Effectiveness and Tolerance of Multi-Corrective Topical Treatment for Infraorbital Dark Circles and Puffiness

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Research Article

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Abstract

Treatment of infraorbital dark circles and under-eye puffiness is challenging due to its multifactorial nature and lack of broadly applicable, effective treatments. A daily skincare treatment option that is multi-modal, effective, and tolerable across a broad patient population is an unmet need. A multi-corrective topical eye cream (MTEC) formulated with Tetrahexyldecyl (THD) ascorbate (vitamin C), prebiotic *Inula Helenium*, bioavailable peptides, botanical extracts, chrysin, and caffeine, is hypothesized to improve the appearance of infraorbital dark circles and under-eye puffiness by targeting micro-vasculature congestion and permeability, melanin accumulation and hemoglobin degradation related pigmentation, and skin health.

An IRB approved, open-label, 12-week clinical study set out to evaluate the efficacy and tolerability of the MTEC across a broad patient population including varying ethnicities and Fitzpatrick Skin Types (FST). Female subjects (n = 40) ages 35 to 60 years old, with moderate to severe under-eye dark circles, moderate under-eye puffiness, and mild-to-moderate fine lines were enrolled into the study. Objective (Chromameter, VISIA® imaging, and Laser Doppler) and subjective assessments (clinical grading and self-assessment questionnaire) were conducted at baseline and post-baseline timepoints.

The MTEC efficaciously demonstrated short-term and long-term improvements in objective and subjective assessments across a broad patient population. Specifically, the MTEC demonstrated significant improvement of infraorbital dark circles, mainly by the reduction of micro-vasculature congestion and permeability, melanin and hemoglobin degradation related pigmentation. Topical application of the MTEC may offer an effective and tolerable treatment option for infraorbital dark circles and puffiness.

Introduction

Infraorbital (under-eye) dark circles are a common cosmetic problem and can have a significant impact on an individual's quality of life due to the perception of tired-looking eyes [17, 25, 26].

Infraorbital dark circles and puffiness result from multifactorial underlying pathogenesis including micro-vasculature congestion and permeability, melanin accumulation and hemoglobin degradation related pigment deposition, and suboptimal skin health [14, 30, 31]. The thin skin of the under-eye region provides heightened visibility to the under-lying microvasculature network. Additionally, the quality of the skin decreases with aging due to the loss of collagen, where it is more prominent in the under-eye region due to the thin tissue further worsening the appearance of infraorbital dark circles [31]. Micro-vasculature congestion and permeability due to stagnant blood in the under-eye micro-vasculature network is a significant contributor to infraorbital dark circles [16, 31].Micro-vasculature congestion and permeability increases hemoglobin accumulation in surrounding thin tissue in which hemoglobin (red) degrades into pigments through an enzymatic process, including iron (brown), hemosiderin (purple), biliverdin (green), and bilirubin (yellow), and in conjunction with thin periorbital skin accentuate infraorbital dark circles and puffiness [10, 11]. Intrinsic and extrinsic factors contribute to infraorbital dark circles and puffiness.

Intrinsic factors include genetic or hereditary predisposition, ethnicity, hormonal changes, and facial skeletal structure that leads to shadowing of the under-eye region. Extrinsic factors include ultraviolet radiation, high energy visible light, pollution, allergies, and chronic irritation to the eye area.

Treatment of infraorbital dark circles and puffiness is challenging because of its multifactorial nature and lack of broadly applicable, effective treatments [21]. Individuals with dark circles and puffiness are perceived as tired, sad, stressed, and aged by societal and cultural communities, significantly impacting an individual's quality of life, and driving the demand and investment into measures to conceal and correct these concerns [5, 31]. Clinical trials for infraorbital dark circles and puffiness have been conducted evaluating different modalities including topical creams and serums, lasers, and other energy-based devices (EBD), injectables (fillers, platelet rich plasma) and surgery, with variable outcomes and patient satisfaction [19, 25, 31]. Furthermore, individuals are faced with a challenge in selecting the right treatment option, as a there is no current gold standard treatment for infraorbital dark circles and puffiness for a broad patient population of all Fitzpatrick Skin Types (FST) and ethnicities due to its multifactorial etiology.

Cosmetic therapies for treatment include topical agents that can improve blood circulation and / or reduce melanin in the periorbital region; hydroquinone, retinoids, and chemical peels [5, 19]. These therapies often have low consumer tolerability due to the delicate thin skin surrounding the eye area. A daily skincare treatment option that is multi-corrective, effective, and tolerable across a broad patient population is an unmet need. A multi-corrective topical eye cream (MTEC) was formulated with tetrahexyldecyl (THD) ascorbate (vitamin C), prebiotic *Inula Helenium*, bioavailable peptides including Palmitoyl Tripeptide-1, Palmitoyl Tripeptide-5, and Palmitoyl Tetrapeptide-7, botanical extracts including *Jasminum sambac*, and *Crataegus monogyna*, Chrysin, and caffeine to improve the appearance of infraorbital dark circles and puffiness by targeting micro-vasculature congestion and permeability, melanin accumulation and hemoglobin degradation related pigmentation, and skin health.

The MTEC was formulated to target multiple pathways to address extrinsic causes. To target micro-vascular congestion and permeability, MTEC contains Palmitoyl Tripeptide-1 and Palmitoyl Tetrapeptide-7. The topical application of these fatty acid-linked bioavailable peptides reinforces and strengthens under-eye micro-vasculature network and reduces micro-vascular congestion and permeability by strengthening the extracellular matrix and increasing collagen production [18, 27]. THD ascorbate and chrysin reduce melanin accumulation and hemoglobin degradation related pigments for an improvement in infraorbital dark circles. THD ascorbate, a lipid-soluble form of vitamin C, has been clinically demonstrated to inhibit melanogenesis, increase dermal collagen, and quench free radicals [15, 20, 34]. Chrysin is a flavone shown to stimulate UDP-glucuronosyltransferase 1A1 (UGT1A1), an essential enzyme for elimination of bilirubin pigmentation and metabolic clearance of bilirubin in skin [29, 36]. Lastly, *Inula Helenium, Jasminium sambac, Crattaegus monogyna,* andPalmitoyl Tripeptide-5 increase collagen production to improve infraorbital dark circles, puffiness, and skin health. *Inula Helenium*, also known as elecampane, clinically demonstrated to diminish pollution-induced and blue light-induced skin damage, strengthen the skin barrier, improve skin elasticity, and skin brightness, while also containing

prebiotic properties [8]. Palmitoyl Tripeptide-5 is a bioavailable peptide, which increases production of collagen I and III in skin [3, 27]. *Jasminium sambac* combats dark circles and under-eye puffiness through its anti-tyrosinase activity and increases collagen content, while*Jasminium sambac* and *Crattaegus monogyna* improve vascularity by optimizing blood circulation decreasing hemoglobin degradation related pigmentation to target infraorbital dark circles and under-eye puffiness [28, 33].

The aim of the study was to evaluate the efficacy and tolerability of a MTEC in the treatment of infraorbital dark circles and under-eye puffiness incorporating both objective and subjective assessments. We hypothesized that the MTEC would demonstrate statistically significant improvement in infraorbital dark circles and puffiness in healthy women after 12-weeks of twice-daily use.

Methods

Study Design and Population

An institutional review board (IRB) approved, 12 week, open-label clinical study was conducted. Female subjects located in New Jersey, USA (n=40) between 35 to 60 years old, FSTs I – VI, with moderate to severe under-eye dark circles (score 4 to 8 based on a photonumeric scale for infraorbital dark circles) [22], moderate under-eye puffiness (score of 4 to 6 based on the modified Griffiths scale) [6], and mild to moderate fine lines (score of 3 to 6 based on the modified Griffiths scale), and dull skin in the periorbital eye area were recruited into the study. Subjects were excluded if they were nursing, pregnant, or planning a pregnancy, had used topical retinoids or topical eye cream / serums within the past 7 days prior to baseline.

At screening eligible subjects commenced a 1-week washout period prior to baseline and instructed to refrain from using any other skincare product outside of the products provided for the duration of the 12-week study. Subjects cleansed face with Gentle Cleansing Lotion (Revision Skincare®, Texas, USA) twice daily, applied a Facial Moisturizer to the global face (Goodier, Texas, USA) twice daily, and applied Neutrogena Ultra Sheer Dry Touch SPF 30 (Johnson & Johnson, New Jersey, USA) in the morning with afternoon reapplication as per FDA recommendation. At baseline, subjects incorporated the MTEC (Revision Skincare®, TX, USA), into their skincare regimen after facial cleansing and instructed to apply a dime size amount onto the under-eye area and crow's feet area in the morning and evening for the duration of the 12-week clinical study.

Clinical Evaluations

Investigator clinical grading was performed at baseline, weeks 4, 8 and 12. A validated photonumeric scale for infraorbital dark circles based on the principles of the modified Griffiths scale was utilized [22], while the modified Griffiths scale was utilized to evaluate under-eye puffiness, and overall appearance of the periorbital eye area.

Objective tolerability was assessed by the clinical investigator using a 5-point scale (score 0 = none to 4 = severe) for dryness, erythema, and edema at all timepoints. Subjective tolerability was assessed using a 4-point scale (score 0 = none to 3 = severe) for itching, burning, tingling, stinging at all timepoints.

Additionally, subjects took a selfie at baseline, that was used as a reference while completing a self-assessment questionnaire at weeks 8 and 12. Subjects stated whether they completely agree, slightly agree, neither agree or disagree, slightly disagree, or completely disagree with each of the 12 statements related to the efficacy of the MTEC.

Clinical Photography

Facial clinical photography of the subject's global face (right, center, and left) were taken at baseline, weeks 4, 8 and 12 under standard, cross-polarized, and UV absorption lighting modalities (VISIA®-CR, Canfield Imaging Systems, Fairfield, New Jersey). Cross-polarized baseline and week 12 images were transformed into RBX color space, creating separate red and brown images that visually represent hemoglobin and melanin, respectively, utilizing VISIA RBX® technology.

Pixel intensity analysis of the RBX® red and brown images were performed of the under-eye area at baseline and week 12 utilizing ImageJ Software (National Institutes of Health, Maryland, USA), an open-source software that allows for image processing and analysis [9].Crescent moon shapes were created in the under-eye region while avoiding the eyelashes and standardized with a fixed size across all subject's photographs.

Bioinstrumentation

A INL 191 Blood FlowMeter (ADInstruments, Colorado, USA) was used to monitor cutaneous blood flow based on laser doppler technology. This is a non-invasive measurement of total, local microvascular flow to evaluate dynamic changes in under-eye microcirculation. A standard surface probe approximately 17mm in diameter was placed on the right or left under-eye area per randomization using an adhesive sticker and measurements in perfusion units (AU) were obtained at baseline, week 8 and week 12.

Chroma Meter CR-200 (Konica Minolta, Tokyo, Japan) was used to quantify product induced skin color changes. A pulsed xenon arc lamp provides diffuse, uniform lighting over the 8mm aperture, and the light reflected perpendicular to the surface is collected by the optical fiber cable for color analysis. Three color value characteristics are evaluated: L* (white-black), a* (red-green), and b*(blue-yellow). Measurements were taken on the right or left under-eye area, per randomization on each subject in triplicate.

Statistical Analysis

Statistical analyses were performed on all subjects who received treatment and completed the study in general accordance with the protocol. A one-sided Wilcoxon signed rank test was performed to determine significance for each clinical parameter. The median percent improvement from baseline at week 4, 8,

and 12 was calculated for each parameter. Objective and subjective tolerability scores for each parameter were used to calculate mean percent improvement from baseline at week 4, 8, and 12.

Laser doppler and Chromameter bioinstrumentation mean percent improvement analysis were performed at week 4, 8, and 12. An increase in laser doppler AU values indicates an increase in blood flow of the skin surface. An improvement in infraorbital dark circles is indicated by a decrease in chromameter a* (redness) and b* (blueness) measurements and an increase in chromameter L* (brightness) measurements.

VISIA RBX® technology images pixel intensity scores from ImageJ software were used to calculate average percent change from week 12 vs baseline, where an increase in pixel intensity indicates an improvement in redness and brown pigmentation.

SAQ responses were analyzed using top box analysis. Percent subject agreement was determined for each parameter and subject satisfaction was considered when subjects scored parameters from 4 (slightly agree) to 5 (completely agree) at week 8 and 12.

Statistical significance was achieved at * $p < 0.05$ and $**p < 0.01$, and highly statistical significance was achieved at $*** p < 0.001$.

Results

Study Population

Thirty-seven (37) female subjects with a mean age of 52 (range: 37 – 60 years) with FST I – V completed the 12-week clinical study, Table 1. This clinical study was conducted in New Jersey, USA, where subjects were of varying ethnicities and FSTs that closely resemble the New Jersey census population [24].

Clinical Grading

Investigator assessment of overall eye appearance of the periorbital area, under-eye puffiness and under eye dark circles demonstrated clinical efficacy after 12 weeks of twice daily application compared to baseline (Fig. I). Specifically, a 14.30%, 16.70%, and 20.00% statistically significant median improvement from baseline was observed at week 12 for these three clinical parameters, respectfully. Improvement in under-eye dark circle was seen as early as 4-weeks, demonstrating a highly statistically significant 12.0% median improvement from baseline ($***p < 0.001$). Clinical significance in under eye puffiness and under-eye dark circles was demonstrated at week 8 and plateaued at week 12.

Clinical Photography and ImageJ

Improvement of overall appearance of the periorbital eye area is demonstrated in subjects across young and mature age groups, FSTs, and ethnicities (Fig. II). Furthermore, improvement in under-eye dark circles, puffiness, and overall appearance of the periorbital eye area was observed as early as 4 weeks across

varying FSTs (Fig. II). The MTEC was efficacious in demonstrating short term (4 week) and long term (12 week) improvements across all parameters.

Under-eye dark circle redness can be caused by extravasation and hemolysis of hemoglobin into the surrounding tissue due to micro-vasculature congestion and increased vascular permeability. VISIA RBX® red analysis demonstrated a decrease in redness indicating an improvement in infraorbital dark circles and skin health. ImageJ analysis of the RBX® red images demonstrated a 1% to 14% range of improvement in redness in subjects with FSTs I – III, and a 1% to 17% range of improvement in redness in subjects with FSTs IV – V from week 12 to baseline. Specifically, a female subject age 58 with FST III saw a 14% improvement in under-eye redness at week 12 compared to baseline (Fig. III).

Brown pigmentation found in the under-eye area is associated with the accumulation of melanin in combination with the release of iron from hemolysis. RBX® brown and UV absorption photography demonstrated a decrease in periorbital brown discoloration at week 12 compared to baseline (Fig. IV and Fig. V). Specifically, ImageJ analysis of the RBX® brown photography demonstrated a 1% to 16% range of improvement in under-eye brown pigmentation in subjects with FST I – III, and a 1% to 14% range of improvement in under-eye brown pigmentation in subjects with FST IV – V. A female subject age 37 with FST III saw a 12% improvement in under-eye brown pigmentation (Fig. IV A,D), and a female subject age 60 with FST IV saw a 14% improvement in under-eye brown discoloration at week 12 compared to baseline (Fig. IV C,F).

Bioinstrumentation

Decreased microcirculation velocity results in an accentuation of infraorbital dark circle and under-eye puffiness due to micro-vasculature congestion and ultimately accumulation of hemoglobin, pigments, and melanin [10, 11]. Laser doppler measurements revealed the MTEC enhanced under-eye microcirculation by 49% ($p = 0.07$) at week 8 compared to baseline. There was no statistically significant difference in laser dropper measurements across FSTs nor across ethnicities across all timepoints, indicating that the MTEC was equally effective among FSTs and ethnicities in improving under-eye micro-vasculature congestion.

Chromameter L* measurements revealed a statistically significant improvement in under-eye brightness at 12 weeks (**$p < 0.01$) and as early as 4 weeks (*$p \leq 0.05$) compared to baseline (Fig. VI). A reduction in under-eye redness (a*) was noted at weeks 4 and 12 compared to baseline. A statistically significant reduction in under-eye blueness (b*) was noted at weeks 4 vs baseline (*$p<0.05$). There was no statistically significant difference in chromameter measurements across FSTs across all timepoints, indicating that the MTEC was equally effective across FSTs in improving infraorbital dark circles. Additionally, no statistically significant difference in chromameter a* and b* measurements was noted across ethnicities. However, a statistically significant difference was noted in chromameter L* measurement across ethnicities, where Caucasians demonstrated statistically significance improvement

in L* value at week 12 compared to baseline compared to Asian, Black, and Hispanic ethnicities (**$p < 0.01$).

Tolerability and Self-Assessment Questionnaire

There was one report of mild erythema and one report of mild dryness at baseline, after the 1-week washout and before MTEC application. These two reports were resolved by week 4 and may not be attributed to the MTEC due to onset prior to MTEC application. At week 4, there were two reports of mild dryness which resolved by week 12.

There were no reports of edema, stinging, tingling, itching, or burning at any timepoint throughout the 12-week clinical study. No serious adverse events were reported in the duration of the 12-week clinical study.

Additionally, the self-assessment questionnaire revealed 86.5% of subjects favorably agreed that their under-eye area looked improved and 83.8% of subjects favorably agreeable that their dark circles looked improved at week 12 *(***$p < 0.001$)*.

Discussion

A multitude of treatments and procedures have been investigated to correct infraorbital dark circles and improve patient satisfaction. When reviewing the current market space and considering the multifactorial underlying causes of infraorbital dark circles, there are limited and inadequate treatment options that are available to target all underlying causes of infraorbital dark circles.

Laser and other energy-based device (EBD) therapy treatment options can be associated with side effects including inducing post-inflammatory hyperpigmentation (PIH), scarring and infection. CO_2, Q-switched alexandrite, PDL, Nd:YAG and Er:YAG were investigated in the treatment of infraorbital dark circles with variable results [28, 29]. Skin resurfacing lasers including CO_2 and Er:YAG lasers show some benefit in improving skin texture and infraorbital dark circles, however these treatments are invasive and can lead to prolonged erythema, scars, and infections [2, 23]. Although the pigment lasers including Q-switched ruby, Q-switched alexandrite, and Nd:YAG laser specifically target dermal melanin pigments, PIH and post-inflammatory hypopigmentation can be serious side effects, especially for patients with darker skin tone [13, 32, 35].

Topical options including bleaching agents (Hydroquinone) and chemical peels (TCA, glycolic acid) have been effective in targeting melanin. However, a reduction in infraorbital dark circles with varying degrees of success and adverse effects make them undesirable options [30, 35]. Less-invasive options like fillers may improve the appearance of dark circles, puffiness, and skin health by correcting volume loss, dehydration, and a thinning dermal layer but the result is too transient and like other options including laser and chemical peels are not accessible to majority of the patients [30].

Treating infraorbital dark circles with non-invasive treatments that are accessible and cost effective with minimal side effects would be an ideal option that can lead to acceptable outcome and high patient satisfaction. In this clinical trial, a novel topical eye cream, MTEC, formulated with Tetrahexyldecyl (THD) ascorbate, prebiotic *Inula Helenium,* bioavailable peptides including Palmitoyl Tripeptide-1, Palmitoyl Tripeptide-5, and Palmitoyl Tetrapeptide-7, botanical extracts including *Jasminum sambac*, and *Crataegus monogyna*, Chrysin and caffeine, was investigated for treatment of infraorbital dark circles and puffiness by using objective and subjective measurements.

Palmitoyl Tripeptide-1, Palmitoyl Tripeptide-5, and Palmitoyl Tetrapeptide -7 have been shown to reinforce and strengthen under-eye micro-vasculature network, and reduce micro-vascular congestion and permeability by strengthening the extracellular matrix and increasing collagen production [3, 7, 18, 27]. This current study showed a significant reduction of vascular features and resolution in skin tone redness by week 12 compared to baseline.

THD Ascorbate and Jaminium sambac inhibit melanogenesis through their anti-tyrosinase activity [20, 28]. Chrysin eliminates the bilirubin pigmentation and enhances metabolic clearance of bilirubin in human body by stimulating UDP-glucuronosyltransferase 1A1 (UGT1A1) [36]. This study demonstrated that periorbital brown discoloration decreased at week 12 compared to baseline as demonstrated by the VISIA® UV absorption lighting modality, VISIA® RBX Brown Technology, and chromameter measurements showed a statistically significant improvement in under-eye brightness as early as 4 weeks (*$p < 0.05$) and at 12 weeks (**$p < 0.01$) and compared to baseline. Additionally, peer publications reported an approximate 3% to 6% improvement in L* measurements between subjects with dark circles to no dark circles [10]. Chromameters results shown in this study are in par with peer publications evaluating L* values on subjects with and without dark circles, indicating an improvement in infraorbital dark circles.

The MTEC was formulated to target multiple extrinsic causes of periorbital dark circles and puffiness, with its multi-corrective approach to target melanin accumulation and hemoglobin degradation related pigmentation, micro-vasculature congestion and permeability, and skin health. However, extrinsic factors including seasonal allergies, and intrinsic factors including bone structure also play a role in the development of periorbital dark circles and puffiness and may be better addressed with cosmetic procedures and medication. The MTEC demonstrated clinical significance in under eye puffiness and under-eye dark circles as early as 4 weeks, and at week 8 and plateaued at week 12. This plateau effect between week 8 and 12 could be attributed to other causes of dark circles such as genetic deposition, allergies (conducted in the spring, New Jersey peak allergy season), smoking, lack of sleep, and rubbing of eyes which were not targeted factors by the MTEC. New Jersey exhibits peak tree pollen allergy seasons from March to April, which corresponds to the week 8 and 12 timepoints of the clinical study, indicating that the week 8 and week 12 plateau effect highly corresponds to high allergy season in New Jersey [1]. Additionally, subjects favorably agreed that their under-eye area looks improved after 12 weeks of twice daily use indicating that the MTEC was successful in improving the perception of dark circles.

Genetics and ethnicity also have an impact in the development of periorbital dark circles. A study surveying 100 participants revealed that vascular related periorbital dark circles is more commonly seen in lighter skin types and Caucasians, while pigmentation related periorbital dark circle is more commonly seen in darker skin types and Blacks [12]. The MTEC efficacy among varying ethnicities and FSTs was evaluated, and demonstrated that the MTEC was equally effective across ethnicities and FSTs I – V.

No serious adverse events were reported in the duration of the 12-week clinical study. The limitation of this study was not including a vehicle control arm and being conducted in the spring with peak allergy season in New Jersey.

Conclusion

A novel topical eye treatment, MTEC, was formulated with THD ascorbate, prebiotic *Inula Helenium*, bioavailable peptides, botanical extracts, chrysin, caffeine, and other novel functional ingredients to target the multiple pathways associated with under-eye dark circles and puffiness. Specifically, the active ingredients were formulated to reduce micro-vascular congestion and permeability as well as inhibit melanin accumulation and hemoglobin degradation related pigment accumulation. The MTEC demonstrated short-term and long-term efficacy, tolerability, and patient approval. Objective and subjective measurements, across a broad patient population validated this as a treatment for patients looking for a targeted solution for brighter under-eye skin.

Declarations

The study was sponsored by Revision Skincare®. Dr. Rajabi-Estarabadi analyzed clinical data, images, and drafted the manuscript. Dr. Rajabi-Estarabadi was a paid consultant for this clinical study. Dr. Hartman has performed clinical trials and consulting for a variety of organizations and served in multiple leadership capacities. Dr. Hartman has served as a clinical investigator for this trial and assisted in drafting the manuscript and served on the Revision Skincare® Scientific Advisory Board. Ms. Iglesia and Dr. Zahr analyzed the images, statistical data, and drafted the manuscript. Both are employees of Revision Skincare®. Ms. Kononov is a consultant for Revision Skincare®.

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References

1. *Allergy Season Report for Newark, NJ*. Pollen.com. Retrieved March 2, 2023, from https://www.pollen.com/research/07101
2. Alster TS, Hirsch RJ (2003) Single-pass CO2 laser skin resurfacing of light and dark skin: extended experience with 52 patients. J Cosmet Laser Ther 5(1):39–42

3. Avcil M, Akman G, Klokkers J, Jeong D, Çelik A. (2020). Efficacy of bioactive peptides loaded on hyaluronic acid microneedle patches: A monocentric clinical study. J Cosmet Dermatol. 19(2):328-337. https://doi.org/10.1111/jocd.13009
4. Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal statistical society: series B (Methodological), 57(1), 289-300. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x
5. Chandrashekar BS, Soumya S. (2022). Effectiveness and Safety of Topical Under-eye Serum in Patients with Periorbital Hyperpigmentation: An Open-label Single Arm Prospective Study. J Clin Aesthet Dermatol. 15(2):18-22.
6. Griffiths, C. E., Wang, T. S., Hamilton, T. A., Voorhees, J. J., & Ellis, C. N. (1992). A photonumeric scale for the assessment of cutaneous photodamage. Arch Dermatol, *128*(3), 347–351.
7. Hahn, H. J., Jung, H. J., Schrammek-Drusios, M. C., Lee, S. N., Kim, J. H., Kwon, S. B., An, I. S., An, S., & Ahn, K. J. (2016). Instrumental evaluation of anti-aging effects of cosmetic formulations containing palmitoyl peptides, *Silybum marianum* seed oil, vitamin E and other functional ingredients on aged human skin. Exp Ther Med, *12*(2), 1171–1176. https://doi.org/10.3892/etm.2016.3447
8. Havas F, Krispin S, Cohen M, Shevach M, Borenstein-Auerbach N. (2021). Restore and Renew: Inula Helenium Powers Up Skin's Anti-Pollution Defenses. Available via Cosmetics and Toiletries. https://www.cosmeticsandtoiletries.com/research/literature-data/article/21836427/cosmetics-toiletries-magazine-restore-and-renew-inula-helenium-powers-up-skins-antipollution-defenses. Accessed 02 MAR 2023
9. ImageJ. *Image Processing and Analysis in Java*. ImageJ. Retrieved March 2, 2023, from https://imagej.nih.gov/ij/index.html
10. Kalakonda A, Jenkins BA, John S. Physiology, Bilirubin. (2022). In: StatPearls. StatPearls Publishing, Treasure Island (FL); PMID: 29261920.
11. Kikuchi K, Masuda Y, Hirao T. (2013). Imaging of hemoglobin oxygen saturation ratio in the face by spectral camera and its application to evaluate dark circles. Skin Res Technol. 19(4):499-507. Doi:10.1111/srt.12074
12. Lim, H. G. Y., Fischer, A. H., Sung, S., Kang, S., & Chien, A. L. (2021). Periocular Dark Circles: Correlates of Severity. Annals of dermatology, 33(5), 393–401. https://doi.org/10.5021/ad.2021.33.5.393
13. Ma G, LinXX, Hu XJ, Jin YB, ChenH (2012) Treatment of venous microvasculature infraorbital dark circles using a long-pulsed 1,064-nm neodymiumdoped yttrium aluminum garnet laser. Dermatol Surg 38(8):1277– 1282
14. Mac-Mary, S., Zornoza Solinis, I., Predine, O., Sainthillier, J. M., Sladen, C., Bell, M., & O'Mahony, M. (2019). Identification Of Three Key Factors Contributing To The Aetiology Of Dark Circles By Clinical And Instrumental Assessments Of The Infraorbital Region. Clin Cosmet Investig Dermatol. 2:919-929. Published 2019 Dec 18. Doi:10.2147/CCID.S217956
15. Maia Campos, P. M., Gianeti, M. D., Camargo, F. B., Jr, & Gaspar, L. R. (2012). Application of tetra-isopalmitoyl ascorbic acid in cosmetic formulations: stability studies and in vivo efficacy. Eur J

Pharm Biopharm. 82(3), 580-586. https://doi.org/10.1016/j.ejpb.2012.08.009

16. Masuda, Y., Takahashi, M., Satou, A., Yanai, M., Yamashita, T., Iikura, T., Ochiai, N., Ogawa, K. and Sayama, K. (2004), Dermatological study on dark eye circles and their treatment with newly developed cosmetics. International Journal of Cosmetic Science, 26: 315-315.
17. Manuskiatti, Fitzpatrick RE, Goldman MP (2000) Treatment of facial skin using combinations of CO2, Q-switched alexandrite, flashlamp-pumped pulsed dye, and Er: YAG lasers in the same treatment session. Dermatol Surg 26(2):114–120. https://doi.org/10.1046/j.1524-4725.2000.98159.x
18. Maquart, F.-X., Gillery, P., Monboisse, J.-C., Pickart, L., Laurent, M. and Borel, J.P. (1990), Glycyl-L-Histidyl-L-Lysine, a Triplet from the α2 (I) Chain of Human Type I Collagen, Stimulates Collagen Synthesis by Fibroblast Cultures. Annals of the New York Academy of Sciences, 580: 573-575. https://doi.org/10.1111/j.1749-6632.1990.tb17997.x
19. Michelle L, Pouldar Foulad, D., Ekelem, C., Saedi, N., & Mesinkovska, N. A. (2021). Treatments of Periorbital Hyperpigmentation: A Systematic Review. Dermatol Surg. 47(1):70-74. https://doi.org/10.1097/DSS.0000000000002484
20. Ochiai, Y., Kaburagi, S., Obayashi, K., Ujiie, N., Hashimoto, S., Okano, Y., Masaki, H., Ichihashi, M., & Sakurai, H. (2006). A new lipophilic pro-vitamin C, tetra-isopalmitoyl ascorbic acid (VC-IP), prevents UV-induced skin pigmentation through its anti-oxidative properties. J Dermatol Sci. 44(1), 37-44 (2006). https://doi.org/10.1016/j.jdermsci.2006.07.001
21. Ohshima, H., Mizukoshi, K., Oyobikawa, M., Matsumoto, K., Takiwaki, H., Kanto, H., & Itoh, M. (2009). Effects of vitamin C on dark circles of the lower eyelids: quantitative evaluation using image analysis and echogram. Skin Res Technol. 15(2):214-217. https://doi.org/10.1111/j.1600-0846.2009.00356.x
22. O'Mahony, M. M., Sladen, C., Crone, M., Banner, E., Newton, V. L., Allen, A., Bell, M., Marlow, I., Acevedo, S. F., & Jiang, L. I. (2021). A validated photonumeric scale for infraorbital dark circles and its application in evaluating the efficacy of a cosmetic treatment product in a split-face randomized clinical trial. Int J Cosmet Sci. 2021;43(1):48-56. Doi:10.1111/ics.12668
23. Park KY, Oh IY,Moon NJ, Seo SJ (2013) Treatment of infraorbital dark circles in atopic dermatitis with a 2790-nm erbium: yttrium scandium gallium garnet laser: a pilot study. Journal of Cosmetic and Laser Therapy. 15(2):102–106 https://doi.org/10.3109/14764172.2012.759236
24. QuickFacts New Jersey; USA. United States Census Bureau. https://www.census.gov/quickfacts/fact/table/NJ,US/PST045221
25. Ranjan , R., Sarkar, R., Garg, V. K., & Gupta, T. (2016). A Comparative Study of Two Modalities, 4% Hydroquinone Versus 30% Salicylic Acid in Periorbital Hyperpigmentation and Assessment of Quality of Life Before and After Treatment. Indian J Dermatol. 61(4):413-417. https://doi.org/10.4103/0019-5154.185707
26. Ranu H, Thng S, Goh BK, Burger A, Goh CL. (2011). Periorbital hyperpigmentation in Asians: an epidemiologic study and a proposed classification. Dermatol Surg. 37(9):1297-1303. https://doi.org/10.1111/j.1524-4725.2011.02065.x

27. Resende D, Resende, D. I. S. P., Ferreira, M. S., Sousa-Lobo, J. M., Sousa, E., & Almeida, I. F. (2021). Usage of Synthetic Peptides in Cosmetics for Sensitive Skin. Pharmaceuticals (Basel). 14(8), 702. https://doi.org/10.3390/ph14080702
28. Sabharwal, S. & Aggarwal, S. & Vats, M. & Sardana, Shivendra. (2012). Preliminary phytochemical investigation and wound healing activity of Jasminum sambac (linn) ait. (Oleaceae) Leaves. International Journal of Pharmacognosy and Phytochemical Research. 4. 146-150.
29. Samarghandian, S., Farkhondeh, T., & Azimi-Nezhad, M. (2017). Protective Effects of Chrysin Against Drugs and Toxic Agents. Dose Response. 15(2):1559325817711782. doi.org/10.1177/1559325817711782
30. Sarkar R. (2012). Idiopathic cutaneous hyperchromia at the orbital region or periorbital hyperpigmentation. J Cutan Aesthet Surg. 5(3):183-184.
31. Vrcek I., Ozgur, O., & Nakra, T. (2016). Infraorbital Dark Circles: A Review of the Pathogenesis, Evaluation and Treatment. J Cutan Aesthet Surg. 9(2):65-72. Doi:10.4103/0974-2077.184046
32. Watanabe S, Nakai K, Ohnishi T (2006) Condition known as “dark rings under the eyes” in the Japanese population is a kind of dermal melanocytosis which can be successfully treated by Q-switched Ruby laser. Dermatol Surg 32(6):785–789
33. Wu, M., Liu, L., Xing, Y., Yang, S., Li, H., & Cao, Y. (2020). Roles and Mechanisms of Hawthorn and Its Extracts on Atherosclerosis: A Review. Front Pharmacol. 2020;11:118. Published 2020 Feb 21. Doi:10.3389/fphar.2020.00118
34. Xiao, L., Kaneyasu, K., Saitoh, Y., Terashima, Y., Kowata, Y., & Miwa, N. (2009). Cytoprotective effects of the lipoidic-liquiform pro-vitamin C tetra-isopalmitoyl-ascorbate (VC-IP) against ultraviolet-A ray-induced injuries in human skin cells together with collagen retention, MMP inhibition and p53 gene repression. J Cell Biochem. 106(4), 589-598. Doi:10.1002/jcb.22032
35. Zamanian A, Azizi M, Ghasemi M, Behrangi E, Naeji S (2019) Comparing the effectiveness of fractional CO2 laser and the combination therapy with micro-needling and topical 10% trichloroacetic acid to remove infra-orbital dark circles in Tehran women. J Cosmet Laser Ther 21(2):61–64
36. Zhu , Y. D., Guan, X. Q., Chen, J., Peng, S., Finel, M., Zhao, Y. Y., Wang, R. M., Bi, H. C., Lei, M., Wang, D. D., & Ge, G. B. (2021). Neobavaisoflavone Induces Bilirubin Metabolizing Enzyme UGT1A1 via PPARα and PPARγ. Frontiers in Pharmacology. *11*, 628314. https://doi.org/10.3389/fphar.2020.628314

Tables

Table 1 is available in the Supplementary Files section.

Figures

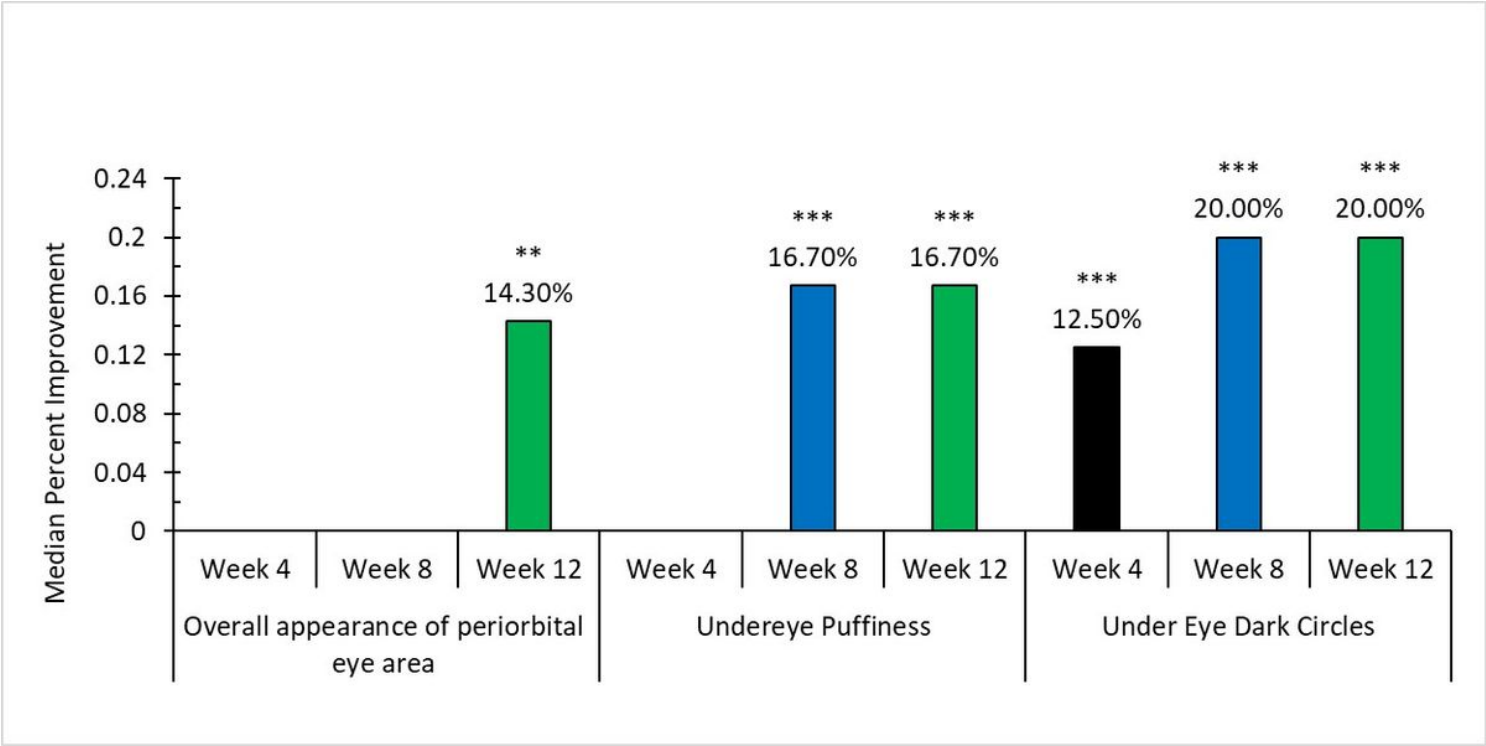

Figure 1

Median Percent Reduction at weeks 4, 8 and 12 from baseline across clinical parameters. Statistical significance was achieved at $^{**}p < 0.01$ and $^{***}p<0.001$

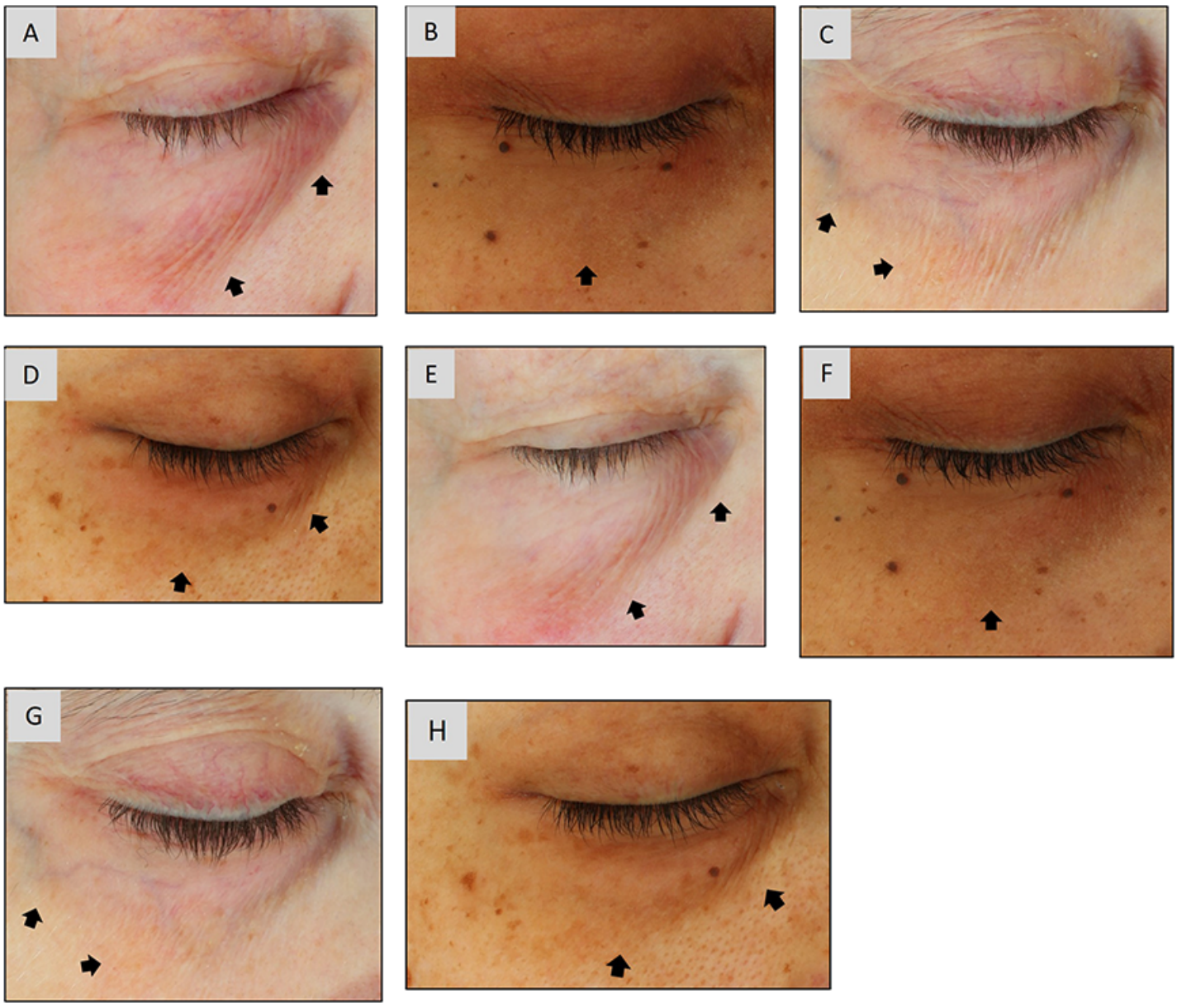

Figure 2

VISIA® CR Cross Polarized Lighting Modality of the right eye at Baseline (A – D), week 4 (E, F) and week 12 (G, H) of female subjects with FST II Age 52 (A, E), FST V Age 45 (B, F), FST II Age 58 (C, G), FST V Age 55 (D, H). Black arrows highlight areas of improvement from baseline.

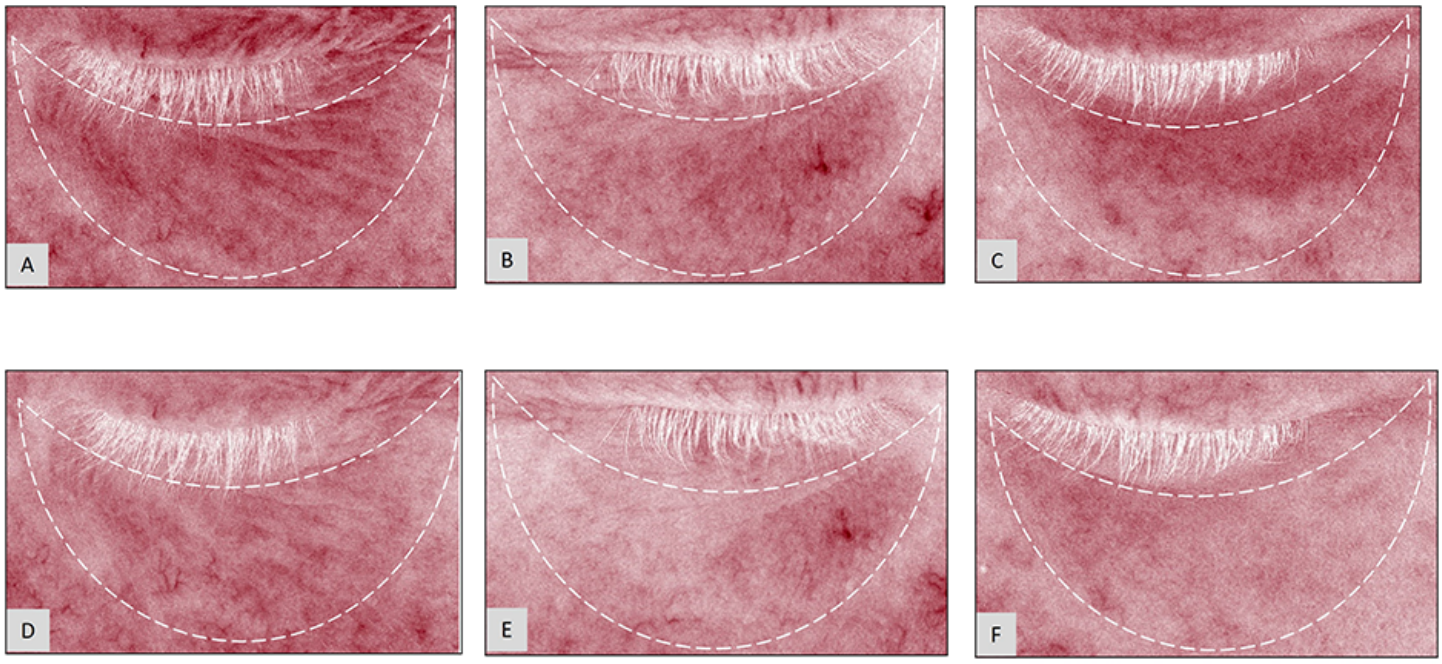

Figure 3

VISIA® RBX Red Technology Clinical Photography at Baseline (A-C) and week 12 (D-F) of female subjects with FST III Age 58 (A, D), FST III Age 37 (B, E), FST V Age 55 (c, f). Crecent moon shape highlights improvement from baseline in under-eye region

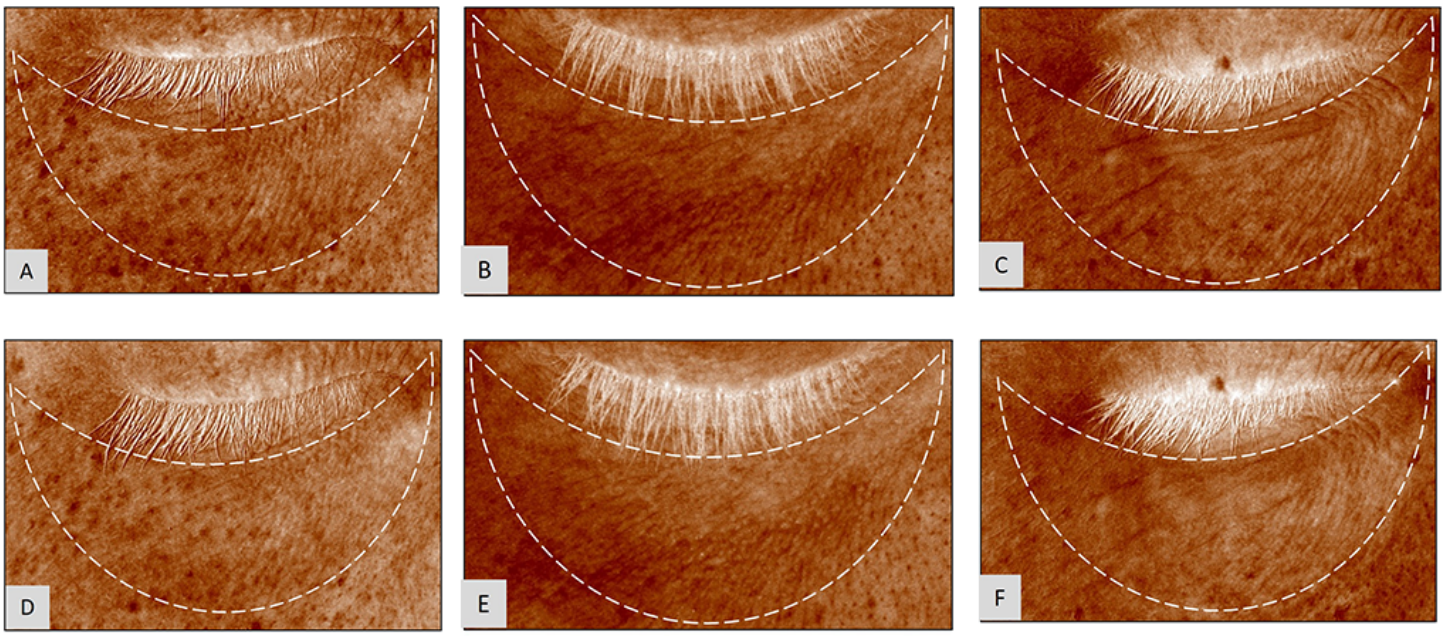

Figure 4

VISIA® RBX Brown Technology Clinical Photography at Baseline (A - C) and week 12 (D - F) of female subjects with FST III Age 37 (A, D), FST I Age 48 (B, E), FST IV Age 60 (C, F). Crecent moon shape

highlights improvement from baseline in under-eye region.

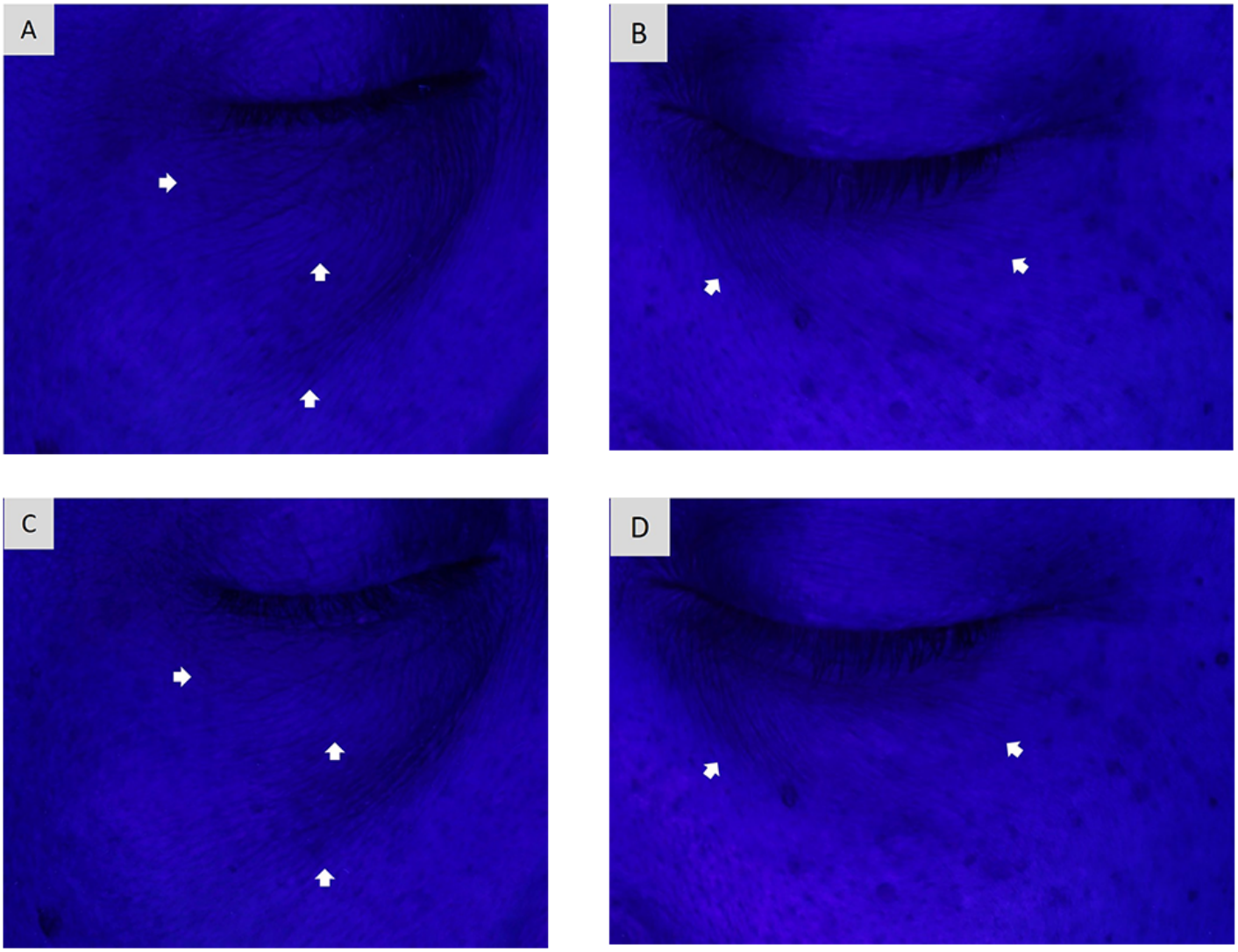

Figure 5

VISIA® CR UV Absorption Lighting Modality at Baseline (A, B) and week 12 (C, D) of female subjects with FST IV Age 54 (A, C), FST V Age 55 (B, D). White arrows highlight areas of improvement from baseline.

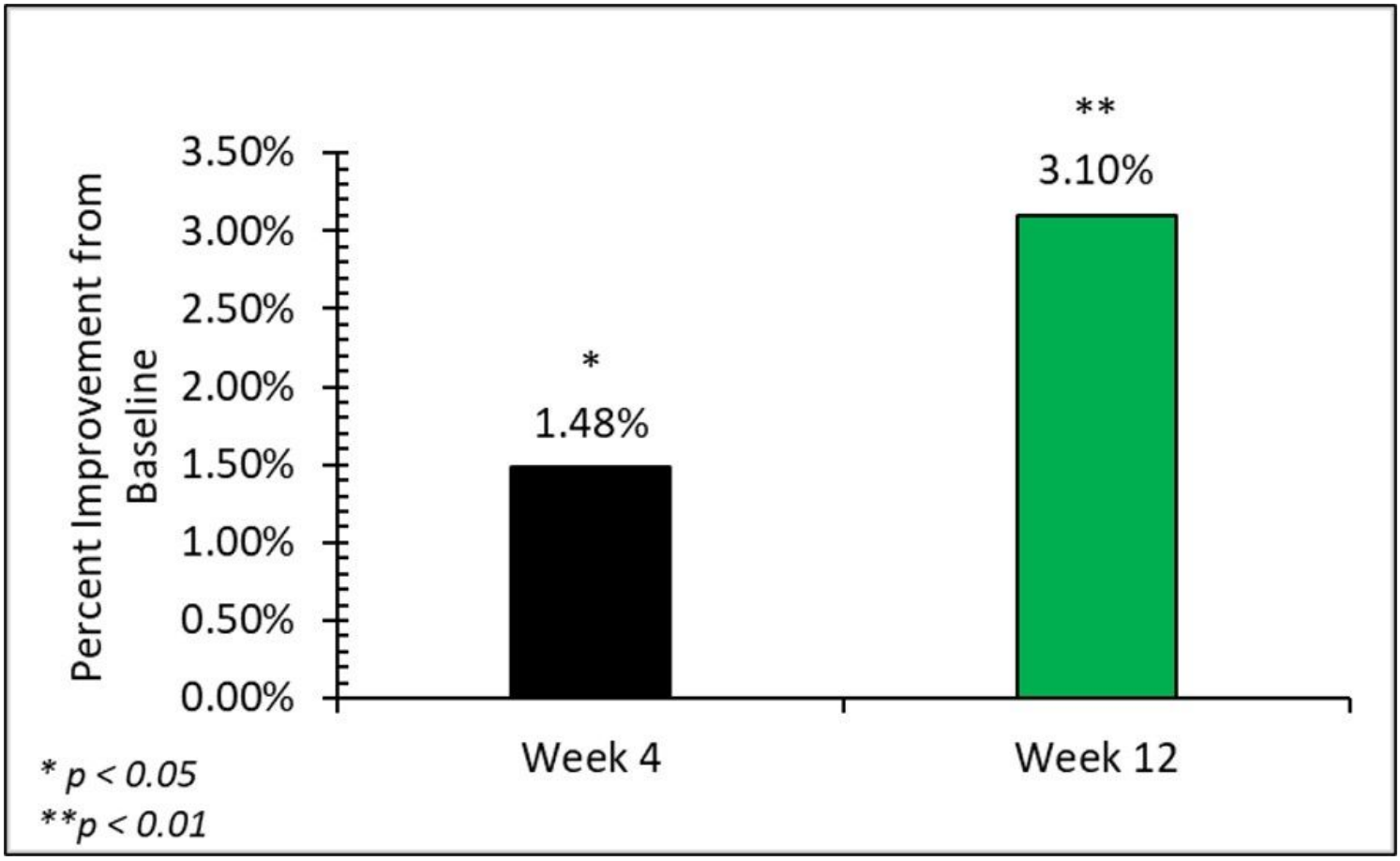

Figure 6

Mean Percent Improvement in Chromameter L* measurements from baseline. Statistical significance was achieved with *$p < 0.05$, **$p < 0.01$.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.jpg
- SupplementarySection.docx
- SupplementaryFigure1A.jpg
- SupplementaryFigure1B.jpg
- SupplementaryFigure1C.jpg
- SupplementaryFigure1D.jpg