredient selection and results in creation of an optimized product for further clinical evaluation. MelanoDerm tissue offers rapid screening of formulations against intrinsic melanin production

FIGURE 4. Skin lightening factor calculated from area under the L* vs Time curve at 3 different levels of initial ultraviolet exposure. Higher value indicates greater overall skin brightness. AUC, area under the curve; MED, minimal erythema doses.



as well as melanin production resulting from stimulation of melanocytes. Short-duration clinical studies with UV exposure can be used either to show prevention of melanin production or reduction in existing melanin, depending on the treatment protocol. Early treatment and initiating treatment after pigment has formed shows the ability of the product to reduce melanin content. In this study, we determined reduction in existing melanin and compared the results to a standard 4% HQ treatment.

CONCLUSION

Many cosmetic products claiming to have skin lightening efficacy equivalent to 4% HQ are available to consumers. However, a review of peer-reviewed literature found only a handful of studies—some only in vitro studies and others including as few as 5 to 10 patients—to substantiate their product efficacy claims.[11-13] Some studies focus on the mechanism of action for specific ingredients, but not on the finished product.[14] Other studies were initiated at the end of summer, when natural reduction in sun exposure leads to improvement in skin pigmentation.[13] While in vitro and in vivo models as well as proof-of-concept clinical studies in a limited patient population are excellent tools for product optimization, their results cannot be used to claim efficacy and must be validated by controlled clinical studies in actual patients. A few examples of published clinical studies that show product efficacy in comparison with 4% HQ in reasonably sized patient groups were identified.[15,16] Studies like these provide a better comparison of the true efficacy of a skin brightener than seasonally adjusted small trials or in vitro models. The product described in this paper was further tested in multiple clinical studies by dermatologist investigators for use as a cosmetic skin brightener to improve the appearance of facial dyschromias.

DISCLOSURES

Financial support for this study was provided by SkinMedica, an Allergan Company.

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Clinical Efficacy and Safety of a Multimodality Skin Brightener Composition Compared With 4% Hydroquinone

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ABSTRACT

There are numerous common skin disorders involving hyperpigmentation, including solar lentigines, postinflammatory hyperpigmentation, melasma, freckles, and dyschromia from photoaging. While these conditions are of an aesthetic nature, there is great interest in newer, safer, and more effective treatment modalities. Topical hydroquinone (HQ) has been the gold standard of skin lighteners for many years. However, regulatory authorities around the world are now questioning its safety. A randomized, double-blind, half-face study was conducted in females with moderate to severe facial hyperpigmentation to assess the efficacy and tolerability of 3 new skin brightener formulations containing SMA-432, a prostaglandin E_2 inhibitor, compared with 4% HQ. Each subject was assigned 2 of the 4 test materials and was instructed to apply the product on the assigned side of the face twice daily for 12 weeks. Evaluation visits were conducted at baseline and at 4, 8, and 12 weeks. At each visit, subjects were evaluated by a blinded investigator for clinical efficacy and tolerability using grading scales. Standardized digital photography and Chroma Meter assessments were also taken. Self-assessment questionnaires were completed at weeks 4, 8, and 12. Sixty-eight Caucasian subjects (136 half faces) completed the study. All test materials significantly reduced Overall Hyperpigmentation and improved the Investigator's Global Hyperpigmentation Improvement rating at weeks 4, 8, and 12 compared with baseline. SMA-432 exhibited a dose-dependent improvement in hyperpigmentation. There were no major tolerability issues with any of the test materials. Self-assessments were generally favorable for all test materials. At the completion of the trial, subjects rated one of the tested multimodality brightener compositions as the most favorable product and 4% HQ as the least favorable. This study demonstrated that the new non–HQ-containing skin brightener formulations were as effective and equally well tolerated as the gold standard, 4% HQ, in females with facial hyperpigmentation.

J Drugs Dermatol. 2013;12(3 suppl 1):s21-s26.

INTRODUCTION

The amount and type of melanin pigments, which are polymers produced inside the melanosomes, determine skin color.[1,2] While there is tremendous diversity worldwide in the color of human skin, uniform or even skin color (particularly across the face) in an individual is considered a sign of health, attractiveness, and youthfulness and, as such, is aesthetically desirable.[3,4] Skin issues involving hyperpigmentation typically arise because of injury and/or advancing age. Exposure to sunlight is the most common cause of hyperpigmentation and is likely a postinflammatory response to ultraviolet (UV) damage to the skin.[5,6] Inflammation may lead to hyperpigmentation via several mechanisms, including direct stimulation of melanocytes by inflammatory mediators and reactive oxygen species (ROS) and release of endocrine inducers of pigmentation such as α-melanocyte-stimulating hormone.[6] The resulting melanin production provides protection against future insult, as melanin has both UV-absorption and ROS-scavenging activities.[7]

Altered production of cutaneous melanin causes problems of an aesthetic nature. Such disorders of hyperpigmentation, including melasma, postinflammatory hyperpigmentation, solar lentigines, freckles, and dyschromia from photoaging, are very common in humans, and there is a broad interest in newer, more effective treatment modalities. Traditionally, the gold standard topical agent for skin lightening was hydroquinone (HQ) 4%, until regulatory agencies around the world began questioning its safety.[8,9] Adverse effects, including skin irritation, contact dermatitis, and exogenous ochronosis may occur with use of this compound. The US Food and Drug Administration has initiated studies to better understand the long-term safety of topical HQ and has not made a determination on its safety[10]; however, many user interest groups have taken the position that products containing HQ should not be used because of potential safety concerns. As a result, there exists a large and growing market for alternative products that effectively lighten the skin.

FIGURE 1. All 4 products demonstrated significant reductions in Overall Hyperpigmentation scores at all visits compared with baseline (all *P*<.001). At week 12, there were no significant differences between BR1, BR3, and 4% hydroquinone (HQ) (P>0.13).

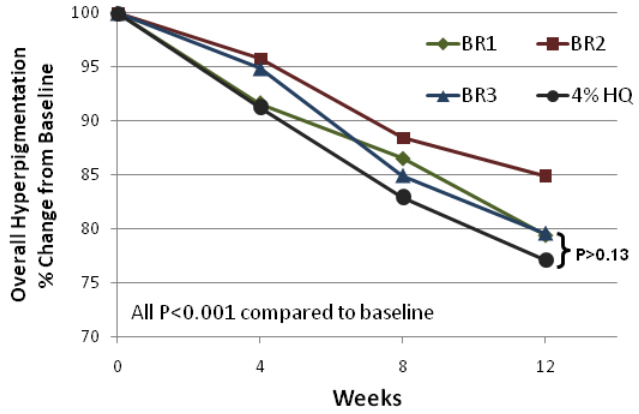
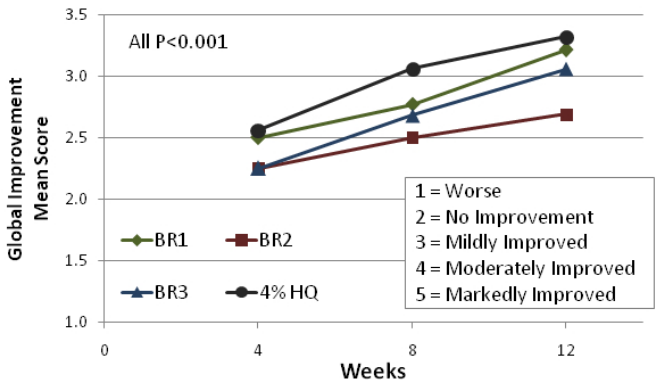


FIGURE 2. All 4 products showed significant improvements in the Investigator's Global Hyperpigmentation Improvement score at all visits compared with baseline (all *P*<.001). HQ, hydroquinone.



While there is an ever-increasing number of cosmetic skin lightening and skin brightening products in the marketplace, the overwhelming majority lack any clinical studies to support their claims. Most often, manufacturers will utilize in vitro studies (such as tyrosinase inhibition) as a support for efficacy or use testimonials from satisfied users.

Employing a unique combination of skin lightening and proprietary ingredients that address various pathways involved in melanin production and control, 3 formulations were developed and tested for safety and efficacy compared with HQ using a randomized, double-blind, half-face clinical design model.

MATERIALS AND METHODS

The criteria for participation in the study included female subjects in good general health between the ages of 30 and 65 years with moderate to severe facial hyperpigmentation as determined by clinical examination. Subjects were required to have a baseline score of 4 to 9 on both sides of the face from the Overall Hyperpigmentation scale and to be willing not to apply any other topical products (skin lightening, retinoids, benzoyl peroxide, steroids, α-hydroxy or β-hydroxy acids) to the facial area or to use any systemic retinoids throughout the duration of the study. Subjects were provided standard skin care products (facial cleanser, moisturizer, and SPF 30 physical sunscreen) to use during the course of the study.

Institutional Review Board approval was obtained for this study. The study was conducted according to ethical and regulatory principles from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Before treatment, the subjects provided informed consent.

The complexity of biochemical processes of melanin formation and distribution necessitates a comprehensive approach to manage pigmentary disorders. Table 1 describes the composition of the multimodality skin brightener formulations used in this study, which contained multiple ingredients designed to address these numerous aspects of melanin formation and removal, and melanocyte activation. Three test formulations (BR1, BR2, and BR3) and a generic 4% HQ cream were studied to compare efficacy and tolerability in subjects with moderate to severe facial hyperpigmentation. Subjects were assigned 2 of the 4 test materials and were instructed to apply them on the assigned side of the face (left or right) according to a predetermined, randomized half-face design. Test materials were applied twice daily, morning and evening. Both the subject and the investigator were blinded to the assigned test materials.

The study was conducted over a 12-week period from June 2011 to October 2011 in Dallas, Texas, and consisted of evaluation visits at baseline, week 4, week 8, and week 12. Subjects arrived at the clinic having removed all makeup at least 20 minutes before the visit. Subjects participated in the following assessments at each visit:

Clinical Efficacy

An investigator evaluated the face (right and left) of each subject for the following parameters using a grading scale (with half points allowed):

- *Overall Hyperpigmentation*: 0 = none, 1 to 3 = mild, 4 to 6 = moderate, and 7 to 9 = severe.
- *Investigator's Global Hyperpigmentation Improvement*: 1 = worse, 2 = no improvement, 3 = mild improvement, 4 = moderate improvement, 5 = marked improvement.

Tolerability

An investigator assessed each subject for erythema and scaling using a 4-point scale (0 = none, 3 = severe). In addition, subjective parameters, including burning/stinging, itching, tightness, and tingling, were assessed by the subjects.

TABLE 1.

Composition for Skin Brightener Products 1, 2, and 3 With Suggested Biochemical Pathway of Action[a]

Pathway	Ingredients	Reference	BR1	BR2	BR3
Reduce Melanocyte Activation					
Reduce free radicals	Tetrahexyldecyl ascorbate	16	√	√	√
Reduce inflammatory cytokines	SMA-432	17	0.5%	0.1%	0.5%
Reduce Melanin Synthesis by Limiting Tyrosinase Availability					
Tyrosinase transcription inhibition	Retinol	18	√	√	√
Tyrosinase degradation	Linoleic acid	19	√	√	√
Tyrosinase transfer inhibition	SMA-013	20	0.1%	0.1%	–
Competitive tyrosinase inhibition	Glabridin	21	√	√	√
Competitive tyrosinase inhibition	Hexylresorcinol	22	√	√	√
Reduce Melanin Transfer to Keratinocytes					
Reduce melanocytic dendrite formation	Niacinamide	23	√	√	√
	SMA-432	17	√	√	√
Remove Epidermal Melanin					
Accelerate keratinocyte turnover	Retinol	24	√	√	√

[a]A checkmark indicates that the ingredient is present in the formula at a therapeutically relevant concentration.

Chroma Meter

A Chroma Meter (CR-400; Minolta, Tokyo, Japan) in conjunction with a computer was used to instrumentally assess skin color. A single measurement was taken on the right and left sides of each subject's face on a hyperpigmented area selected by the expert grader. The location was recorded on a facial diagram to ensure consistency of measurement location at each visit.

Digital Photography

Digital photographs using a Nikon camera (Canfield VISIA-CR® camera system; Fairfield, NJ) were taken of the right and left sides of the face of each subject with standard and cross-polarized lighting conditions to document changes in facial hyperpigmentation.

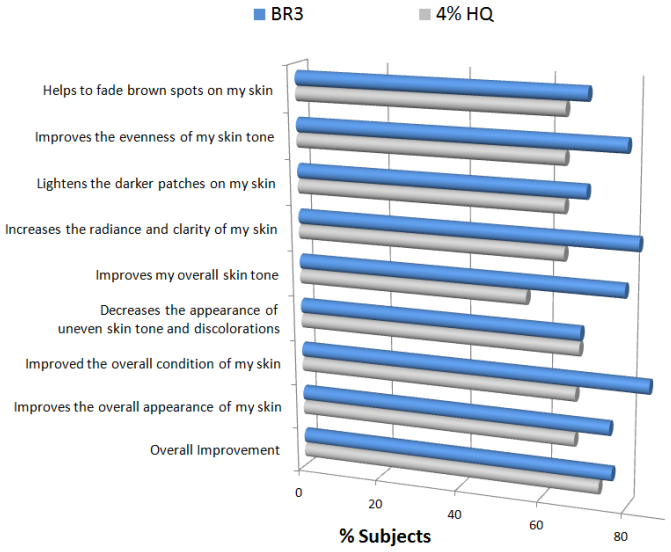
Self-Assessment Questionnaires

Subjects completed a self-assessment questionnaire regarding various skin parameters on the right and left sides of the face.

Statistical Analysis

Clinical grading scores and Chroma Meter measurement values at week 4, week 8, and week 12 were compared with baseline scores/values using a paired *t* test. The average percent change from baseline was calculated for all parameters at each postbaseline visit. Comparisons among the test materials were performed using analysis of variance with paired comparisons using Fisher's least significant difference. All differences were considered to be statistically significant at the $P<.05$ level.

FIGURE 3. Subject self-assessment questionnaire results at week 12, reflecting the percentage of subjects who responded "strongly agree" or "agree." HQ, hydroquinone.



RESULTS

Seventy-five Caucasian female subjects were enrolled in the study. Of those, 68 subjects (136 half faces) completed the 12-week study and were included in the analysis. Of the 136 half faces, BR1 = 35, BR2 = 34, BR3 = 33, and 4% HQ = 34. Demographic information on the 68 subjects is presented in Table 2.

Efficacy Assessments

The mean Overall Hyperpigmentation score at baseline for all subjects was between 5 and 5.5 (moderate). Figure 1 shows a statistically significant reduction in Overall Hyperpigmentation score for all treatment groups when compared with baseline. BR1 and BR3 produced a reduction statistically equivalent to 4% HQ at 12 weeks (P>.13). BR1 appears to have a faster onset of action, with greater improvement at 4 weeks as compared with BR3. This may be attributed to the activity of SMA-013, a targeted inhibitor of tyrosinase transfer, present in BR1 but not in BR3. SMA-432, an inhibitor of prostaglandin E_2, shows a dose-dependent reduction in hyperpigmentation as seen when compared with BR1 and BR2, which contain 0.5% and 0.1% SMA-432, respectively.

A similar trend is seen in rating of Global Improvement from baseline. As seen in Figure 2, SMA-432 exhibits a dose response, strongly indicating a significant contribution of this patented ingredient in the combination product. In addition, BR1 shows improvement that is statistically equivalent to that seen with 4% HQ.

The most relevant data from the Chroma Meter measurements related to changes in L* values (skin tone brightening). Analysis of the change from baseline scores indicated a statistically significant improvement in L* for BR1, BR2, and BR3 at week 8.

TABLE 2.

Study Subject Demographics	
Age, years	
Range	33-65
Mean	52.2
Fitzpatrick skin type	
I	5.9%
II	48.5%
III	45.6%

Tolerability

There was significantly greater erythema observed for all products at week 4 compared with baseline. However, by week 12, there were no significant differences in erythema for any products compared with baseline. Scaling was not an issue for any of the formulations. In subject assessments, mean scores for burning/stinging were mild or below at weeks 4 and 8 for BR1, BR2, and BR3. Subjects also reported transient and intermittent skin tightness with BR1 and BR2. Itching and tingling were of minor or no concern to subjects for all formulations.

Self-Assessment Questionnaires

The self-assessment questionnaires were generally favorable for all 4 products. After completion of the 12-week trial, subjects were asked to indicate overall satisfaction with the treatment. BR3 was the most favorable product, and 4% HQ was the least favorable product. Figure 3 is a comparison of subject responses to BR3 and 4% HQ. Significant improvements in melasma and mottled pigmentation are seen in photographs of the subjects at 12 weeks compared with baseline, as shown in Figures 4 and 5.

DISCUSSION

Humans seem to be preoccupied with altering their natural skin color, either making it darker or lighter. Skin pigmentation depends on the amount and type of melanin synthesized by the melanosomes. Melanin, particularly eumelanin (brown-black pigment), protects underlying tissues from harmful UV radiation.[7,11,12] Even considering the biological importance of melanin, there are differing perceptions regarding the "ideal" skin color according to various cultures around the world. In Western society, tanned skin has recently been perceived as a healthy look, despite warnings about the consequences of excessive UV exposure.[12] However, in the Eastern world, a light complexion is more desirable, as it is regarded as equivalent to youth and beauty.[13] Not only does skin lightness affect perceptions of a woman's beauty

FIGURE 4. A 35-year-old female with Fitzpatrick skin type III **a)** at baseline and **b)** after 12 weeks of twice-daily application of BR3.

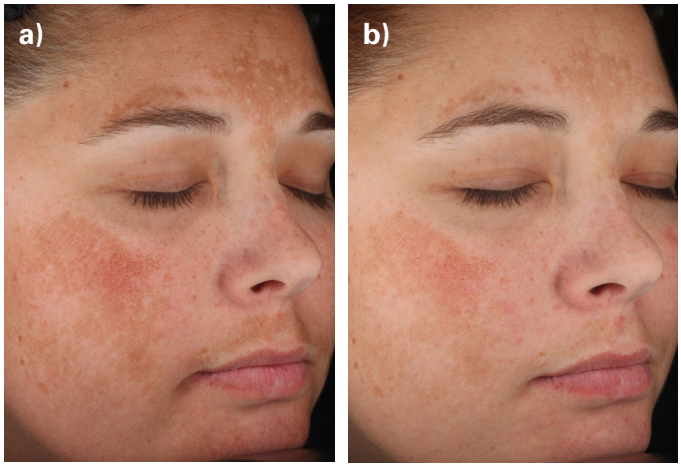
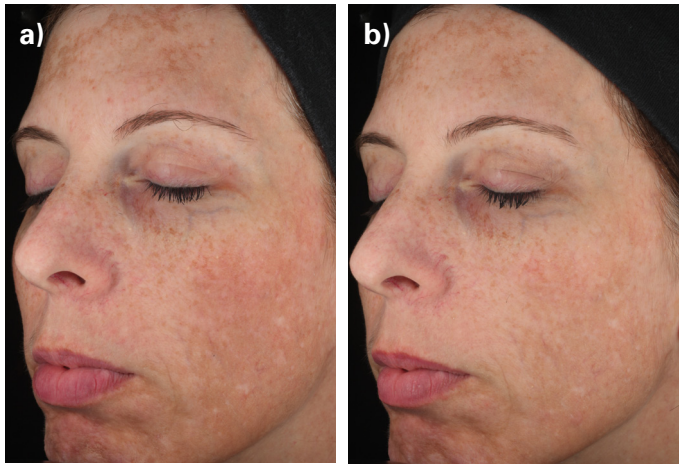


FIGURE 5. A 36-year-old female with Fitzpatrick skin type III **a)** at baseline and **b)** after 12 weeks of twice-daily application of BR3.



in Asian cultures, it also affects social standing, job and marital prospects, and even earnings potential.[13] Whitening and lightening skin products have achieved dramatic growth and are among the best-selling product categories in the Asian beauty industry. The desire for fair skin is not, however, limited to Asian cultures. It is a global phenomenon also seen in African, South American, and Middle Eastern cultures. Skin whitening is a rapidly growing segment of the global beauty industry. Today, skin lightening products are used worldwide for their ability not only to lighten darker complexions, but also to control age-related hyperpigmentation.

"Today, skin lightening products are used worldwide for their ability not only to lighten darker complexions, but also to control age-related hyperpigmentation."

Concerns about the safety of topical HQ have resulted in its removal from certain European and Japanese markets and potential withdrawal in the US market. These actions led to a host of new skin lighteners being added to the cosmetic marketplace as "safe" alternatives. The majority of these products lack any clinical evidence to demonstrate that they can lighten hyperpigmented human skin.

Some of these new alternative products to HQ employ a related agent, arbutin. This β-D-glucopyranoside derivative of HQ is available in both natural and synthetic forms. Studies have shown that following oral ingestion, arbutin is metabolized and excreted in humans as HQ, HQ glucuronide, and HQ sulfate.[14] Normal skin microflora (*Staphylococcus epidermidis* and *Staphylococcus aureus*) can hydrolyze arbutin, converting it to HQ.[15] Thus, these arbutin-containing skin lighteners are not HQ free.

Inadvertent exposure to UV radiation plays a major role in melanin control during execution of clinical studies. Studies conducted over winter months tend to exaggerate the benefits of skin brighteners; therefore, studies assessing efficacy of skin brighteners should be conducted during the summer months to simulate worst-case scenarios.

The 3 skin brightener formulations were developed based on an understanding of the pathway for melanogenesis and employ a combination of ingredients that intervene with differing components of this pathway. These include suppression of tyrosinase production, enhancement of tyrosinase degradation, prevention of tyrosinase transport to melanosomes, inhibition of tyrosinase activity, and inhibition of melanosome transport. Other ingredients provide anti-inflammatory, antioxidant, and exfoliant properties. This multimodality approach delivers a truly comprehensive cosmetic solution to management of pigmentary conditions that provides efficacy comparable to a well-established prescription product.

CONCLUSIONS

The results of this blinded and controlled, half-face clinical use study indicate that the 3 skin brightener formulations and 4% HQ cream were all effective in reducing pigmentation after 4, 8, and 12 weeks of use, based on investigator assessments. A dose-dependent response was observed for proprietary skin brightening agent SMA-432. There were no major tolerability issues with any product. At study completion, subjects reported highest satisfaction with BR3 and lowest satisfaction with 4% HQ. This new skin lightener has been clinically demonstrated as an effective non–HQ-containing product.

DISCLOSURES

Financial support for this study was provided by SkinMedica, an Allergan Company. Ms. Makino, Mr. Garruto, and Dr. Mehta are employees of SkinMedica, an Allergan Company. Mr. Gotz is a consultant for SkinMedica, an Allergan Company.

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Safety and Efficacy of a Novel Multimodality Hydroquinone-Free Skin Brightener Over Six Months

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ABSTRACT

Background: Abnormal accumulation of melanin is a common aesthetic skin concern. For years, the gold standard for the treatment of hyperpigmentary disorders has been 4% hydroquinone (HQ). Due to regulatory agencies around the world questioning the safety of HQ, there has been interest in developing new HQ-free skin brightening/lightening products. A multimodality product (skin brightening complex) addressing various pathways for melanogenesis was developed as an alternative to HQ.

Objective: The skin brightening complex was studied for efficacy and tolerability in subjects with moderate to severe facial hyperpigmentation.

Methods: Subjects were instructed to apply skin brightening complex to the entire face twice daily and to follow a standard skin care regimen (facial cleanser, moisturizer, and sunscreen) during the course of the study. The study was conducted over a 12-week period and consisted of evaluation visits at baseline and at weeks 4, 8, and 12. At each visit, subjects were evaluated by an investigator for clinical efficacy and tolerability using grading scales. Standardized digital photographs and spectrophotometric assessments were also taken. Self-assessment questionnaires were completed at weeks 4, 8, and 12. To assess longer-term safety and efficacy, 10 subjects elected to continue treatment for an additional 12 weeks (24 weeks total), with evaluations at weeks 18 and 24.

Results: Twenty-six subjects completed the 12-week study, and 8 subjects completed treatment for an additional 12 weeks (24 weeks in total). In the 12-week study, the skin brightening complex was shown to be effective and significantly improved Overall Hyperpigmentation at weeks 4, 8, and 12 compared with baseline. The skin brightening complex also significantly improved the Mottled Pigmentation Area and Severity Index ([MoPASI], a modified Melasma Area and Severity Index [MASI] scale) at weeks 8 and 12 compared with baseline. These efficacy benefits continued at 24 weeks. The product was well tolerated at all evaluation visits. Subject questionnaires showed 80% or more of the subjects reporting pigmentation improvement and satisfaction with the skin brightening complex at all evaluation visits.

Conclusion: This HQ-free skin brightening complex was effective and well tolerated in subjects with facial hyperpigmentation who were treated for as long as 24 weeks.

J Drugs Dermatol. 2013;12(3 suppl 1):s27-s31.

INTRODUCTION

Melanin is an inert polymer pigment produced by the melanosomes, and it determines the color and gradation of skin.[1,2] Skin tone and the uniformity or evenness of skin color are important cosmetic concerns throughout the world. Hyperpigmentary disorders of the skin are commonly seen in dermatology practices. Both sexes and all Fitzpatrick skin types are susceptible to these aesthetic skin conditions. Such hypermelanotic disorders typically result from advancing age, hormonal imbalance (changes that may be caused by pregnancy or use of contraceptives), and/or injury. Exposure to ultraviolet light (which produces inflammation and resultant cellular damage) is the most common cause of skin hyperpigmentation.[3,4]

The gold standard for skin lightening was hydroquinone (HQ) until regulatory agencies in Europe, Japan, and most recently in the United States questioned the safety of this agent.[5-8] While the drug has been used as a skin lightener for over 50 years without evidence of human cancers,[6] studies in rodents have produced renal tubule adenomas in male F-344 rats and liver adenomas and thyroid gland follicular cell hyperplasia in mice.[9]

Many currently available skin lightening agents (including HQ, arbutin, kojic acid, and others) act via inhibition of tyrosinase, the key enzyme involved in melanin production. However, tyrosinase is not the only pathway of interest for skin lightening ingredients. With an improved understanding of the complexities of melanogenesis, several other pathways are being pursued as targets for skin lightening agents. Rationally designed combination products can target several pathways to disrupt melanin.

Previously, a unique formulation containing several ingredients that address multiple pathways involved in melanin production and control was tested against the gold standard, 4% HQ, in subjects with moderate to severe facial hyperpigmentation. This HQ-free formulation was shown to be as effective and well tolerated as 4% HQ in a randomized, double-blind, half-face model.[10] The present study was performed to gain additional safety and efficacy data on the skin brightening complex from an additional study site and also to assess long-term treatment effects.

MATERIALS AND METHODS

The criteria for participation in this study included subjects with Fitzpatrick skin types I to IV in good general health between the ages of 18 and 65 years with moderate to severe facial hyperpigmentation as determined by clinical examination. Subjects were required to have a baseline score of 4 to 9

on both sides of the face from the Investigator's Overall Hyperpigmentation scale. Subjects also had to be willing not to use any other topical products (skin lightening, retinoids, benzoyl peroxide, steroids, α/β hydroxyl acids) on the facial area or any systemic retinoids throughout the duration of the study, and to avoid extended periods of sun exposure. Subjects were provided standard skin care products (facial cleanser, moisturizer, and SPF-30 physical sunscreen) with instructions for use during the course of the study.

Institutional Review Board approval was obtained for this study. The study was conducted according to ethical and regulatory principles from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Prior to treatment, the subjects provided informed consent. The study was conducted in Houston, Texas from January to August 2012.

The skin brightening complex was studied to assess efficacy and tolerability in subjects with moderate to severe facial hyperpigmentation. Subjects were instructed to apply a thin layer of the skin brightening complex to the entire facial area twice daily, morning and evening.

This single-center study was conducted over a 12 week period. Ten subjects elected to continue treatment for an additional 12 weeks (24 week total). Evaluation visits were conducted at baseline, week 4, week 8, and week 12 (and at weeks 18 and 24 in the extension).

Subjects arrived at the clinic having removed all makeup at least 20 minutes prior to the visit. Subjects participated in the following assessments at each visit:

Clinical Efficacy

An investigator evaluated the face of each subject for the following parameters using a grading scale (with half-points allowed):

- *Overall Hyperpigmentation*: 0 = none, 1-3 = mild, 4-6 = moderate, and 7-9 = severe.

- *Mottled Pigmentation Area Severity Index (MoPASI)*: This modified scale is derived from the validated Melasma Area and Severity Index (MASI) scale for melasma. Mottled pigmentation is assessed in 4 sections of facial skin, with a weight assigned to each section: forehead (0.2), nose, upper lip, and chin (0.2), left cheek and periorbital region (0.3), and right cheek and periorbital region (0.3). Three variables are assessed within each facial region: A = percentage of area involved, D = darkness of pigment in the area, and P = pattern of involvement in the area. Total MoPASI score is calculated as: forehead 0.2 (D + P)A + right cheek and periorbital 0.3 (D + P)A + left cheek and periorbital 0.3 (D + P)A + nose, upper lip and chin 0.2 (D + P)A.

Tolerability

An investigator assessed each subject for erythema, edema, and scaling. Subjects assessed themselves for burning/stinging, itching, and redness. All parameters were assessed using a 4-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe).

Spectrophotometer

Spectrophotomer (Minolta Model 600d; Tokyo, Japan) measurements for L* (brightness) were taken at baseline and at weeks 4, 8, 12, and 24.

Digital Photography

Digital color photographs were taken at baseline and at weeks 4, 8, 12, 18, and 24 using a Nikon camera (Canfield VISIA-CR® camera system, Fairfield, NJ). They were taken frontal and 45° lateral with standard and cross-polarized lighting conditions to document changes in facial hyperpigmentation.

Subject Self-Assessment Questionnaires

Subjects completed a self-assessment questionnaire regarding their experience with the products at weeks 4, 8, and 12 (and at weeks 18 and 24 in the extension).

Statistical Analysis

Clinical grading scores and spectrophotometer measurement values at each evaluation visit were compared with baseline scores/values using a paired *t* test. The average percentage of change from baseline was calculated at each postbaseline visit. All differences are considered to be statistically significant at the $P<.05$ level.

RESULTS

Thirty-two subjects were enrolled, and 26 completed the 12-week study. Five subjects were lost to follow-up, and one discontinued due to mild burning/stinging. Demographics of subjects completing the 12-week study are presented in Table 1. Ten subjects agreed to continue treatment for an additional 12 weeks and 8 subjects completed the full 24-week assessment. Two subjects were lost to follow-up. Demographics of these subjects are presented in Table 2.

In the 12-week study, the skin brightening complex demonstrated significant reductions in mean Overall Hyperpigmentation scores at weeks 4, 8, and 12 compared with baseline (all $P\leq.016$, n=26). Reductions continued at 24 weeks (Figure 1). Significant reductions in MoPASI scores were seen at weeks 8 and 12 compared with baseline (all $P\leq.013$, n=26). Reductions continued at weeks 18 and 24 (Figure 2). Spectrophometer readings for L* increased progressively with each visit but did not reach statistical significance at 12 weeks ($P=.063$).

The skin brightening complex was well tolerated. The tolerability assessments (erythema, edema, and scaling by the investiga-

TABLE 1.

Demographics of 12-Week Study Subjects (n=26)		
		Skin Brightening Complex
Subjects (n)		26
Age (years)	Mean	50.9
	Range	33-64
Sex (%)	Female	96
	Male	4
Fitzpatrick skin type (%)	I	7.7
	II	30.8
	III	30.8
	IV	26.9
	V	3.8

TABLE 2.

Demographics of 24-Week Study Subjects (n=8)		
		Skin Brightening Complex
Subjects (n)		8
Age (years)	Mean	48.5
	Range	33-60
Sex (%)	Female	100
	Male	0
Fitzpatrick skin type (%)	I	0
	II	50
	III	25
	IV	25
	V	0

tor, and burning/stinging, itching, and redness by the subject) showed mean scores of "mild" or less at each evaluation time.

Self-assessments by the subjects showed high levels of satisfaction with the skin brightening complex and consistent improvements over the 24-week study (Figures 3-5). Figure 5 illustrates treatment effects over the 24-week study.

DISCUSSION

There is great diversity in what is considered an ideal skin color throughout the world. In the West, despite repeated warnings regarding the consequences of excessive ultraviolet exposure, tanned skin is considered a healthy appearance, whereas in Eastern cultures a light complexion is preferable and regarded as equivalent to youth and beauty.[11,12] The desire for lighter skin also extends to South American, African, and Middle Eastern societies. The quest for lighter skin, combined with regulatory agency concerns about HQ, has prompted cosmetic and beauty manufacturers to develop new non–HQ-based products to address this need. Skin lightening is one of the most rapidly growing segments of the global beauty industry. Despite the proliferation of new skin lightening products added to the cosmetic marketplace, the majority of these products lack clinical evidence of the ability to lighten hyperpigmented human facial skin.

The MASI was originally developed by Kimbrough-Green[13] to provide a more accurate quantification of the severity of melasma and changes during therapy. The MASI was used for almost 20 years as the predominant outcome measure in the assessment of melasma. Until recently, the MASI had never been tested for reliability or validity. The MASI has now been shown to be a reliable measure of melasma severity.[14] The MoPASI is a dermatologist-developed modified MASI assessment, created prior to the initiation of the present study for use as a more quantitative assessment of cosmetic changes in mottled pigmentation.

This study confirms results from an earlier randomized, HQ-controlled, double-blind, half-face trial[10] and demonstrates that the skin brightening complex formulation was effective in reducing pigmentation after 4, 8, and 12 weeks based on primary investigator assessments, including a more quantitative assessment of the severity of mottled pigmentation using MoPASI. No major tolerability issues were observed with the skin brightening complex. Data obtained on a small subset of 8 subjects who received the skin brightening complex for a total 24 weeks demonstrated continued reductions in pigmentation without tolerability issues. Subject questionnaires showed 80% or more of subjects reported improvement in pigmentation and satisfaction with the skin brightening complex at all evaluation visits.

"Subject questionnaires showed 80% or more of subjects reported improvement in pigmentation and satisfaction with the skin brightening complex at all evaluation visits."

The skin brightening complex was developed with a combination of ingredients to address key aspects in the melanogenesis pathway. Limiting tyrosinase availability is addressed by the inhibition of tyrosinase transcription (retinol),[15] enhancement of tyrosinase degradation (linoleic acid),[16] and competitive tyrosinase inhibition (glabridin and hexylresorcinol).[17,18] Reduction of melanocytic dendrite formation, (niacinamide and 4-eth-

FIGURE 1. Reduction in Overall Hyperpigmentation scores at weeks 4, 8, 12, 18, and 24 compared with baseline (significant changes at weeks 4, 8, and 12; $P \leq .016$).

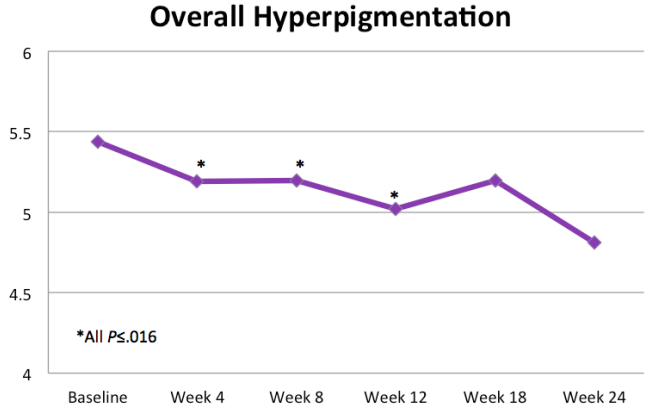


FIGURE 2. Reduction in MoPASI scores at weeks 4, 8, 12, 18, and 24 compared with baseline (significant changes at weeks 8, 12, 18, and 24; $P \leq .013$). MoPASI, Mottled Pigmentation Area and Severity Index.

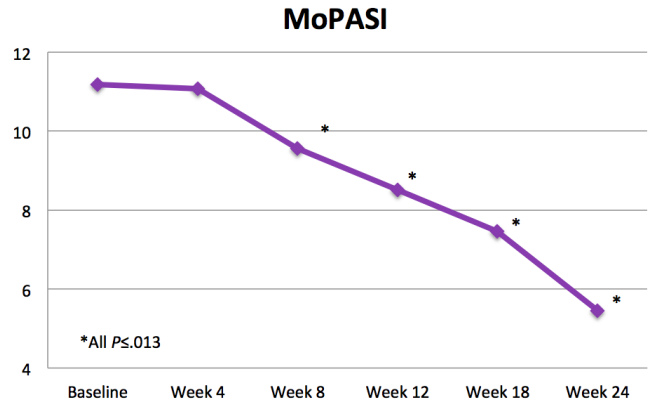
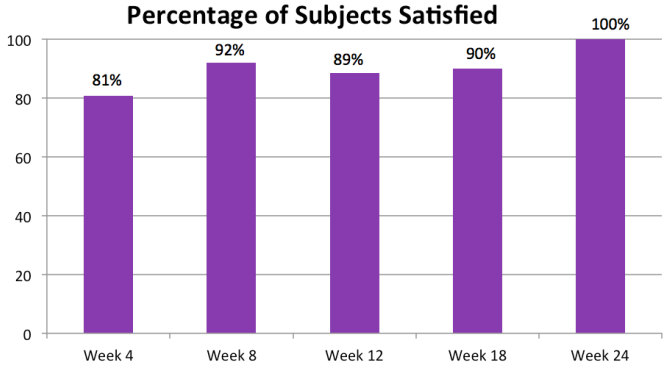


FIGURE 3. Subject self-assessment questionnaire: percentage satisfied with skin brightening complex.



oxybenzaldehyde)[19,21] helps diminish the transfer of melanin to keratinocytes. Lastly, limiting melanocyte activation is addressed by reducing free-radical formation (tetrahexyldecyl ascorbate)[20] and reducing inflammatory cytokines (4-ethoxybenzaldehyde).[21]

FIGURE 4. Subject self-assessment questionnaire: percentage experiencing improvement with skin brightening complex.

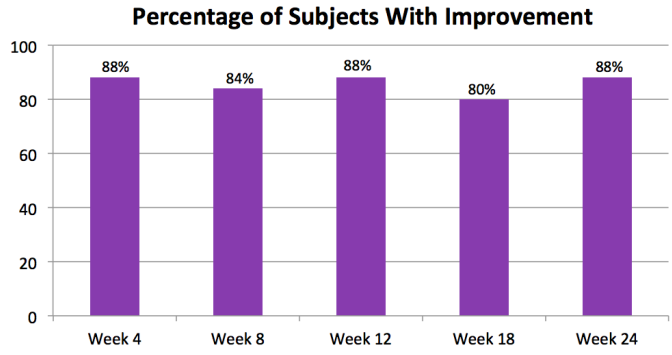
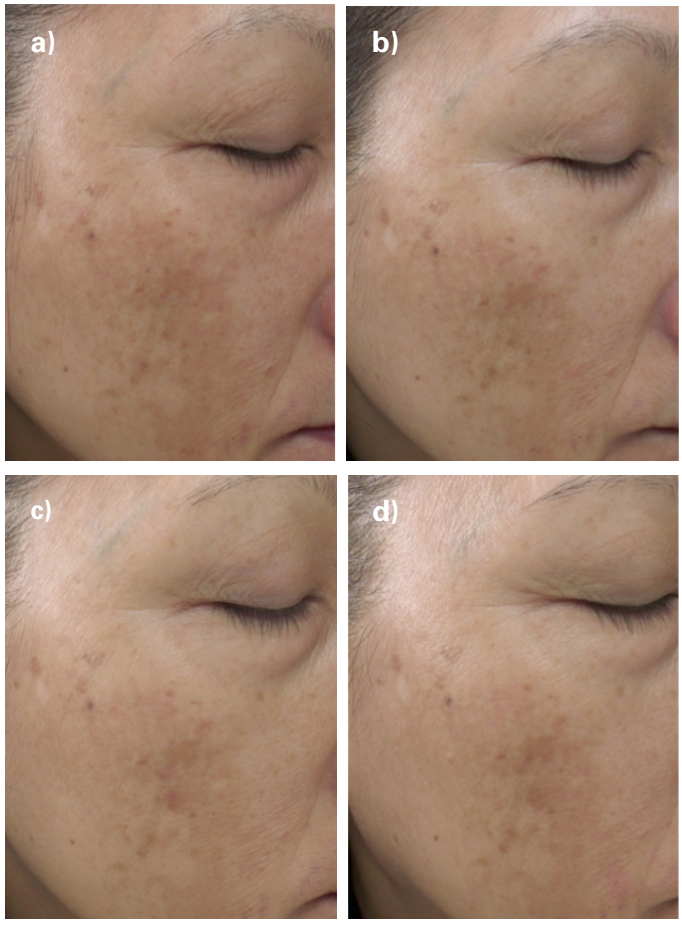


FIGURE 5. A 60-year-old Asian female with Fitzpatrick skin type IV at **a)** baseline, **b)** week 12, **c)** week 18, and **d)** week 24.



CONCLUSIONS

This new skin brightening complex was again shown to be a well tolerated and effective alternative to HQ in treating hyperpigmentary disorders of the face. Similar to a previous 12-week clinical study, the specific combination of ingredients in this skin brightening complex provided improvements in moderate

to severe facial hyperpigmentation in as few as 4 weeks, with continued improvements through week 12. However, unique to this study, treatment for an additional 12 weeks (24 weeks total) provided further improvements in hyperpigmentation with continued favorable tolerability.

DISCLOSURES

Dr. Bruce is a consultant for SkinMedica, an Allergan company. Financial support for this study was provided by SkinMedica, an Allergan Company.

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Comparative Study of Hydroquinone-Free and Hydroquinone-Based Hyperpigmentation Regimens in Treating Facial Hyperpigmentation and Photoaging

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ABSTRACT

Background: Photoaged skin, characterized by mottled, irregular areas of pigmentation, is a common skin condition that is often difficult to treat. The areas of hypermelanosis are an aesthetic concern to subjects and may lead to social distress and quality of life issues. There are many commercial hyperpigmentation regimens marketed to lighten dark spots and improve overall skin dyschromia. However, data to support efficacy of such kits are often lacking.

Objective: This investigator-blinded, randomized trial was conducted to compare a new hydroquinone (HQ)-free hyperpigmentation regimen against a leading HQ-based hyperpigmentation regimen for the treatment of facial hyperpigmentation and photoaging.

Methods: Subjects with mottled pigmentation and photodamaged facial skin were randomized to treatment with either the new 4-product (HQ-free) SkinMedica® Hyperpigmentation System (SKM; SkinMedica, an Allergan Company, Carlsbad, CA) kit or the 7-product (HQ-containing) Obagi Nu-Derm System (OMP; Obagi Medical Products, Long Beach, CA) kit. Subjects were evaluated by a blinded investigator for clinical efficacy and tolerability using grading scales at baseline and at weeks 4, 8, and 12. Standardized digital photographs were taken at baseline and week 12. Self-assessment questionnaires were completed at week 12.

Results: Thirty-six female subjects (16: SKM; 20: OMP) completed the 12-week comparative study. Both hyperpigmentation regimens significantly reduced Overall Hyperpigmentation, Mottled Pigmentation Area and Severity Index (MoPASI), global photoaging, and sallowness at week 12 compared to baseline. Significant reductions in tactile roughness were seen with the OMP regimen at week 12. In these investigator-blinded assessments, there were no significant differences between treatment groups, nor was there a difference in global response to treatment. Investigator assessments of tolerability showed mean scores were mild or below for all parameters with both treatment regimens.

Conclusion: A new 4-product (HQ-free) regimen was shown to be as effective and tolerable as a 7-product (HQ-based) regimen in reducing facial hyperpigmentation and photoaging in females with mottled pigmentation and photodamaged facial skin.

J Drugs Dermatol. 2013;12(3 suppl 1):s32-s37.

INTRODUCTION

As humans age, irregular areas of facial hyperpigmentation, resulting from a combination of intrinsic aging and long-term exposure to ultraviolet light, become more common.[1,2] While there is great variation in the color of human skin worldwide, a uniform or even facial skin color is considered a sign of health, attractiveness, and youthfulness, and is therefore aesthetically desirable.[3,4] Hyperpigmentary skin disorders can cause emotional and psychological effects and a decreased quality of life.[5,6] In our image-conscious society, affected individuals are increasingly requesting treatment for this aesthetic problem to improve appearance. Hydroquinone (HQ) has long been considered the gold standard for skin lighteners,[7-9] despite a rather modest efficacy requiring several weeks of treatment before its depigmenting effects are readily seen. More recently, various regulatory agencies around the world, including the US Food and Drug Administration (FDA), have raised questions related to the safety of HQ.[7-10] This has prompted efforts to develop options for alternative and HQ-free treatments for hyperpigmentation.

Overall treatment success for hyperpigmentation is best achieved by combining various agents that work at different stages of melanogenesis. Thus, providing patients with a comprehensive regimen that lightens existing hyperpigmentation, prevents new pigment formation, and minimizes stimulation by ultraviolet rays may further enhance overall treatment success.

A comprehensive and HQ-free hyperpigmentation regimen was developed to address these key areas, combining 4 products including a novel skin brightening complex, facial cleanser, tretinol 1.1%, and sunscreen. The present study compares this new 4-product HQ-free SkinMedica® Hyperpigmentation System (SKM; SkinMedica, an Allergan Company, Carlsbad, CA) regimen against a 7-product HQ-based Obagi Nu-Derm System (OMP; Obagi Medical Products, Long Beach, CA) regimen in the treatment of facial hyperpigmentation and photoaging.

This study was conducted using the same design as a recently published study where 2 HQ-based hyperpigmentation kits were shown to be equally effective in significantly improving mottled pigmentation and photodamage in females.[11] However, to further explore the effects of this multimodality skin brightening complex, HQ was replaced with the skin brightening complex in the SKM regimen.

MATERIALS AND METHODS

The criteria for study participation included adult subjects aged 35 to 65 years with Fitzpatrick skin types I to IV, having at least mild mottled hyperpigmentation of the face (corresponding to a score of 2 or more on a 5-point hyperpigmentation scale) and photodamaged facial skin (score of 2 or above on a 5-point global photoaging scale). Subjects had to be willing not to use any other topical products (skin lightening, retinoids, α/β-hydroxyl acids, salicylic acid, vitamins C or D, steroids, or antibiotics) on the facial area, systemic retinoids, or steroids, nor to have facial peels or laser procedures throughout the duration of the study. Subjects had to be willing to use only the facial skin care product regimen provided for the study and to avoid extended periods of sun exposure and the use of tanning beds during the study.

Institutional Review Board approval was obtained for this investigator-blinded, parallel-arm, randomized, single-center comparison study. The study was conducted according to ethical and regulatory principles from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Prior to treatment, the subjects provided informed consent. The study was conducted in San Diego, CA, from March to September 2012.

In accordance with a predetermined randomization schedule, subjects were assigned to either the HQ-free 4-product SKM kit, which included cleanser, skin brightening complex, sunscreen SPF30 +, and tri-retinol 1.1% products (Facial Cleanser, Lytera™ Skin Brightening Complex, Daily Physical Defense™ SPF 30+ Sunscreen, Tri-Retinol Complex ES™ [SkinMedica]) or the 7-product OMP kit, which included cleanser, toner, HQ 4% (applied twice daily), exfoliant, another HQ 4% (applied once daily), sunscreen SPF 35, and tretinoin 0.025% (Foaming Gel, Toner, Clear Exfoderm®, Blender®, Healthy Skin Protection SPF 35 , Tretinoin Cream [Obagi Medical Products]). In addition to receiving written instructions, subjects were given verbal directions for use of the products.

The study was conducted over a 12-week period and consisted of evaluation visits at baseline, week 4, week 8, and week 12. Subjects arrived at the clinic having removed all makeup at least 20 minutes prior to the visit. Subjects participated in the following assessments at each visit:

Clinical Efficacy

A blinded investigator evaluated the face of each subject for the following parameters using a grading scale:

- *Mottled Pigmentation Area and Severity Index* (MoPASI): This modified scale is derived from the validated Melasma Area and Severity Index (MASI) scale for melasma. Mottled pigmentation is assessed in 4 sections of facial skin, with a weight assigned to each section: forehead (0.2), nose, upper lip, and chin (0.2), left cheek and periorbital region (0.3), and right cheek and periorbital region (0.3). Three variables are assessed within each facial region: A = percentage of area involved, D = darkness of pigment in the area, and P = pattern of involvement in the area. Total MoPASI score is calculated as: forehead 0.2 (D + P)A + right cheek and periorbital 0.3 (D + P)A + left cheek and periorbital 0.3 (D + P)A + nose, upper lip, and chin 0.2 (D + P)A.

- *Evaluation of hyperpigmentation*: 0 = none; 1 = trace, with light hyperpigmentation involving small areas; 2 = mild, with moderate hyperpigmentation involving small areas *or* light hyperpigmentation involving moderate areas; 3 = moderate, with moderate hyperpigmentation involving moderate areas *or* light hyperpigmentation involving all areas; and 4 = severe, with marked hyperpigmentation.

- *Global photoaging:* 0 = smooth without significant fine lines or unevenness in pigmentation; 1 = facial skin shows one area (cheeks, forehead, or the perioral area) of significant roughness, dyspigmentation (hypopigmentation or hyperpigmentation), or fine lines; 2 = facial skin shows 2 areas of significant roughness, dyspigmentation, or fine lines, or shows roughness, dyspigmentation, and fine lines in one area; 3 = facial skin shows 3 areas with significant roughness, dyspigmentation, or fine lines, or shows roughness, dyspigmentation, and fine lines in 2 areas; and 4 = facial skin shows any degree of photodamage greater than criterion #3.

- *Fine lines/wrinkles*: 0 = none; 1 = trace with rare fine lines that are widely spaced; 2 = mild with several, discrete fine lines; 3 = moderate number of fine lines in close proximity; and 4 = severe, with many fine lines, densely packed.

- *Tactile roughness*: 0 = none, normal, smooth skin; 1 = trace, smooth skin, with occasional rough areas; 2 = mild roughness; 3 = moderate roughness; 4 = severe roughness.

- *Sallowness*: 0 = normal, pink skin; 1 = trace, skin is pale; 2 = mild, skin has a slight suggestion of yellowness; 3 = moderate, skin is pale, with a moderate suggestion of yellowness; and 4 = skin is pale, with a distinct suggestion of yellowness.

- *Global response to treatment:* 0 = completely cleared; 1 = almost complete improvement of the condition with a trace of signs and/or symptoms remaining (approximately 90% improvement); 2 = marked improvement of the condition with some signs and/or symptoms remaining (approximately 75% improvement); 3 = moderate improvement of the condition with a fair amount of signs and/or symptoms remaining (approximately 50% improvement); 4 = mild improvement of the condition with a distinctive amount of signs and/or symptoms remaining (approximately 25% improvement); 5 = no change; and 6 = exacerbation. This evaluation was made by the investigator comparing the appearance at the final visit with the baseline visit.

TABLE 1.

Demographics of Study Subjects by Treatment Group, SKM vs OMP

	SKM Group	OMP Group
Subjects completing the study (n)	16	20
Mean age (years)	48.4	45.6
Age range (years)	36-61	37-54
Fitzpatrick Skin Types (%)		
I	6	5
II	18	5
III	38	35
IV	38	55
Evaluation of hyperpigmentation score (mean baseline)	2.75	2.75
Global photoaging score (mean baseline)	2.95	2.75

OMP, Obagi Nu-Derm System; SKM, SkinMedica Hyperpigmentation System.

Tolerability

Local tolerability, including erythema, burning/stinging, dryness, peeling, and tenderness on the face, was assessed by the investigator using a 4-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe).

Clinical Photography

Subjects were photographed at baseline and week 12 using a digital photography system (Canfield VECTRA® camera system; Fairfield, NJ) at highest resolution in a consistent position.

Subject Self-Assessment Questionnaire

Subjects completed a questionnaire regarding the effectiveness and tolerability of the treatment regimen at each follow-up visit.

Statistical Analysis

Statistical analysis was conducted on an intent-to-treat basis (all randomized subjects with at least 1 follow-up visit were included). All statistical tests were 2-sided and interpreted at a .05 significance level. The primary analyses of efficacy were based on evaluation of hyperpigmentation, MoPASI, and global photoaging scores. Scores at week 12 were compared to baseline scores using a paired *t* test. Comparisons between treatment groups were performed using single-factor analysis of variance.

RESULTS

Forty subjects who met the inclusion/exclusion criteria were enrolled in the study and randomized to treatment with either the SKM kit or the OMP kit. Thirty-six females completed the 12-week trial: 20 subjects were in the OMP group and 16 subjects were in the SKM group. Four subjects in the SKM group were lost to follow-up. One of these subjects discontinued the study due to experiencing an adverse event (AE) of itching, erythema, and swelling, which resolved without sequelae. Data for these 4 subjects were included in the analysis for their completed visits. The 2 groups were similar and demographic information is presented in Table 1. Significant reductions in MoPASI scores (all $P \leq .013$; Figure 1) and evaluation of hyperpigmentation scores (all $P \leq .008$; Figure 2) were seen for both treatments at week 12. Significant reductions in global photoaging (all $P \leq .009$) and sallowness (all $P < .001$) were seen with both treatments at week 12. The OMP group showed statistical improvement in tactile roughness at week 12 ($P < .001$; Figure 3). There were no other differences between the 2 treatment groups in these efficacy parameters at any visit. In addition, there were no significant differences in global response to treatment between the 2 groups (Figure 4).

Investigator assessments of tolerability showed mean scores were mild or lower for all parameters in both treatment regimens. Two subjects in the OMP group experienced AEs: 1 subject experienced contact dermatitis and the other subject

FIGURE 1. Reduction in MoPASI scores at weeks 4, 8, and 12 compared with baseline ($P \leq .013$ at week 12 for both regimens; no significant differences between treatment groups). MoPASI, Mottled Pigmentation Area and Severity Index; OMP, Obagi Nu-Derm System; SKM, SkinMedica Hyperpigmentation System.

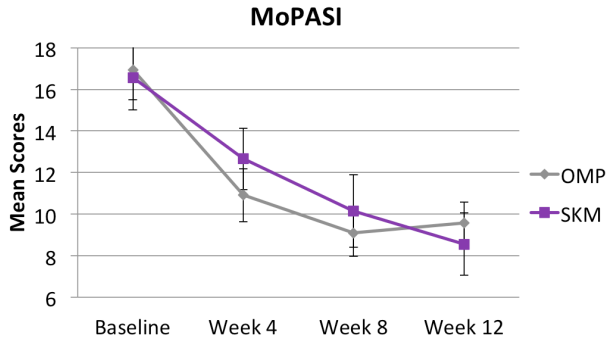


FIGURE 2. Reduction in Overall Hyperpigmentation scores at weeks 4, 8, and 12 compared with baseline ($P \leq .008$ at week 12 for both regimens; no significant differences between treatment groups). OMP, Obagi Nu-Derm System; SKM, SkinMedica Hyperpigmentation System.

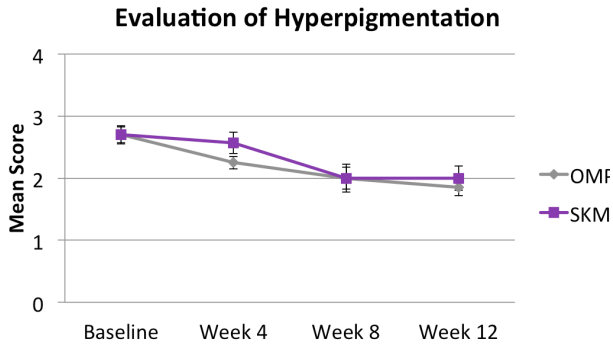


FIGURE 3. Reductions in global photoaging, tactile roughness, and sallowness scores at weeks 4, 8, and 12 compared with baseline (global photoaging: $P \leq .009$ at week 12 for both regimens; tactile roughness: $P < .001$ at week 12 for OMP; sallowness: $P < .001$ at week 12 for both regimens; no significant differences between treatment groups). OMP, Obagi Nu-Derm System; SKM, SkinMedica Hyperpigmentation System.

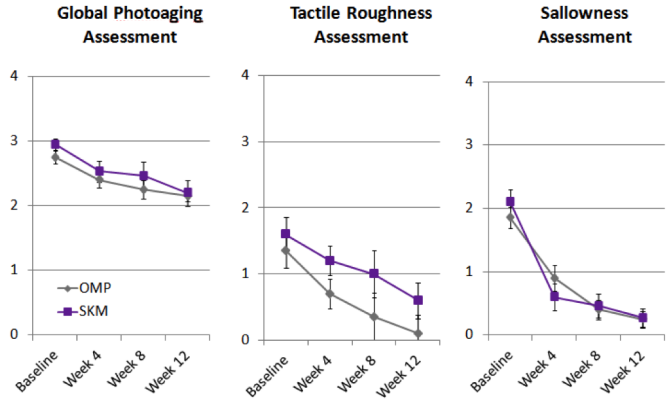


FIGURE 4. Comparison of global response to treatment after 12 weeks ($P \leq .009$ for both regimens; no significant differences between treatment groups). OMP, Obagi Nu-Derm System; SKM, SkinMedica Hyperpigmentation System.

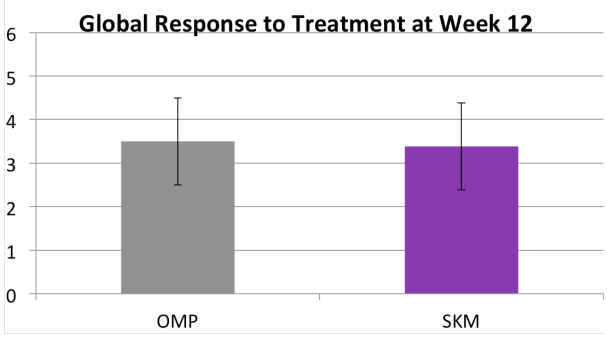


FIGURE 5. Subject comparison of convenience of 2 regimens (2 = strongly agree; 1 = agree; –1 = disagree; –2 = strongly disagree). OMP, Obagi Nu-Derm System; SKM, SkinMedica Hyperpigmentation System.

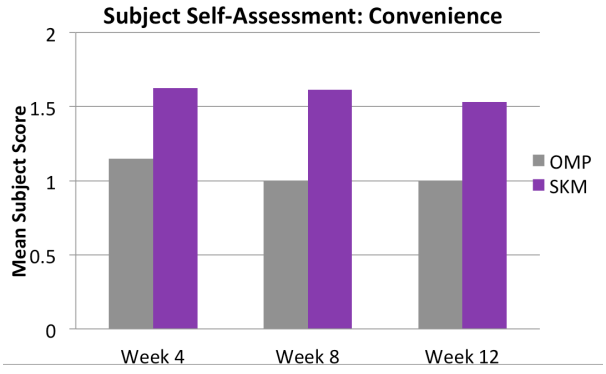


FIGURE 6. A 40-year-old Asian female with Fitzpatrick skin type IV **a)** at baseline and **b)** after 12 weeks of treatment with the SkinMedica Hyperpigmentation System regimen.

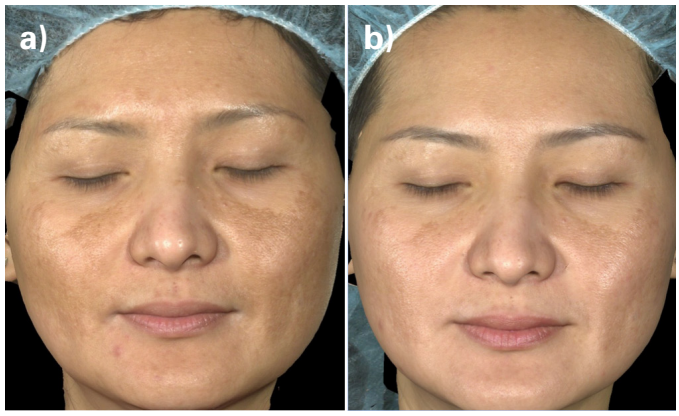
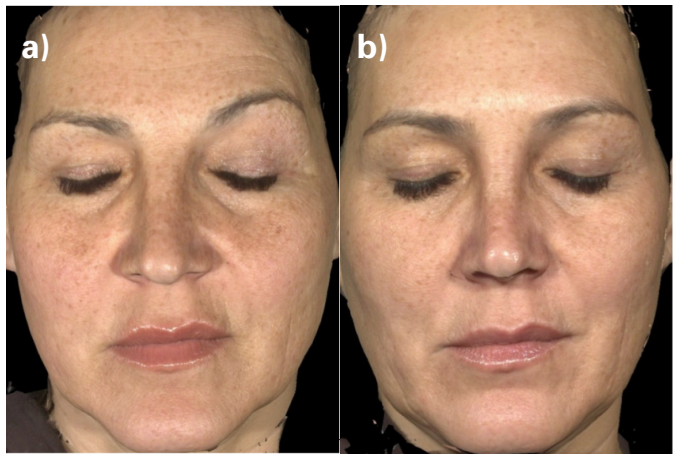


FIGURE 7. A 52-year-old Caucasian female with Fitzpatrick skin type III **a)** at baseline and **b)** after 12 weeks of treatment with the Obagi Nu-Derm System regimen.



experienced erythema. Two subjects in the SKM group also experienced AEs, with 1 subject experiencing itching, erythema, and swelling, and the other subject experiencing erythema. All AEs resolved without sequelae.

In self-assessment questionnaires, subjects considered the SKM kit more convenient to use than the OMP kit at all visits (Figure 5), although the difference did not reach statistical significance. Representative photographs of subjects at baseline and after 12 weeks of treatment are shown for the SKM regimen in Figure 6 and for the OMP regimen in Figure 7.

DISCUSSION

Although HQ has been the gold standard for the treatment of hyperpigmentation for many years, the FDA has raised some safety concerns (based on animal studies)[10] that have prompted the development of alternative skin lightening/brightening products. A host of new skin lighteners have been added to

the cosmetic marketplace as "safe" alternatives. The majority of these products lack any clinical evidence to demonstrate efficacy in lightening hyperpigmented human skin. Some of these new alternative products to HQ contain arbutin, a β-D-glucopyranoside derivative of HQ. Following oral ingestion, arbutin is metabolized and excreted in humans as HQ, HQ glucuronide, and HQ sulfate.[12] Additionally, normal skin microflora (*Staphylococcus epidermidis* and *Staphylococcus aureus*) can hydrolyze the conversion of arbutin to HQ.[13] Thus, arbutin-containing skin lighteners are not truly HQ free, and do not meet the needs of those seeking alternative HQ-free skin lighteners.

Results from this study demonstrated that the 4-product SKM (HQ-free) regimen was as effective and tolerable as the 7-product OMP (HQ-based) regimen over the 12-week study period, suggesting that the SKM regimen may provide an alternative to HQ-containing regimens. In addition, the following important distinctions exist between these 2 regimens: the OMP system utilizes 3 prescription products (tretinoin 0.025% and 2 products containing HQ 4%) while the SKM regimen does not utilize any prescription products.

Recently, a clinical study comparing 2 commercial hyperpigmentation kits utilizing a very similar clinical trial design was published.[11] The study compared a 4-product kit containing HQ with a 7-product kit containing HQ. The results demonstrated that both kits were equally effective at reducing hyperpigmentation and global photoaging in females with mottled pigmentation and photodamaged facial skin.

The present study substituted the HQ 4% product in the SKM kit with a non-HQ, multimodality skin brightening complex. This skin brightening complex, which addresses multiple pathways involved in melanin production and control, was recently shown to be as effective and well tolerated as 4% HQ in females with facial hyperpigmentation in a randomized, double-blind, half-face comparative study.[14] The skin brightening complex was formulated based on an understanding of the melanogenesis pathway and specifically employs a combination of ingredients to intercede with the different aspects affecting this pathway. This includes the reduction of melanocyte activation by reducing free-radical formation (tetrahexyldecyl ascorbate)[15] and reducing inflammatory cytokines (4-ethoxybenzaldehyde).[16] In addition, the reduction of melanin synthesis by limiting tyrosinase availability is targeted through tyrosinase transcription inhibition (retinol),[17] enhancement of tyrosinase degradation (linoleic acid),[18] competitive tyrosinase inhibition (glabridin[19] and hexylresorcinol).[20] Lastly, the reduction of melanocytic dendrite formation (niacinamide[21] and 4-ethoxybenzaldehyde[17]) diminishes the transfer of melanin to keratinocytes.

The present study also employed the MoPASI, a dermatologist-developed modification of the previously validated MASI,[22] to achieve a more quantitative assessment of cosmetic changes in the treatment of mottled pigmentation.

Product efficacy alone does not automatically lead to treatment success; patient adherence to a recommended regimen is essential for positive treatment outcomes. Factors affecting patient adherence include cost, complexity, and the aesthetic feel of the treatment regimen, and may motivate or deter the patient from regimen compliance.

In general, adherence to topical treatment regimens in dermatology is poor.[23,24] In an assessment of compliance to a topical corticosteroid regimen, 2 of the major reasons for non-compliance included "application was time-consuming" and "interfered with daily activities". Inconvenience is considered a major factor contributing to intentional nonadherence with topical treatments.[25] The greater number of products in the OMP regimen along with the greater number of steps involved likely contributed to the higher convenience ratings for the SKM regimen.

"Clinical results show a hydroquinone-free alternative to a hydroquinone-based regimen for control of pigment disorders."

CONCLUSIONS

Clinical results show an HQ-free alternative to an HQ-based regimen for control of pigment disorders. A new 4-product (HQ-free) regimen was shown to be as effective and tolerable as a 7-product (HQ-containing) regimen in reducing facial hyperpigmentation and photoaging in females with mottled pigmentation and photodamaged facial skin.

DISCLOSURES

Dr. Goldman is a consultant for SkinMedica, an Allergan Company, and Obagi Medical Corporation. Dr. Fabi and Dr. Goldman have performed clinical studies for SkinMedica, an Allergan Company. Medical writing assistance was provided by Vincent Gotz MS MBA of ProPharmaCon, LLC, Carlsbad, CA.

Financial support for this study was provided by SkinMedica, an Allergan Company.

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Assessment of a Superficial Chemical Peel Combined With a Multimodal, Hydroquinone-Free Skin Brightener Using In Vivo Reflectance Confocal Microscopy

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ABSTRACT

The combination of in-office procedures such as chemical peels with topical maintenance therapies has been shown to provide greater efficacy than either treatment by itself in the management of melasma. A series of 3 case studies were conducted to evaluate the efficacy and tolerability of one superficial chemical peel (containing a proprietary blend of resorcinol, lactic acid, salicylic acid, and retinol) combined with a topical multimodal, hydroquinone-free skin brightener as postpeel maintenance therapy. Patients presented with moderate to severe facial hyperpigmentation. At baseline, subjects received the superficial chemical peel treatment followed by a standard postpeel skin care regimen (cleanser, moisturizer, and SPF 30+ sunscreen). Approximately 1 week after the peel procedure, subjects initiated twice-daily application of the skin brightener. Subjects were then evaluated for Global Improvement in Hyperpigmentation by the investigator for up to 7 weeks postpeel. Standardized digital photographs of the subjects facial skin and in vivo reflectance confocal microscopy (RCM) images were taken of a target hyperpigmented lesion at baseline and at follow-up. Standardized photography and in vivo RCM images at baseline and at postpeel show the improvements observed by the investigator. Results from these case studies suggest that the combination of a superficial chemical peel with topical maintenance and the multimodal skin brightener may provide an effective treatment approach for subjects with moderate to severe facial hyperpigmentation.

J Drugs Dermatol. 2013;12(3 suppl 1):s38-s41.

INTRODUCTION

A combination of treatments targeting various points in the sequence of pigment formation is becoming a more common option for hyperpigmentation therapy. Indeed, treatment success is often facilitated by a combination of therapies, including topical treatments and chemical peels.[1-3] Chemical peels focus on the removal of hyperpigmented lesions and have been established as effective treatments.[4] However, exfoliation of hyperpigmented lesions only addresses one aspect of the pigmentation pathway. A unique multimodal and hydroquinone (HQ)-free skin brightener has been clinically shown to provide reductions in moderate to severe facial hyperpigmentation when used as monotherapy.[5] The ingredients of the skin brightener were selected to address key pathways in pigmentation including melanocyte activation, melanin synthesis, and melanin transfer, as described previously.[5] Combining a chemical peel with such a skin brightener may provide subjects with an effective option for managing hyperpigmentation.

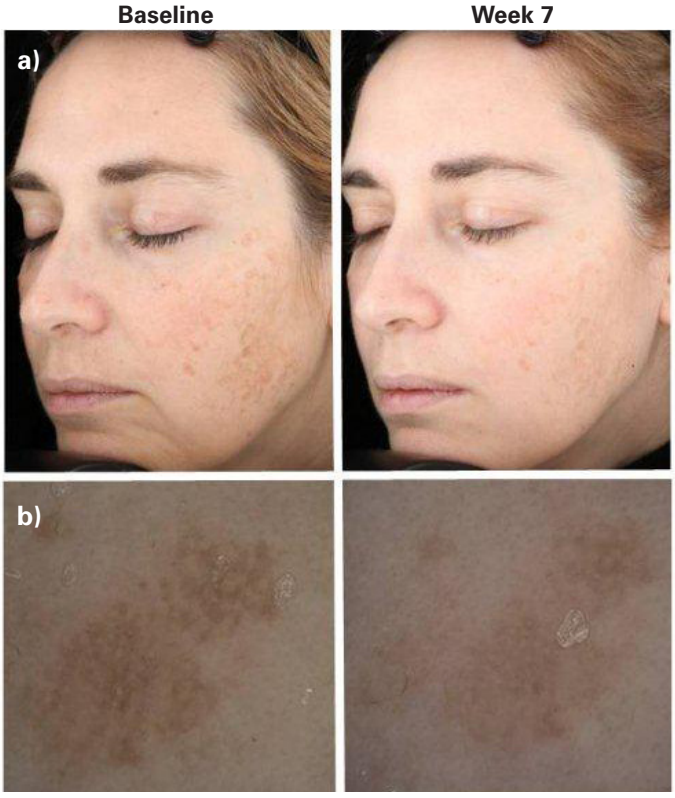
In the case studies presented below, patients received 1 superficial chemical peel treatment (containing a proprietary blend of resorcinol, lactic acid, salicylic acid, and retinol) followed by up to 6 weeks of maintenance therapy with a topical multimodal and HQ-free skin brightener. Investigator assessments, standardized digital photography with standard lighting, and cross-polarized brown channel lighting (Canfield VISIA-CR®; Fairfield, NJ) as well as dermoscopy and in vivo reflectance confocal microscopy (RCM) images (VivaScope 1500; Caliber Imaging and Diagnostics, Inc., Rochester, NY) were taken at baseline and at follow-up visits.

The use of in vivo RCM to observe pigmentary changes produced by the treatment of a superficial chemical peel and skin brightener in these case studies presents a novel application of this instrument. In recent years, in vivo RCM has become an effective noninvasive tool, used by clinicians to support the diagnosis of skin cancers.[6-9] Due to melanin's high reflectance index (1.7), pigmented keratinocytes and melanocytes appear as bright white structures relative to the surrounding skin.[10] Generally, reductions in pigment result in a decreased quantity and intensity of bright white structures and appear similar to the surrounding normal skin.

Case Report 1

A 46-year-old Caucasian female patient with Fitzpatrick skin type III presented with moderate facial hyperpigmentation, as

FIGURE 1. a) A 46-year-old female with Fitzpatrick skin type III at baseline and after 7 weeks of treatment (one Vitalize Peel, followed by 6 weeks of twice-daily treatment with Skin Brightening Complex). **b)** Subject dermoscopy of a target lesion characterized by a pigment network at baseline and after 7 weeks of treatment.



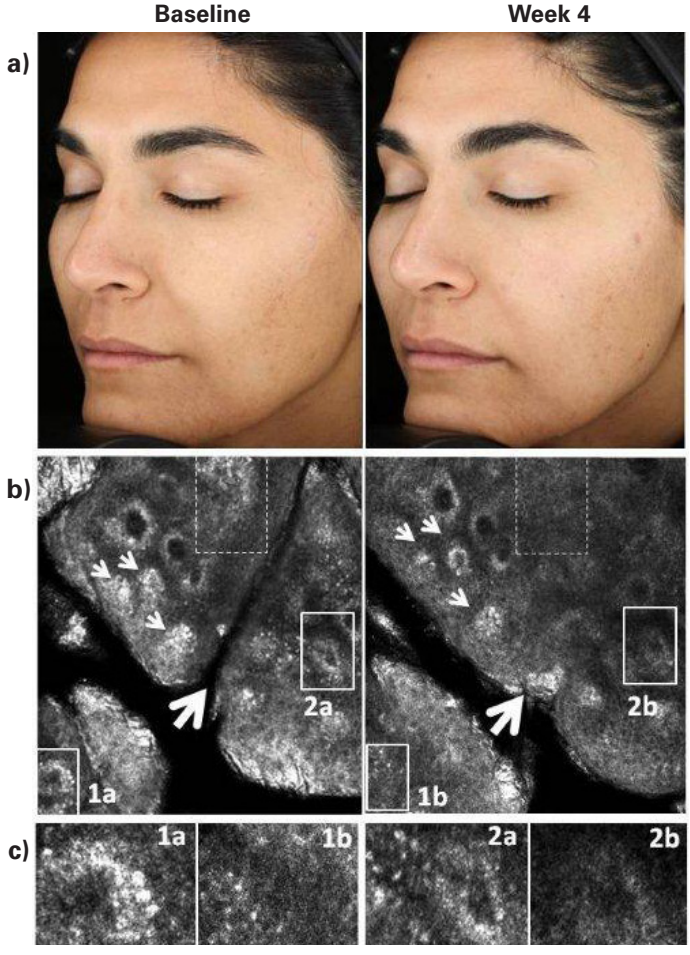
determined by a grade of 6 on the Overall Hyperpigmentation scale (0 = none, 1-3 = mild, 4-6 = moderate , 7-9 = severe). At baseline, the patient was treated with 1 superficial chemical peel on the facial skin (Vitalize Peel®; SkinMedica Inc., Carlsbad, CA). The patient followed a standard skin care regimen (cleanser, moisturizer, and SPF 30+ sunscreen). Approximately 1 week after the peel procedure, when the skin completed the peeling process, the patient initiated topical application of the skin brightener twice daily for 6 weeks.

The patient returned for a follow-up visit approximately 7 weeks after the baseline visit. Global Improvement in Hyperpigmentation was graded by the investigator as "marked improvement (approximately 75% overall improvement), a distinctive improvement of the condition with some signs/symptoms remaining." Standardized digital photographs of the patient's face using standard lighting and dermoscopy of a target hyperpigmented lesion located on the left lower malar area were taken at baseline and at week 7 and are presented in Figure 1.

Case Report 2

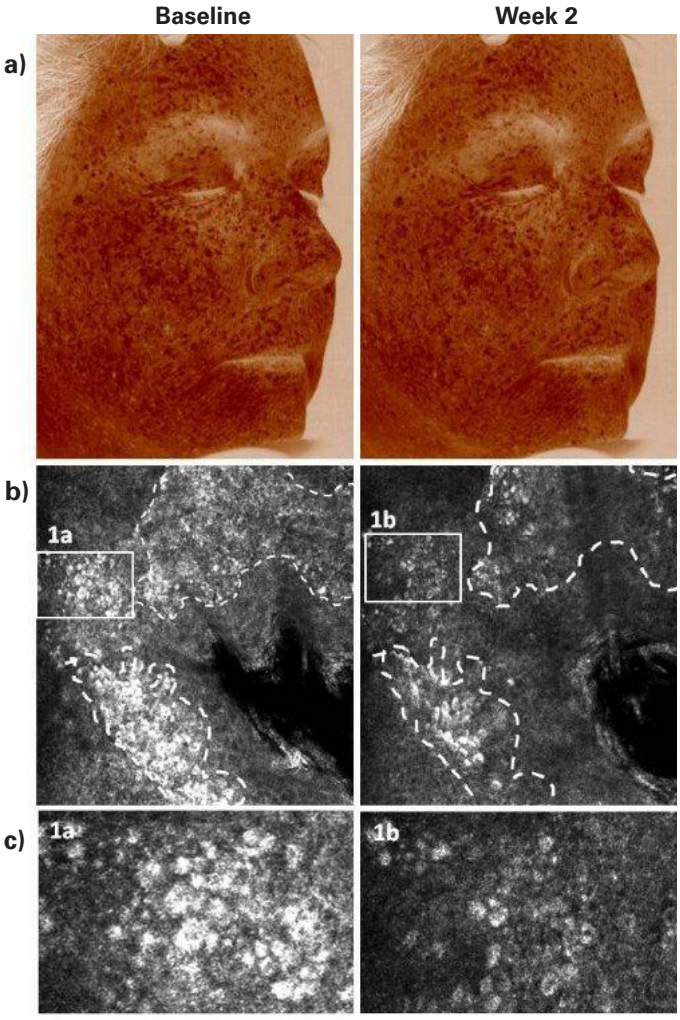
A 42-year-old Middle Eastern female patient with Fitzpatrick skin type IV presented with moderate facial hyperpigmentation,

FIGURE 2. a) A 42-year-old female with Fitzpatrick skin type IV at baseline and after 4 weeks of treatment (one Vitalize peel followed by 3 weeks of twice-daily treatment with Skin Brightening Complex). **b)** Reflectance confocal microscopy (RCM) images taken using Lucid Vivascope 1500 at baseline and after 4 weeks of treatment. RCM single frame (0.5 x 0.5 mm) at the superficial epidermis (granulosum-spinosum) level. At baseline, a characteristic honeycombed pattern with mottled pigmented areas and abundant pigmented keratinocytes are observed (continuous and discontinuous outlined bright white areas as well as small arrowheads). A skin furrow is indicated by the large arrowhead in the figure. After 4 weeks of treatment, a marked reduction in the intensity and number of pigmented keratinocytes was observed (continuous and discontinuous outlined areas as well as small arrowheads) and a smoothing of the skin (large arrowhead). **c)** A close-up of outlined areas 1a and 2b show detailed changes previously described in **b**.



as determined by a grade of 4 on the Overall Hyperpigmentation scale (0 = none, 1-3 = mild, 4-6 = moderate, 7-9 = severe). At baseline, the patient was treated with 1 superficial chemical peel on the facial skin (Vitalize Peel). The patient followed a standard skin care regimen (cleanser, moisturizer, and SPF 30+ sunscreen). Approximately 1 week after the peel procedure, the patient initiated twice-daily application of the skin brightener for 3 weeks.

FIGURE 3. a) A 52-year-old female with Fitzpatrick skin type III at baseline and after 2 weeks of treatment (one Vitalize Peel followed by 1 week of twice-daily treatment with the skin brightener). Photographs were taken with cross-polarized brown channel lighting showing pigment present at baseline and after 2 weeks of treatment. **b)** Reflectance confocal microscopy (RCM) single frame (0.5 x 0.5 mm) at the level of the stratus spinosum. Mottled pigmentation, pigmented keratinocytes (outlined bright white areas) in the context of a honeycombed pattern was observed at baseline. Two weeks later, we observed a reduction in the number and intensity of pigmented keratinocytes (outlined areas). **c)** A close-up of outlined areas 1a and 1b, showing detailed changes previously described in **b**.



The patient returned for a follow-up visit approximately 4 weeks after the baseline visit. Global Improvement in Hyperpigmentation was assessed by the investigator as "mild improvement (approximately 25% overall improvement), a noticeable improvement of the condition with a distinctive amount of signs/symptoms remaining." Standardized digital photographs of the patient's face using standard lighting and in vivo RCM images of a target hyperpigmented lesion located on the left lower malar area were taken at baseline and at week 4 and are presented in Figure 2.

Case Report 3

A 52-year-old Caucasian female patient with Fitzpatrick skin type III presented with severe facial hyperpigmentation, as determined by a grade of 7 on the Overall Hyperpigmentation scale (0 = none, 1-3 = mild, 4-6 = moderate, 7-9 = severe). At baseline, the patient was treated with one superficial chemical peel on the facial skin (Vitalize Peel). The patient followed a standard skin care regimen (cleanser, moisturizer, and SPF 30+ sunscreen). Approximately 1 week after the peel procedure, the patient initiated twice-daily application of the skin brightener for 3 weeks.

The patient returned for a follow-up visit at 2 weeks and 4 weeks after the baseline visit. At week 2, the investigator observed no changes in Global Improvement in Hyperpigmentation. However, as presented in Figure 3, subsurface reductions in hyperpigmented areas on the right facial side were observed in the standardized digital photographs using cross-polarized brown channel lighting and in vivo RCM images.

At week 4, subsurface pigmentary changes continued to be observed with standardized digital photography and the in vivo RCM images. The investigator graded Global Improvement in Hyperpigmentation as "mild improvement (approximately 25% overall improvement), a noticeable improvement of the condition with a distinctive amount of signs/symptoms remaining."

> "Combining a chemical peel with such a skin brightener may provide subjects with an effective option for managing hyperpigmentation."

DISCUSSION

Reflectance confocal microscopy was originally invented in 1955 and has since become a useful tool for the diagnosis of malignant lesions in human skin.[7] Due to recent technological advances incorporating the use of laser beams at various wavelengths, features of the skin can be visualized in real time. Using in vivo RCM, pigmented keratinocytes can be easily detected due to their strong contrast, presenting as bright white. We have been able to use this tool to effectively show the changes in the skin, such as pigmentation at a cellular level with application of a treatment product.

In these case studies, by incorporating the novel use of in vivo RCM along with digital photography taken with cross-polarized brown channel lighting, we were able to detect early subsurface pigmentary changes in hyperpigmentation at week 2, as in the case of patient 3. Global Improvement in Hyperpigmentation of at least 25% was observed by the investigator

for all 3 patients by week 4. Longer term treatment is typically required for approximately a 25% Global Improvement in Hyperpigmentation. In addition to changes in pigmentation, in vivo RCM was able to show the smoothing of a skin furrow at week 4 that was originally present at baseline.

These case studies demonstrate that combination treatment with 1 superficial chemical peel procedure followed by maintenance therapy with a novel multimodal skin brightener can provide an effective and synergistic hyperpigmentation regimen for patients.

DISCLOSURES

Financial support for this study was provided by SkinMedica, an Allergan Company.

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Hydroquinone-Free Multimodal Topical Regimen for Facial Hyperpigmentation

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ABSTRACT

To assess the treatment of hyperpigmentation, a series of 5 case studies were conducted to evaluate the efficacy and tolerability of a novel hydroquinone-free treatment regimen combining a multimodal skin brightener with a cleanser, high strength retinol product and sunscreen SPF 30+. Patients presented with moderate to severe facial hyperpigmentation as determined by a score of 4 to 8 on the Overall Hyperpigmentation scale. Physician-graded Overall Hyperpigmentation, Global Improvement in Hyperpigmentation, and standardized photography were conducted at weeks 3, 6, and 12. At week 12, the majority of patients demonstrated Global Improvements in Hyperpigmentation of at least 50%, with at least a 2-grade reduction in Overall Hyperpigmentation scores, as assessed by the physician. Standardized photographs also support the physician and patient findings. Results from these case studies demonstrate that this unique 12-week treatment regimen can provide an effective and simple option for patients with facial hyperpigmentation.

J Drugs Dermatol. 2013;12(3 suppl 1):s42-s44.

INTRODUCTION

Hyperpigmentation, presenting as dark spots or patches, results from excess melanin in the skin and can be caused by hormonal or endocrinal disorders such as melasma or by long-term sun exposure resulting in photodamage. Successful treatment of hyperpigmentation often proves difficult and challenging for patients due its recurrent nature.[1] Several cutaneous pathways contribute to hyperpigmentation, including melanocyte activation, melanin synthesis, and melanin transfer. Topical therapies have the opportunity to target these areas in the sequence of pigment production. Recently, a multimodal skin brightener was found to provide comparable efficacy to 4% hydroquinone (HQ) in patients with moderate to severe facial hyperpigmentation.[2] Case studies are presented herein using this unique multimodal skin brightener with a facial cleanser, a high strength retinol product, and a sunscreen SPF 30+ in patients with facial hyperpigmentation.

METHODS

Five female patients between the ages of 30 and 62 years with Fitzpatrick skin types II or III are presented herein. At baseline, each patient manifested moderate to severe facial hyperpigmentation (from sun exposure or melasma) as assessed by a grade of 4 to 9 on an Overall Hyperpigmentation scale. The combination regimen was composed of 4 products, including a cleanser, a novel mulimodal skin brightener, sunscreen SPF 30+, and a high strength retinol product (Facial Cleanser, Lytera™ Skin Brightening Complex, Daily Physical Defense™ SPF 30+ Sunscreen, Tri-Retinol Complex ES™; SkinMedica Inc., Carlsbad, CA). For 1 of the patients, patient 3, the combination regimen was combined with a superficial chemical peel procedure received at week 6. The remaining 4 patients only used the topical regimen for 12 weeks. Patients returned to the office at weeks 3, 6, and 12 for physician grading of Global Improvement in Hyperpigmentation and Overall Hyperpigmentation as well as standardized digital photography. At week 12, patients were also asked about their self-assessed improvement with the treatment program. The grading scales for Global Improvement and Overall Hyperpigmentation are:

- *Global Improvement in Hyperpigmentation*: 0 = no change or worsening; 1 = mild improvement, a noticeable improvement of the condition with a distinctive amount of remaining signs/symptoms (approximately 25% overall improvement); 2 = moderate improvement, a very noticeable improvement of the condition with a fair amount of remaining signs/symptoms (approximately 50% overall improvement); 3 = marked improvement (approximately 75% overall improvement); 4 = complete clearing, nearly complete improvement of the condition with a trace of remaining signs/symptoms (approximately 95% or more overall improvement).
- *Overall Hyperpigmentation*: 0 = none; 1-3 = mild; 4-6 = moderate; 7-9 = severe.

FIGURE 1. Physician's Global Improvement assessment scores for all 5 patients (0 = no change or worsening; 1 = 25% overall improvement; 2 = 50% overall improvement; 3 = 75% overall improvement; 4 = 95% or more overall improvement).

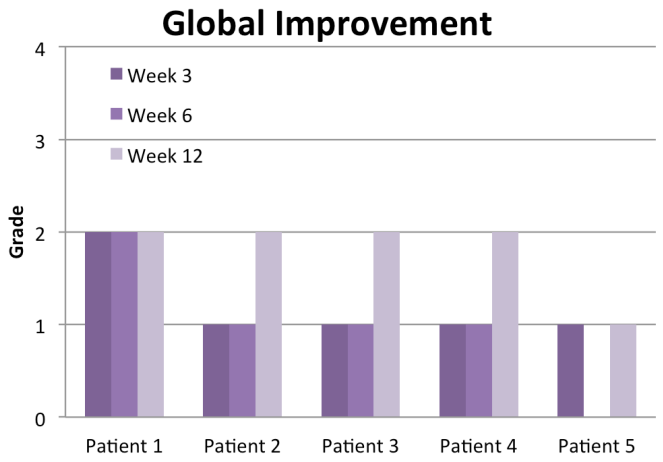
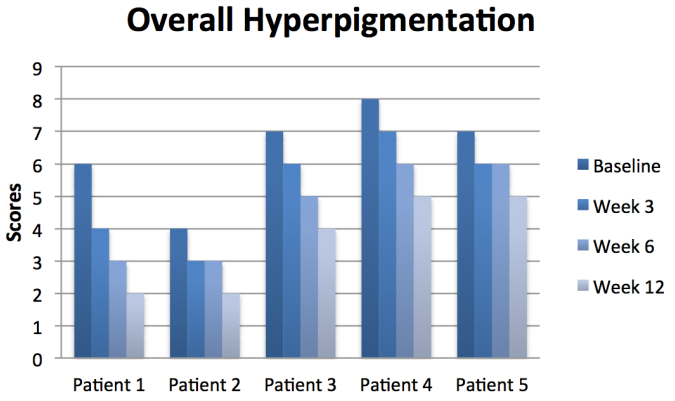


FIGURE 2. Overall Hyperpigmentation assessment scores for all 5 patients (0 = none; 1-3 = mild; 4-6 = moderate; 7-9 = severe).



RESULTS

At week 12, all 5 patients demonstrated Global Improvements in Hyperpigmentation of at least 25%, with 4 of the 5 patients showing at least a 50% improvement at week 12 as shown by physician grading presented in Figure 1. At least a 2-grade reduction in Overall Hyperpigmentation scores was observed by week 12 as shown in Figure 2.

In the patient self-assessment questionnaires, 100% of the patients noticed at least a 25% improvement with the treatment regimen, consistent with the physician grading.

Standardized photography of patients presented in Figures 3 to 5 are representative of the improvements observed by both the physician and patient. The treatment regimen was well tolerated with no treatment-related adverse events.

FIGURE 3. Patient 1. Female patient aged 41 years with Fitzpatrick skin type II presenting with an Overall Hyperpigmentation score of **a)** 6 at baseline and **b)** 2 at week 12.

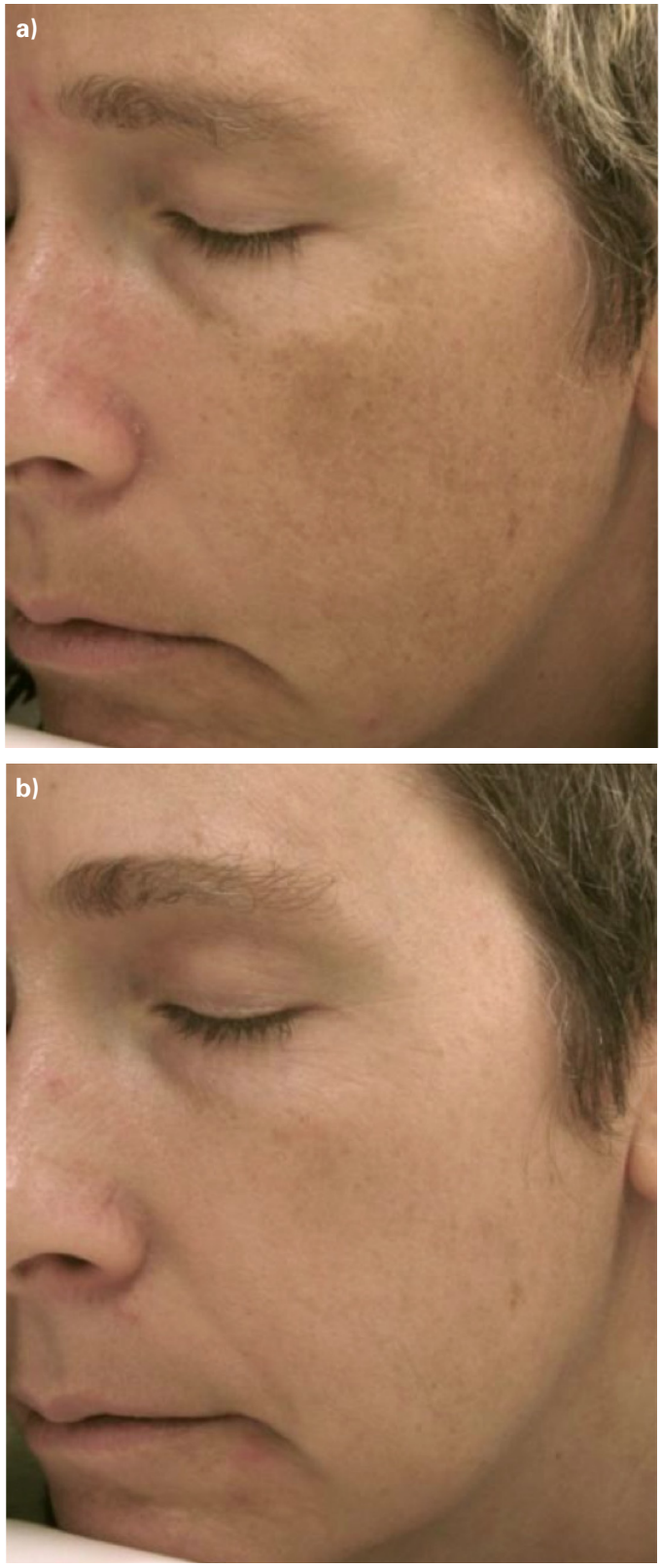


FIGURE 4. Patient 2. Female patient aged 25 years with Fitzpatrick skin type II presenting with an Overall Hyperpigmentation score of **a)** 4 at baseline and **b)** 2 at week 12.

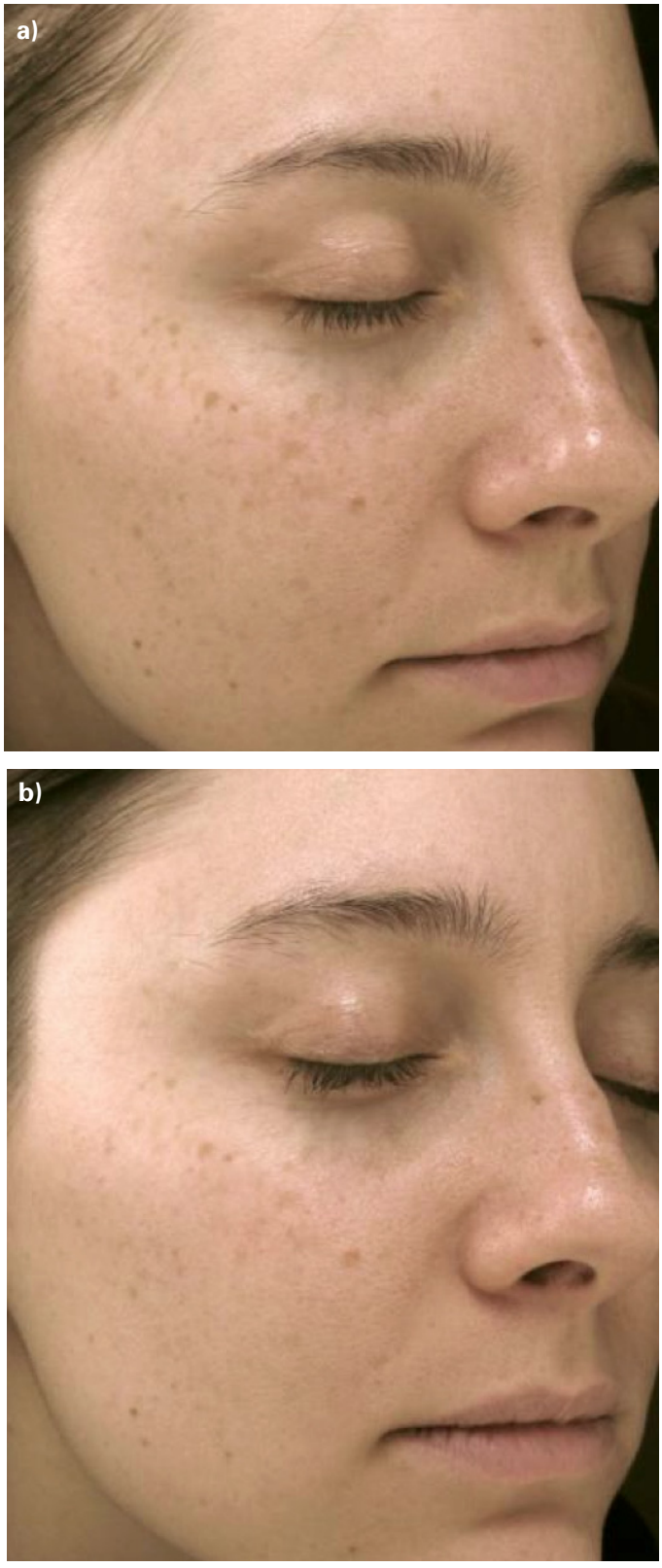
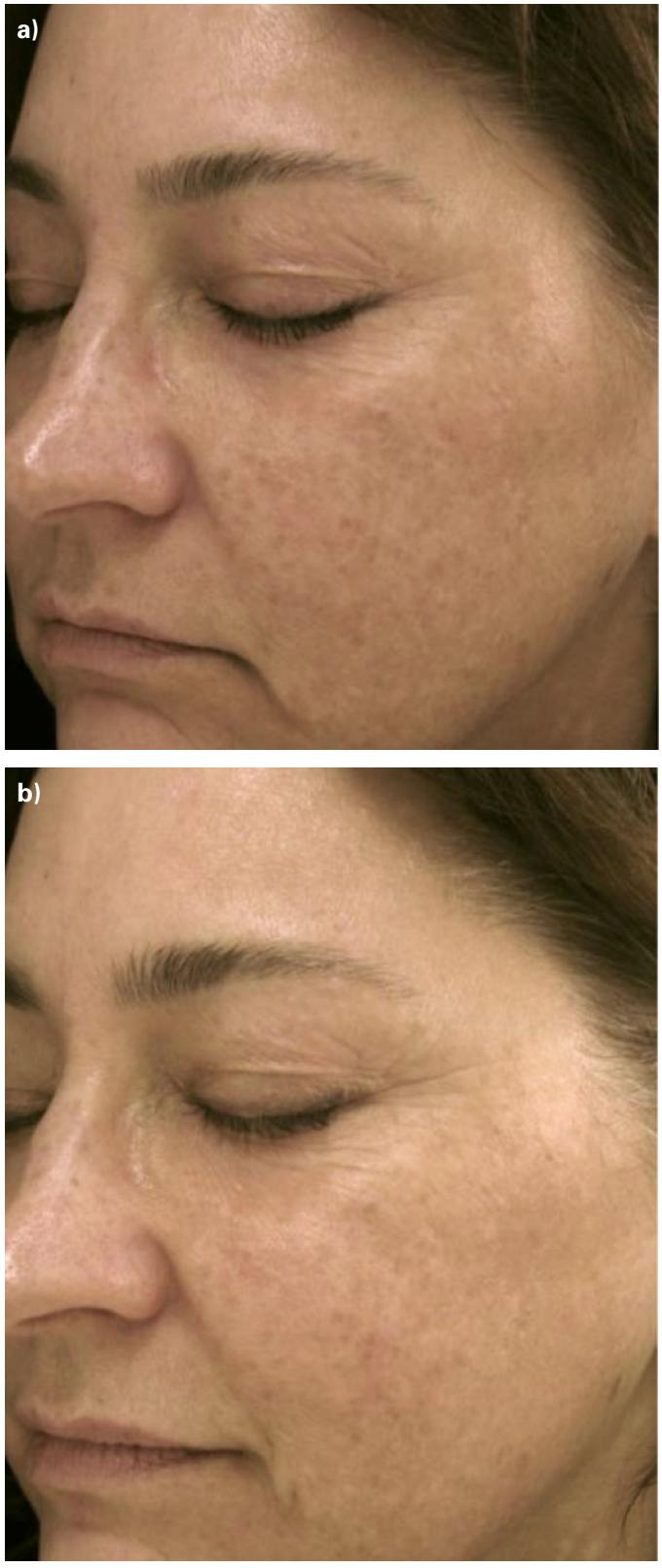


FIGURE 5. Patient 4. Female patient aged 62 years with Fitzpatrick skin type III presenting with an Overall Hyperpigmentation score of **a)** 8 at baseline and **b)** 5 at week 12.



"Results from these case studies demonstrate that this unique 12-week treatment regimen can provide an effective and simple option for patients with facial hyperpigmentation."

DISCUSSION

These case studies demonstrate that this simple and comprehensive regimen of a multimodal skin brightener, cleanser, retinol product, and sunscreen SPF 30+ may provide an effective and well-tolerated hyperpigmentation treatment program for patients with moderate to severe facial hyperpigmentation. The multimodal skin brightener contains key ingredients, including tetrahexyldecyl ascorbate and 4-ethoxybenzaldehyde, which reduce melanocyte activation through free-radical scavenging and inflammatory cytokine suppression, respectively.[4,5] Several other ingredients, including retinol, linoleic acid, glabridin, and hexylresorcinol help to limit the availability of tyrosinase, which is a key enzyme in melanin synthesis.[6-9] The ingredient 4-ethoxybenzaldehyde has another function of reducing melanin transfer to keratinocytes, as does niacinamide.[5,10] Lastly, to address existing melanin present in the epidermis, retinol reduces hyperpigmentation through exfoliation.[11] By adding the sunscreen to prevent further stimulation of melanin production, the regimen represents a comprehensive approach in the treatment of hyperpigmentation. Indeed, 3 of the patients (patients 3, 4, and 5) presented with a history of resistant melasma, treated for several years with hydroquinone, retinol, and chemical peels with limited success, but after 12 weeks of treatment with this topical regimen, it is notable that Global Improvements in Hyperpigmentation of at least 25% were observed for these patients. In addition, with only 4 products, the regimen is also convenient and easy to use, which may further support patient compliance. The latter is important for treatment efficacy,[3] especially considering the highly recurrent nature of hyperpigmentation disorders.

DISCLOSURES

Financial support for this study was provided by SkinMedica, an Allergan Company.

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