

Open-Label Evaluation of a Novel Skin Brightening System Containing 0.01% Decapeptide-12 for the Treatment of Mild to Moderate Facial Melasma

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Conflict of Interest: None

Financial Support: Estelena, S.A, provided financial support for this study.

Keywords: Melasma, MASI, Decapeptide-12,

Short Title: Treatment of melasma with decapeptide-12

Abstract

Melasma is a cutaneous disorder that primarily affects females of Hispanic and Asian descent. Previous studies have shown that use of a brightening system comprised of a 0.01% decapeptide-12 cream, an antioxidant cleanser, a 20% glycolic acid lotion and a broad spectrum SPF 30 sunscreen yields good clearance of mild-to-moderate melasma in Caucasian and Asian volunteers. The present open-label, prospective and multicenter study sought to determine the tolerability and efficacy of the above-mentioned brightening system on mild-to-moderate melasma in 33 Hispanic females over 16 weeks. Clinical measures included self-assessment of tolerability, clinical grading, determination of Melasma Area and Severity Index (MASI) scores and standardized clinical photography. Results showed that the system was well tolerated with no adverse events reported. Mean decreases of 36%, 46%, 54% and 60% in MASI scores were observed at weeks 4, 8, 12 and 16, respectively, which were further corroborated by standardized photography showing visible reduction in the appearance of melasma. Results suggest that the brightening system consisting of a 0.01% decapeptide-12 cream, an antioxidant cleanser, 20% glycolic acid lotion and broad spectrum SPF 30 sunscreen is safe and efficacious for the treatment of mild-to-moderate melasma in Hispanic females.

(Word Count: 194)

Introduction

Melasma is a common cutaneous disorder that presents as patches of darker pigmentation on the cheeks, forehead, upper-lip, nose and chin.¹ Melasma most commonly affects females of Asian and Hispanic descent having Fitzpatrick phototypes IV and higher and only a very small percentage of men.² Moreover, pregnancy appears to be a contributing factor in bringing about the onset of melasma in females, supporting the proposed role of hormones in the regulation of melanogenesis in women.^{3,4} Various skin lightening agents such as kojic acid, azelaic acid, ascorbic acid (and its derivatives), and hydroquinone (and its arbutin derivatives) are currently used to treat melasma but are either efficacious and cytotoxic or are mildly efficacious and non-toxic.⁵ Although hydroquinone is one of the most effective and popular skin lightening compounds, it has been shown to cause irritant contact dermatitis (up to 70% of patients), followed by PIH, hypopigmentation and allergic contact dermatitis.⁶⁻⁸ In 2006, the FDA proposed a new ruling that would ban hydroquinone, and any ingredients with “skin bleaching” claims, from all cosmetics (currently HQ is allowed in the US at 2% or less concentrations) and require a new drug application for products containing higher concentrations of hydroquinone. The FDA proposed such a ban on the basis of 1) suspected high absorption rates, 2) reports of exogenous ochronosis in humans and 3) murine hepatic adenomas, renal adenomas and leukemia after large doses over an extended duration.⁹ Although the FDA has not yet taken further action, it is clear that there is a need for novel compounds that strike a balance between skin lightening efficacy and dermal/systemic toxicity.

Tyrosinase is a key enzyme involved in producing melanin and other pigments in plants and animals. It has been previously demonstrated that a novel synthetic oligopeptide (decapeptide-12) competitively inhibits both mushroom and human tyrosinase enzymes more potently than hydroquinone.¹⁰ Moreover, cell culture studies with human melanocytes confirmed that it also inhibited intracellular tyrosinase more potently than hydroquinone and this effect was without cytotoxicity. A subsequent pilot clinical study consisting of five female volunteers of Asian and Hispanic descent with a Fitzpatrick phototype of IV and moderate recalcitrant melasma showed that a cream containing 0.01% decapeptide-12 was well tolerated and reduced the appearance of melasma after 16-weeks of twice-daily topical use.¹¹ Another study consisting of 15 female volunteers, of Caucasian and Asian descent, having Fitzpatrick I – IV skin types with moderate to severe melasma or solar lentigenes showed that twice daily application of an antioxidant cleanser, twice daily application of a 0.01% decapeptide-12 cream, daily or alternate

day application of a 20% glycolic acid exfoliating lotion as well as daily application of a broad-spectrum SPF 30 sunscreen significantly reduced the appearance of hyperpigmentation in all study volunteers.¹² A recently published case report with three female volunteers of Caucasian descent and one male volunteer of Hispanic descent, between the ages of 30 and 47 with Fitzpatrick type III skin and mild to moderate facial hyperpigmentation, also reported significant visual improvement in the appearance of melasma after 12 – 24 weeks of using the above mentioned treatment regimen in a similar manner.¹³ Given the prevalence of hyperpigmentation in Hispanic women, the aim of the present study was to further characterize the tolerability and efficacy of the aforementioned product regimen in 33 Hispanic women over 16-weeks.

Materials and Methods

Study Design: An open-label, prospective and multi-center (six clinical sites located in the city of Medellin, Colombia) study was conducted to assess the ability of a cream containing 0.01% decapeptide-12 (a cosmetic skin brightening peptide under the trade name, Lumixyl[®]) to diminish the appearance of facial melasma (hyperpigmentation) when used in conjunction with a system of products consisting of an antioxidant cleanser, a 20% glycolic acid lotion and a broad spectrum SPF 30 sunscreen containing 8.4% titanium dioxide. The secondary objective of the study was to determine the tolerability of the test regimen when used as described in the present study. This study was approved by the local institutional review board (IRB) and was conducted following the guidelines of the Declaration of Helsinki.

Inclusion/Exclusion Criteria: Thirty-three healthy females were enrolled in the study. Volunteers that were eligible for inclusion in the study were between the ages of twenty-five and fifty, having Fitzpatrick Phototypes I – V, and mild-to-moderate epidermal or mixed epidermal and dermal melasma. Melasma severity was determined using the visual grading scale by Pandya et al¹⁴ and epidermal and dermal melasma was determined using a Wood's lamp and dermoscopy (epiluminescence microscopy). Grounds for exclusion included pregnancy, overly sensitive skin, use of oral or topical retinoids in the past 3 months, use of hydroquinone or other prescription skin lightening products in the past three months, having received a chemical peel, microdermabrasion or laser resurfacing in the past three months, use of corticosteroids or immunosuppressive prescription drugs in the past 6 months and pre-existing dermatologic condition(s) that would interfere with the conduct of this study.

Treatment Regimen: Consent was obtained from all study volunteers prior to participation in the study. In the morning, volunteers were instructed to cleanse their face with an antioxidant cleanser, apply a 0.01% decapeptide-12 cream and then apply a 20% glycolic acid lotion, as directed, followed by application of a broad spectrum SPF 30 sunscreen. In the evening, volunteers were instructed to cleanse their face with an antioxidant cleanser, apply a 0.01% decapeptide-12 cream and then apply a 20% glycolic acid lotion, as directed. The 20% glycolic acid lotion was applied with varying frequency throughout the study. Volunteers were instructed to apply the 20% glycolic acid lotion once every other morning from week zero to week four, then to apply it every morning from week five to week eight, followed by application every morning and every other evening from week nine to week 12 and then finally application twice daily from week 13 to week 16.

Measures of Clinical Efficacy and Safety: Volunteers were clinically evaluated for melasma severity at weeks 0, 4, 8, 12 and 16. Clinical evaluation of melasma severity was conducted according to the modified Melasma Area and Severity Index (MASI) proposed by Pandya and co-workers.¹⁴ Very briefly, area of involvement (A) of melasma for the forehead (f), left malar (lm), right malar (rm) and chin (c) areas was graded as 0 (absent), 1 (< 10%), 2 (10 – 29%), 3 (30 – 49%), 4 (50 – 69%), 5 (70 – 89%) and 6 (90 – 100%). Darkness (D) of melasma for the forehead (f), left malar (lm), right malar (rm) and chin (c) areas was graded as 0 (absent), 1 (slight), 2 (mild), 3 (marked) and 4 (severe). A MASI score was then calculated using the below equation:

$$\text{Modified MASI Score} = 0.3 A(f) D(f) + 0.3 A(lm) D(lm) + 0.3 A(rm) D(rm) + 0.1 A(c) D(c)$$

Melasma severity was also documented through the use of standardized digital photography taken by the same professional photographer at all study sites. Standardized photos of each volunteer were taken at weeks 0 and 16. Photos were not re-touched other than cropping and assembling into before and after photo composites.

Tolerability toward the treatment regimen was also evaluated at weeks 4, 8, 12 and 16. Tolerability was evaluated via volunteer self-assessment grading using the tolerability scale described by Tanghetti and co-workers.¹⁵ Volunteers graded stinging/burning, erythema, skin dryness and pruritus as 0 (none), 1 (mild), 2 (moderate) and 3 (severe) at each clinical visit.

Statistical Method(s): All statistical data is presented as mean (\pm SD). Statistical difference ($p \leq 0.05$, two-tailed) between MASI scores at weeks 4, 8, 12 and 16 compared to baseline MASI values was determined using one-way ANOVA with a Dunnett's post-test. Statistical significance ($p \leq 0.05$, two-tailed) for percent change in MASI scores from baseline was determined using a Wilcoxon Signed Rank Test. All evaluations were performed using the Prism 5 (Graphpad Software, Inc., La Jolla, CA) statistical software suite.

Results

Thirty-three healthy females were enrolled in the study, with a mean age of 42 years, and 26 volunteers completed the study. One volunteer dropped out due to pregnancy, three discontinued the study due to severe irritation, caused by the 20% glycolic acid lotion, and three volunteers were lost to follow-up for reasons un-related to the study. Data for those volunteers that discontinued from the study were omitted from subsequent tolerability and MASI analyses reported herein. Fifty-five percent (55%) of the volunteers had Fitzpatrick Phototype III skin, 33% had Fitzpatrick Phototype IV skin and 12% had Fitzpatrick Phototype V skin. As for sebum production, 30.3% of volunteers had combination skin, 30.3% of the volunteers had oily skin, 27.3% had normal skin and 12.1% had dry skin.

The treatment regimen was generally well tolerated with no serious adverse events reported. Self-assessment of tolerability showed that the majority of study volunteers experienced no or mild stinging/burning, erythema, dryness and pruritus over the duration of the study (Figure 1). Very mild desquamation was observed only in volunteers having dry skin types.

MASI scores indicated that melasma severity was significantly reduced from baseline values at weeks 4, 8, 12 and 16 (Figure 2). Normalized (percent change from baseline scores) MASI data indicate an average 36%, 46%, 54% and 60% reduction in melasma area and severity at weeks 4, 8, 12 and 16 (Table 1). Moreover, standardized before and after photos also demonstrated a marked reduction in the appearance of melasma at week 16 (Figures 3,4 & 5).

Table 1: Mean percent change in MASI scores from baseline over time.

<i>Week</i>	<i>n</i>	<i>Mean % Change in MASI from Baseline (±SD)</i>	<i>P-value</i>
4	26	-35.58 (± 22.25)	< 0.0001
8	26	-46.24 (± 31.84)	= 0.0001
12	26	-53.58 (± 26.99)	< 0.0001
16	26	-60.45 (± 32.73)	< 0.0001

Discussion

An extensive literature review of articles published in English and Spanish over 15 years (1991-2006), by Pawaskar and co-workers, revealed that melasma severely affects social life, emotional well-being, physical health and money matters in Hispanic women.¹⁶ First-line therapy for treating melasma in Hispanic and Latin-American patients typically involves the use of effective topical therapies including hydroquinone or a fixed triple combination of hydroquinone, retinoic acid and fluocinolone acetonide.¹⁷ It is important to note, however, that products or treatment regimens containing 4% hydroquinone and a retinoid such as Tri-Luma[®] Cream (Galderma, Inc., Fort Worth, TX.)¹⁸⁻²⁰ and the Obagi Nu-Derm[®] System (Obagi Medical Products, Inc., Long Beach, CA)²¹, respectively, typically cause mild to moderate, and in some cases, severe irritation, erythema, dry skin, pruritus and desquamation. Moreover, it is recommended that these hydroquinone-containing products be used in 4-month cycles, alternating with non-hydroquinone tyrosinase inhibitors, in order to prevent the occurrence of exogenous ochronosis (blue-black hyperpigmentary macules consisting of polymerized homogentisic acid).²² Results, presented herein, suggest that the tested skin care regimen, consisting of an antioxidant cleanser, a 0.01% decapeptide-12 cream, a 20% glycolic acid lotion and a broad-spectrum SPF 30 sunscreen, is well tolerated by Hispanic females with the majority of study volunteers experiencing no to mild stinging/burning, erythema, dry skin and pruritus. Only those study volunteers with dry skin presented mild desquamation, presumably due to the use of the 20% glycolic acid lotion. No cases of ochronosis have been reported, thus far, with the use of decapeptide-12 thus supporting its potential use in long-term treatment of hyperpigmentary dyschromias and maintenance thereof.

The efficacy of the skin care regimen, tested in the present study, on volunteers of Caucasian and Asian descent over 24 weeks has recently been reported by Kassim and co-workers.¹² Results showed that 85% of volunteers, who presented with moderate to severe facial hyperpigmentation at baseline, presented with mild or completely cleared

hyperpigmentation at 24 weeks. The present study quantitatively demonstrates that 85% of study volunteers experienced greater than 50% reduction in melasma area and severity, with 35% of all volunteers experiencing greater than 80% reduction, after using the test regimen for 16 weeks. The study population, as a whole, experienced a mean reduction in melasma area and severity of 60%. This comparatively represents a 20% improvement over results obtained using the 0.01% decapeptide-12 cream alone, twice daily over 16 weeks, as previously reported by Hantash and Jimenez.¹¹ The data presented herein suggests that use of the 20% glycolic acid lotion and the SPF 30 sunscreen may account for roughly 20% of the observed efficacy of the tested skin care regimen, thus supporting previous reports that glycolic acid^{23,24} and use of a sunscreen²⁵ can augment the efficacy of hypopigmenting agents. Standardized photos further corroborate the efficacy of the test regimen by showing a visible reduction in the intensity of the hyperpigmented spots as well as a reduction in their overall size. The photos further demonstrate that volunteers are nearly devoid of erythema and desquamation that is characteristic of comparable anti-hyperpigmentation therapies.

Conclusion

Results of the study described herein show that the 0.01% decapeptide-12 cream, combined with an antioxidant cleanser, a 20% glycolic acid lotion and broad spectrum SPF 30 sunscreen, is an effective new treatment regimen for mild to moderate melasma that is safe for use with women of Hispanic descent. The limitations of this study are that it was un-controlled and that the study population was very small. Controlled studies, with a larger, more representative study population, are necessary to confirm the findings presented herein.

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Figure Legends

Figure 1: Percent of study volunteers experiencing none, mild, moderate or severe stinging/burning (A), erythema (B), dry skin (C) or pruritus (D) at weeks 4, 8, 12 and 16.

Figure 2: Mean MASI scores (\pm SD) at weeks 0, 4, 8, 12 and 16. Mean MASI scores at weeks 4, 8, 12 and 16 are statistically different from the baseline MASI score (**p < 0.0001).

Figure 3: Standardized photography taken at baseline and week 16. Volunteer is a 38 year-old female presenting bilateral melasma on the malar region.

Figure 4: Standardized photography taken at baseline and week 16. Volunteer is a 31 year-old female presenting melasma on the upper forehead region.

Figure 5: Standardized photography taken at baseline and week 16. Volunteer is a 42 year-old female presenting melasma on the lower forehead, glabellar region and nose.

Figures

Figure 1

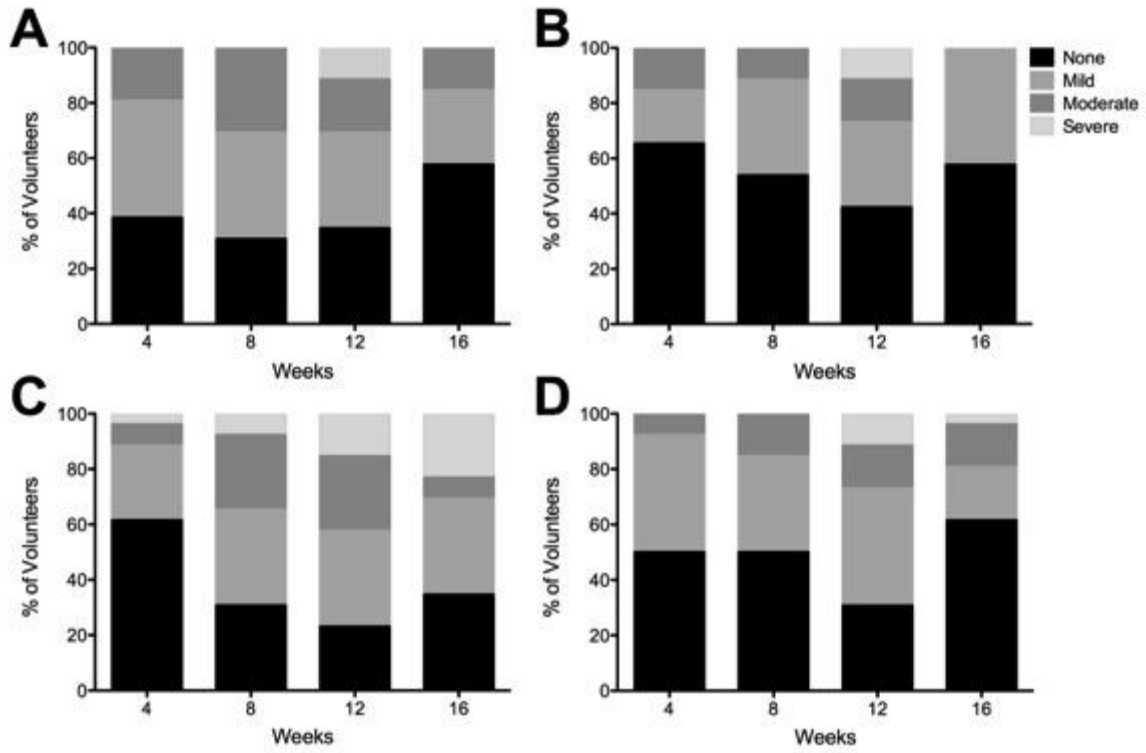


Figure 2

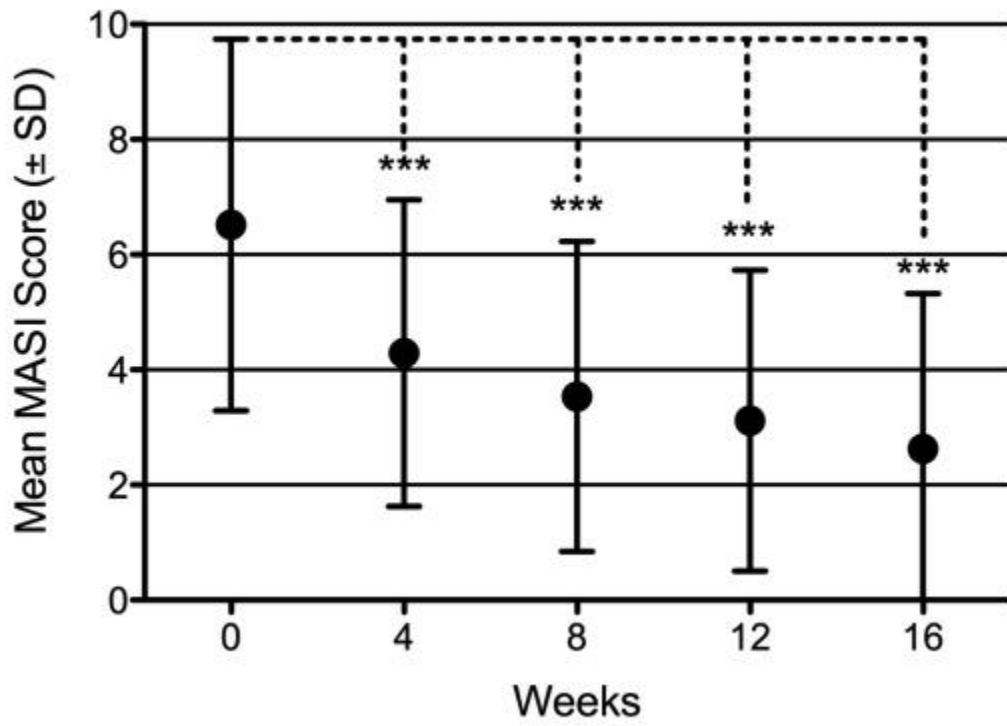


Figure 3



Figure 4



Figure 5

