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Research Article

A Prospective, Placebo-Controlled, Double-Blinded, Randomized Clinical Trial Evaluating Cellular Senescence Markers, Efficacy and Tolerability of Pre and Post Care Skincare Regimen Paired with 1927 nm Diode Fractional Laser for Photodamage on the Face

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Abstract

Background: The 1927 nm non-ablative fractional diode laser is used to correct photodamage. The synergistic potential of pairing it with topical antioxidants to improve results in an inclusive population has been explored.

Objective: Assess the efficacy, tolerability and impact on clinical and histological markers of cellular senescence with 1927 nm non-ablative fractional diode laser and pre- and post-treatment topical containing 15% L-ascorbic acid, 1% vitamin E and 0.5% ferulic acid.

Methods: This was a prospective, double-blind, placebo-controlled randomized trial of 40 subjects with mild to moderate photoaging who received an antioxidant serum or a placebo. All subjects received two treatments of 1927 nm diode laser to the face. Efficacy was assessed via modified Griffith scale, subject assessment and histopathology of skin biopsies to analyze biomarkers of senescence (MMP-2, MMP-9, p16, p21, β-galactosidase).

Results: Treatment with laser and antioxidant serum showed statistically significant improvement in skin tone evenness, radiance, hyperpigmentation and texture compared to control ($p<0.05$), along with higher patient satisfaction. The active group also demonstrated an inclination to reduce MMP2, MMP9 and β-galactosidase staining.

Conclusion: Combination treatment of 1927 nm diode laser with a topical antioxidant enhances both clinical and molecular improvements. This is a well-tolerated, effective treatment with high patient satisfaction.

Keywords: Photoaging; 1927 nm Diode Fractional Laser; Non-Ablative Fractional Laser; Vitamin C; L-Ascorbic Acid; Ferulic Acid; Vitamin E; Antioxidant; Cellular Senescence; Skin Rejuvenation; Inflammaging

Abbreviations

MMP2: Matrix Metalloproteinases 2; MMP9: Matrix Metalloproteinases 9; CEF: CE Ferulic® Serum; HQ: Hydroquinone

Introduction

Photodamaged, dyspigmented skin is one of the most common reasons for consultations with a dermatologist. These changes, in addition to fine lines, wrinkles, melasma, freckles and uneven skin texture can stem from both extrinsic and intrinsic factors such as ultraviolet A and B, cigarette smoking and genetic determinants [1-6]. As the skin gets further exposure to the sun, type

I and type III collagen synthesis decline with increased collagen degradation, elastin synthesis declines with increased elastic fiber destruction and overall dehydration of the skin from increased transepidermal water loss and decreased lipids occurs [4-7].

At the molecular level, these age-related skin changes can be attributed to damage to nuclear and mitochondrial DNA, generation of reactive oxygen species from oxidative stress and elevated expression of matrix metalloproteinases, resulting in a reduction of collagen synthesis and increased connective tissue damage [3,5,8]. Aging overall occurs by twelve pathways, including key processes such as genomic instability, proteostasis, chronic inflammation, cellular senescence and stem cell exhaustion, among others. Of these, cellular senescence is thought to be a key player and one of increasing interest in the regenerative medicine space. Cellular senescence is a state of permanent cell cycle arrest due to DNA damage and other stressors [9,10]. Senescent cells produce a secretory phenotype known as the Senescent-Associated Secretory Phenotype (SASP), which is believed to influence surrounding cells and further progress the aging of tissues [9,10]. Specific markers of cellular senescence have been identified that indicate the presence of senescent cells, including Matrix Metalloproteinase 9 (MMP-9), matrix metalloproteinase 2 (MMP-2), beta-galactosidase, p16 and p21, among others [11,12].

Over the last decade, regenerative medicine has sought to identify treatments and interventions that can help reverse signs of aging on both a macroscopic and a molecular level. Lasers are a powerful treatment modality which are believed to create a cascade of effects that stimulate collagen production, improve dyspigmentation and reverse signs of aging. Fractional non-ablative laser technology has gained attention for its ability to trigger a dermal wound healing response by creating multiple microscopic treatment zones of thermal injury without damaging the overlying epidermis. Non-ablative diode lasers, including both 1440 nm and 1927 nm wavelengths, have been shown to improve the appearance of wrinkles, texture and hyperpigmentation of the skin and are notably safe in all skin types [13,14]. A prior study showed non-ablative fractional 1,927-nm diode laser treatment for facial hyperpigmentation and melasma in Fitzpatrick skin types III-V, either in combination with hydroquinone 2% or control moisturizer, was well tolerated with no adverse events, post inflammatory hyperpigmentation or melasma worsening and had improvement in pigmentation by 50% after four treatments with maintenance of results 12 weeks after treatment [14].

Laser pretreatment with topicals has the potential to enhance skin permeability and improve topical uptake, thereby further improving clinical outcomes and patient satisfaction with dermatologic treatments. In a prior study, pre-treatment with the 1927 nm diode laser treatment increased the permeation of ascorbic acid by 10%, 33 times more than control, at 24 hours post-treatment [15]. Topicals applied after laser treatment can also help reduce downtime and improve wound healing following laser treatment, as demonstrated in a study examining a multi-component peptide cream applied after ablative resurfacing, which showed fibroblast stimulation by biomarker analysis [16]. Another study evaluating a topical serum containing vitamin C, vitamin E and ferulic acid (Skinceuticals® CE Ferulic Serum) showed a decrease in post-laser resurfacing erythema and edema with use of the topical [17].

Given the clinical improvement shown in prior studies with use of non-ablative fractional diode lasers and other reports showing potentiation of this clinical benefit by application of topicals, the current study sought to evaluate the clinical efficacy and tolerability of a combination treatment regimen using non-ablative fractional 1927 nm diode laser treatment with topical serum containing vitamin C, vitamin E and ferulic acid (SkinCeuticals C E Ferulic®). Furthermore, this study sought to evaluate the impact of this combination treatment on reversing cellular senescence and skin aging on a molecular level.

Methodology

This was a prospective, double-blinded, placebo-controlled, randomized clinical trial conducted from August 2024 to April 2025. The study was approved by a centralized institutional review board (Advarra IRB, Inc.) and conducted in accordance with Good Clinical Practices conforming to the ethical guidelines of the 1975 Declaration of Helsinki. Forty-six adults aged 30 to 70 years old of all Fitzpatrick skin types I-VI with mild to moderate photoaging (defined as a modified Griffith score of 3-6 for all the categories were enrolled and forty subjects completed the study. This study was designed as a pilot, randomized, placebo-controlled trial to generate preliminary estimates of clinical and biomarker effects and to inform future adequately powered studies. Exclusion criteria included energy-based device or injectable treatments of the face within 6 months before enrollment in the study, using topical agents with active ingredients such as steroids, retinoids, hydroquinone four weeks before enrollment

in the study, having scarring, tattoos or rashes in the treatment site, taking isotretinoin, having a history of any medical conditions that would impact wound healing or pregnancy. Patients with a history of melasma were included in the study. Age ranges for Fitzpatrick V-VI were extended from 65 years to 70 years to account for potential differences in photoaging progression and treatment responses in darker skin types.

Participants were randomized into one of two treatment groups. Participants were randomized in a 3:2 ratio (active: placebo) using a computer-generated randomization schedule prepared before study initiation. Study products were identical in appearance and packaging. Participants in the active group applied a serum containing 15% L-ascorbic acid, 1% vitamin E and 0.5% ferulic acid (SkinCeuticals C E Ferulic® serum) (CEF) once daily to the full face and bilateral postauricular area, alongside a standardized regimen that was provided to all patients (gentle cleanser, moisturizer, SPF50). Participants in the control group used an identical regimen but substituted CEF with a matched placebo serum with no active ingredients. Both groups pre-treated for two weeks with the assigned regimen and then underwent two 1927 nm non-ablative fractional diode laser treatments (Clear + Brilliant® Perméa, treatment level: high) at Day 0 and Day 28, with immediate post-laser application of assigned serums. The post-auricular region was treated with lasers and the application of skin care products in all participants.. Post-treatment care included using only the provided skin products and sun protection. Both participants and investigators performing clinical assessments were blinded to treatment allocation throughout the study period. Allocation concealment was maintained by labeling products with coded identifiers.

Efficacy was evaluated through blinded investigator assessments using the modified Griffiths 10-point scale (Supplement 1) to grade signs of photoaging, examining global fine lines, hyperpigmentation, skin tone evenness, elasticity, firmness, radiance/brightness, smoothness both tactile and visual and global wrinkles. Investigator assessments were performed at baseline, day 0 (after 14 days of topical pre-treatment), day 28 (following the first laser treatment), day 56 (one month following the second laser treatment) and day 84 (final follow-up two months after two laser treatments).

To evaluate the impact of treatment on a molecular level, a 4 mm punch biopsy was performed in 20 subjects from the right post-auricular area at baseline and at study end. Biopsies were stained for both Hematoxylin and Eosin (H&E) and immunofluorescence to evaluate biomarkers of cellular senescence, including MMP 9, MMP 2, beta-galactosidase, p16 and p21. Degree of staining was assessed by a dermatopathologist in both pre- and post-treatment samples. The post-auricular region was selected for biopsies to minimize visible scarring on a cosmetically sensitive facial area. This is a relatively sun-protected region as well, with similar structural characteristics to facial skin. Immunofluorescence staining was evaluated qualitatively by a blinded dermatopathologist. No standardized quantitative scoring system (e.g., H-score) or automated digital image analysis was employed.

Secondary efficacy measures included subject-reported outcomes via a 5-point Self-Assessment Questionnaire (Supplemental 2), Dermatology Quality of Life Index (DLQI) scores and compliance rates tracked through diary logs and product returns. Safety assessments focused on investigator-rated tolerance evaluation scores (erythema, edema, irritation) (Supplemental 3), adverse event incidence/severity and post-procedure comfort levels.

Statistical Analysis

All randomized subjects who completed at least one follow-up visit were included in an intent-to-treat analysis. Continuous outcomes were analyzed using a two-way mixed-effects ANOVA with treatment group (active vs control) and time as fixed effects and subject as a random effect. The Geisser-Greenhouse correction was applied when appropriate, followed by Šidák's post hoc test for multiple comparisons. Baseline characteristics were compared using independent t-tests for continuous variables and chi-square tests for categorical variables. Descriptive statistics (mean ± standard deviation) were calculated for continuous variables and frequencies were reported for categorical variables. Statistical significance was set at $p < 0.05$. Analyses were performed using GraphPad Prism (Version 10.4.2).

Results

Subjects

A total of 46 participants (40 females and 6 males), aged 30 to 70 years old (predominantly in their 40-50s), were enrolled and randomized. Forty subjects completed the study; six subjects discontinued the study due to compliance, personal reasons, screen

failures and an unrelated adverse event. All Fitzpatrick skin types were included: type I (n=2), type II (n=16), type III (n=11), type IV (n=8), type V (n=2) and type VI (n=1). Ethnicities reported included 60% (n=24) White, 12.5% (n=5) Hispanic, 10% (n=4) Asian, 5% (n=2) Pacific Islander or Alaska Native, 2.5% (n=1) Black or African American and 10% (n=4) Other [Supplement 4].

Efficacy

Significant improvement was observed in the active group (receiving CEF) compared to placebo-controlled serum in multiple outcome measures. Skin tone evenness was significantly improved on day 28 ($p=0.037$), day 56 ($p<0.001$) and day 84 ($p=0.002$). There was significant improvement in skin radiance and brightness as well in the active group compared to placebo on day 28 ($p<0.001$), day 56 ($p=0.002$), day 84 ($p<0.001$) (Fig. 1,2). By day 84, both tactile and visual skin texture were improved ($p=0.006$ and $p=0.033$, respectively). Skin hyperpigmentation/discoloration improvement was significant at day 84 ($p=0.017$) (Supplemental 5-8).

Satisfaction

Self-assessment questionnaires demonstrated positive outcomes in the active compared to the placebo group as well. 91.67% of the active group agreed or strongly agreed that their skin looks renewed/revitalized on day 84 (compared to 75.00% in the placebo group). Similarly, 91.67% of the active group agreed or strongly agreed that their skin looks firmer on day 84 (versus 62.50% in the placebo group) and 83.33% noted improved elasticity on day 84 versus 50.00% in the placebo group). 87.50% of the active group agreed or strongly agreed on day 84 that they were more satisfied with their procedure results when using the products, compared to 62.50% in the placebo group. Mean DLQI scores decreased from 2.04 ± 1.84 at baseline to 1.08 ± 1.26 at Day 84 in the active group and from 1.94 ± 1.62 to 1.19 ± 1.32 in the placebo group, with no statistically significant difference between groups.

Safety

Both active and control groups demonstrated a favorable safety profile, with most subjects reporting no to mild transient side effects (stinging/burning, itching, tightness) associated with combined laser and topical treatment. Moderate stinging/burning and tightness were rare and comparable between groups, with only one severe stinging/burning event reported in the control group. No treatment-related discontinuations occurred, supporting the tolerability of combining CEF topical regimens with 1927nm fractional diode laser treatments for photoaging. One patient discontinued the study due to angioedema, which was determined to be unrelated to the laser or treatment products.

Biopsy Results

A total of 20 subjects underwent pre-treatment biopsy in the post-auricular area and 19 (10 active group, 9 placebo) subjects completed the post-treatment biopsy for biomarkers. The extent of skin staining for each biomarker of senescence was noted in all biopsies and compared between pre-treatment and post-treatment. Matrix Metalloproteinase 2 (MMP 2) staining decreased in 90.0% of subjects in the active group (n=9/10), compared to 44.4% of the placebo group (n=4/9) (Fig. 3). Matrix Metalloproteinase 9 (MMP 9) staining similarly decreased in 90.0% of subjects in the active group (n=9/10), compared to 55.6% of the placebo group (n=5/9) (Fig. 4). Beta-galactosidase staining decreased in 50.0% of subjects in the active group (n=5/10) and 44.4% (n=4/9) of the placebo group (Supplement 9). Staining for p16 and p21 was inconsistent across both treatment groups, with both p16 and p21 having a decrease in staining in 20% or less (n=2/10) of the active group and 22.2% or less (n=2/9) of the placebo group.

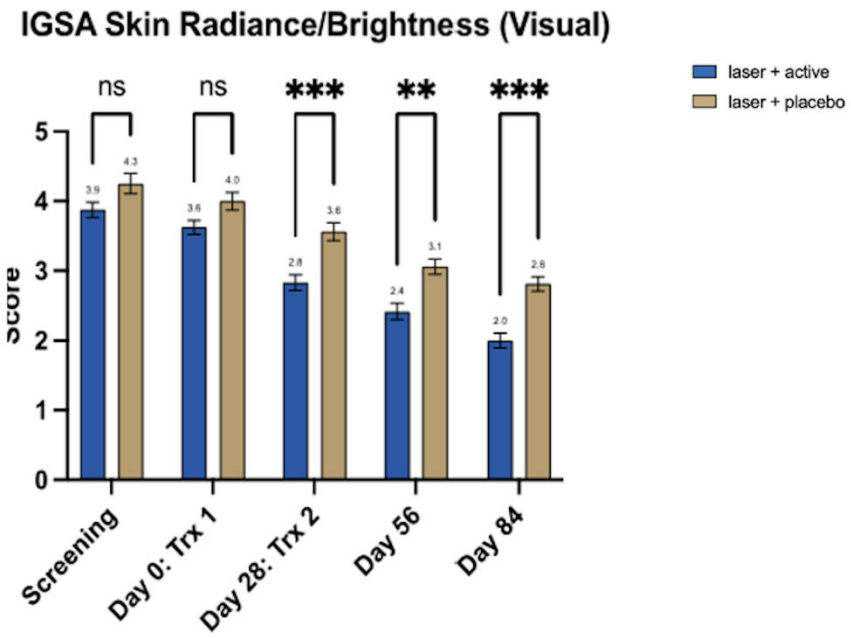

Figure 1: Mean IGSA visual scores for skin radiance/brightness over time show significantly greater improvement in the laser + active group compared to the laser + placebo group at Days 28, 56 and 84 (***p < 0.001, **p < 0.01, *** p<0.001).

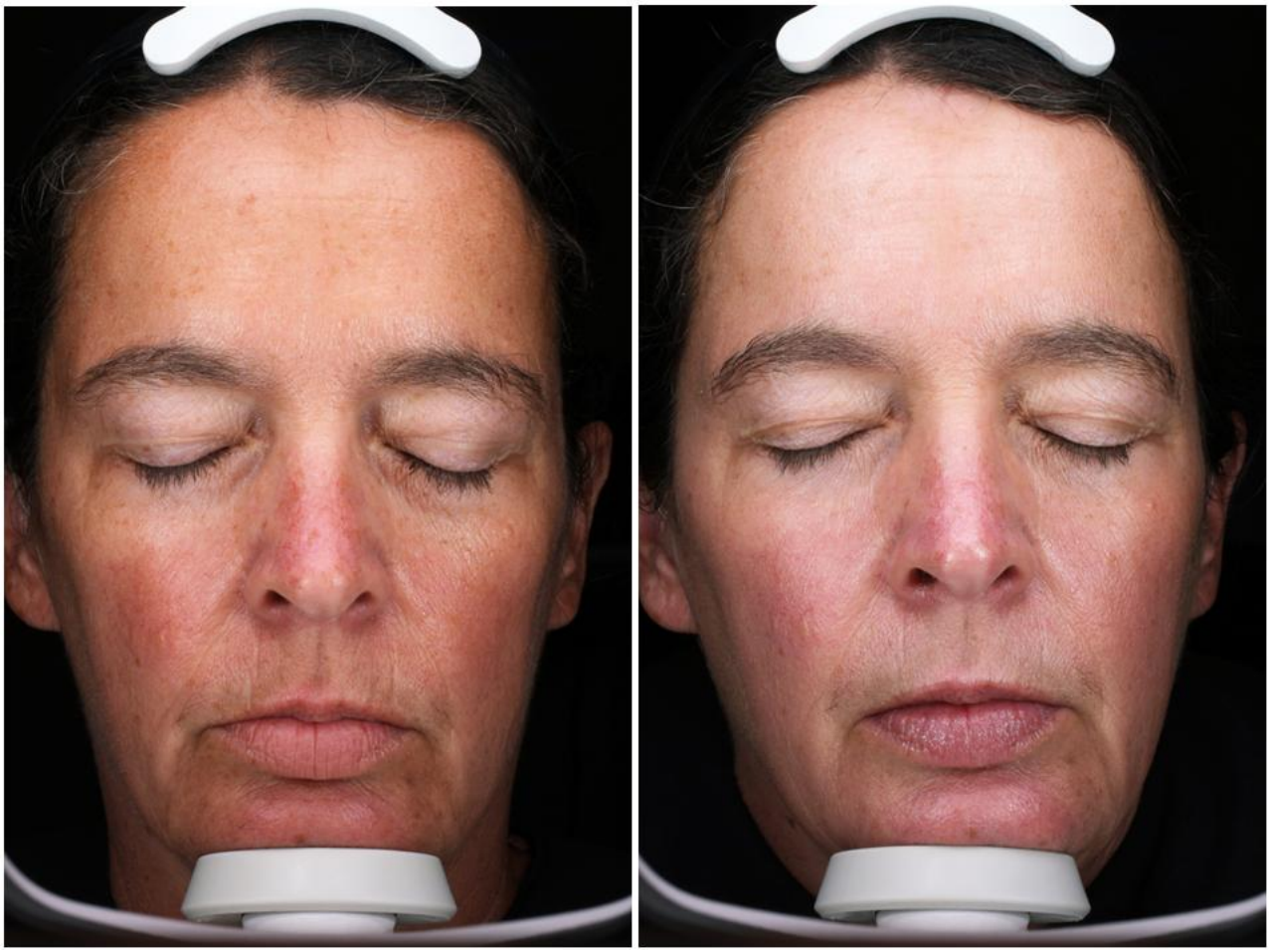

Figure 2: 51-year-old Fitzpatrick IV female in the active group showing skin changes from baseline (A)) to final visit two months post-treatment #2 (B).

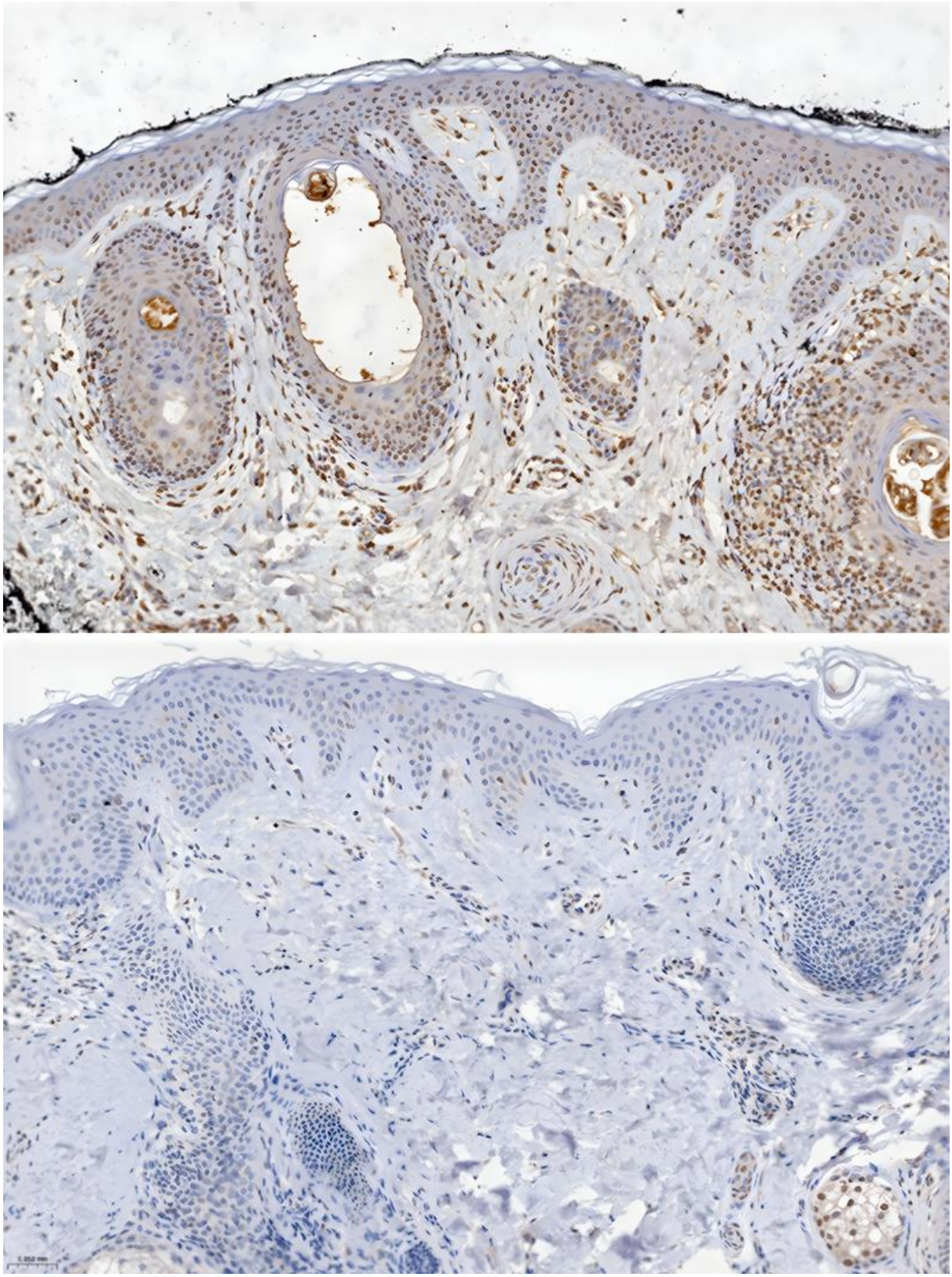

Figure 3: MMP2 expression prior tobefore active regimen treatment (A) in a 50-year-od Fitzpatrick II female, where strong MMP2 staining is observed in nearly all fibroblasts (AB) and two months following second laser treatment, MMP2 staining is markedly reduced (B).

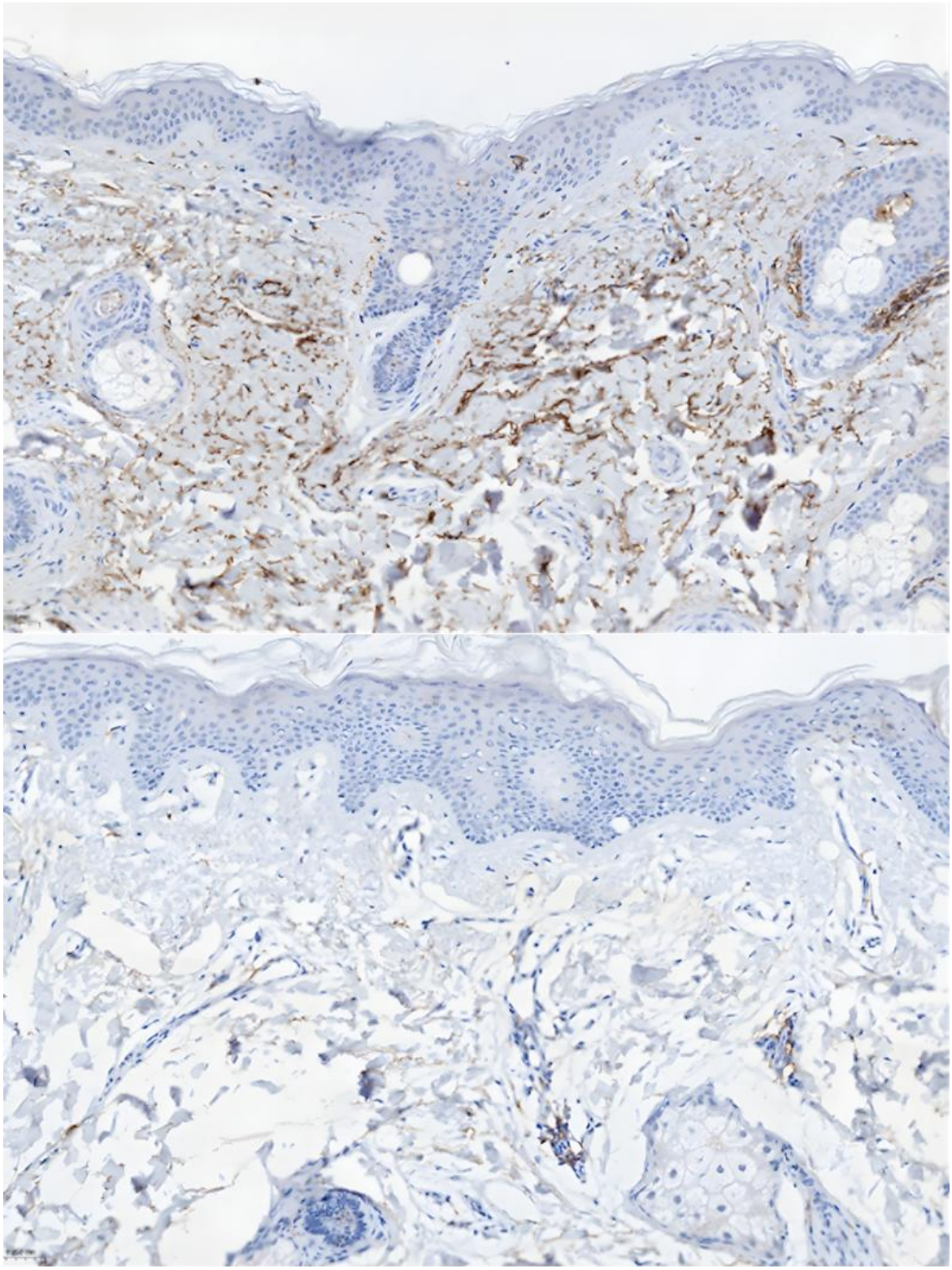

Figure 4: MMP9 expression prior tobefore active regimen treatment in a 45-year-old Fitzpatrick II female, where nearly all of the fibroblasts show positivity for MMP9 (A) and two months following second laser treatment, MMP9 staining is markedly reduced (B).

Discussion

This randomized, double-blind, placebo-controlled clinical trial demonstrates that the combination of a 1927nm fractional non-ablative diode laser with a topical antioxidant serum containing vitamin C, vitamin E and Ferulic acid (CEF) significantly improves both the clinical and molecular hallmarks of skin photoaging. The use of CEF enhanced investigator-reported

outcomes, patient satisfaction and appeared to be synergistic with the laser in reducing biomarkers associated with cellular senescence and aging. Our study adds to the growing body of literature suggesting that post-treatment topical agents not only improve treatment outcomes, but also it can modulate biomarkers of aging and inflammation [16].

Our biopsy analysis focused on key biomarkers of cellular senescence, one of 12 major hallmarks of aging.18 MMP-2, MMP-9, beta-galactosidase, p16 and p21 were selected due to their association with Senescence-Associated Secretory Phenotype (SASP). MMP-2 and MMP-9, extracellular matrix-degrading enzymes secreted by senescent fibroblasts, were markedly decreased in both treatment groups, but a greater reduction was observed in the active CEF group. This suggests that the combined treatment may help to reduce macromolecular damage and proteolytic activity, two features of senescent cells. Beta-galactosidase, a common marker of lysosomal dysfunction in senescent cells, was expressed less in the active group, demonstrating that the addition of the CEF to the post-laser regimen was associated with reduction is select biomarkers of reversed aspects of senescence-associated cellular dysfunction.

Although staining for p16 and p21, cell-cycle regulators associated with senescent cells, was not as notable across both groups, this may be due to marker sensitivity, staining variability and the time point of the biopsy. The lack of significant changes may also simply suggest that this treatment primarily targets SASP pathways and does not alter the cell-cycle arrest pathways.

This study touches on the broader topic of inflammaging, a term used to describe chronic, low-grade inflammation associated with aging, partly driven by the accumulation of senescent cells [19,20,22]. These senescent cells adopt a Senescence-Associated Secretory Phenotype (SASP) resulting in the secretion of pro-inflammatory cytokines. This cascade of events then promotes chronic inflammation, extracellular matrix degradation and impaired tissue repair, which contributes to clinical signs of skin aging [21,22]. Through reduced expression of multiple biomarkers of cellular senescence, the combination treatment of 1927 nm fractional diode laser and CEF serum helped synergistically to mitigate inflammaging.

This synergy can also be explained by the regenerative concept of hormesis, where controlled cellular stress (microscopic zones of thermocoagulation via a laser) stimulates an adaptive response of repair [18]. The laser induces a temporary inflammatory response that promotes collagen remodeling and cell turnover and through increased penetration of CEF serum, there is reduced oxidative damage. Recent studies suggest that laser-induced injury may also trigger beneficial epigenetic reprogramming, including changes in DNA methylation and histone acetylation, which can reactivate genes involved in collagen production and tissue regeneration [23]. By modulating these epigenetic pathways, laser therapy may help restore a more youthful gene expression profile, further contributing to long-term skin rejuvenation.

Several factors limited this study. Only a subset of subjects underwent biopsy, which limits the generalizability of the biomarker results and statistical power; therefore, biomarker results should be interpreted as exploratory. Although histological analysis was performed blinded, interpretation of immunostaining is subjective. Histologic assessment was qualitative and therefore subject to interpretive variability. Quantitative measurements, such as molecular assays (PCR), would have reduced this limitation and provided more information on the degree of reduction of these senescence biomarkers. The biopsy location of the post- auricular was a second limitation, as although it shares similar histologic and cellular characteristics with facial skin, the molecular changes observed are not a direct assessment of facial skin. A third limitation includes the 14-day pre-treatment period before laser therapy, which may have contributed to antioxidant priming of the skin before treatment. It is difficult to distinguish whether the enhanced outcomes observed in the active group were primarily attributable to pre-treatment conditioning, post-laser enhanced penetration or a synergistic effect of both phases.

Conclusion

This was the first study to evaluate the impact of 1927nm fractional non-ablative diode laser treatment with adjuvant topical containing vitamin C, vitamin E and ferulic acid (CEF) on improving both clinical and molecular markers of facial photoaging. Our data demonstrated notable improvement in skin radiance, brightness, hyperpigmentation, smoothness and tone evenness as well as a reduction in biomarkers in cellular senescence such as MMP-2, MMP-9, beta-galactosidase. These findings suggest that combination treatment of topical agents with energy-based devices not only provides better clinical results but is also associated with reductions in select biomarkers of cellular senescence.

Conflict of Interest
The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Financial Disclosure
This study was supported by SkinCeuticals through a medical grant, which provided funding and study products. The sponsor had input in study design but had no role in data analysis, data interpretation, or final manuscript drafting. All statistical analyses were performed independently. The sponsor reviewed the manuscript for factual accuracy but had no control over the interpretation of results or the decision to submit for publication.

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Ethical Statement
IRB approval received from Advarra IRB, Inc.
Clinical trials Registration information: NCT06603857
IRB Approval Code: Pro00081937

Informed Consent Statement
Consent for the publication of all patient photographs and medical information was obtained by the authors at the time of article submission to the journal stating that all patients gave consent for their photographs and medical information to be published in print and online with understanding that this information may be publicly available. Informed consent for publication was obtained from the participant involved in this study.

Data Availability Statement
Not applicable.

Authors' Contributions
All authors have contributed equally to this work and have reviewed and approved the final manuscript for publication.

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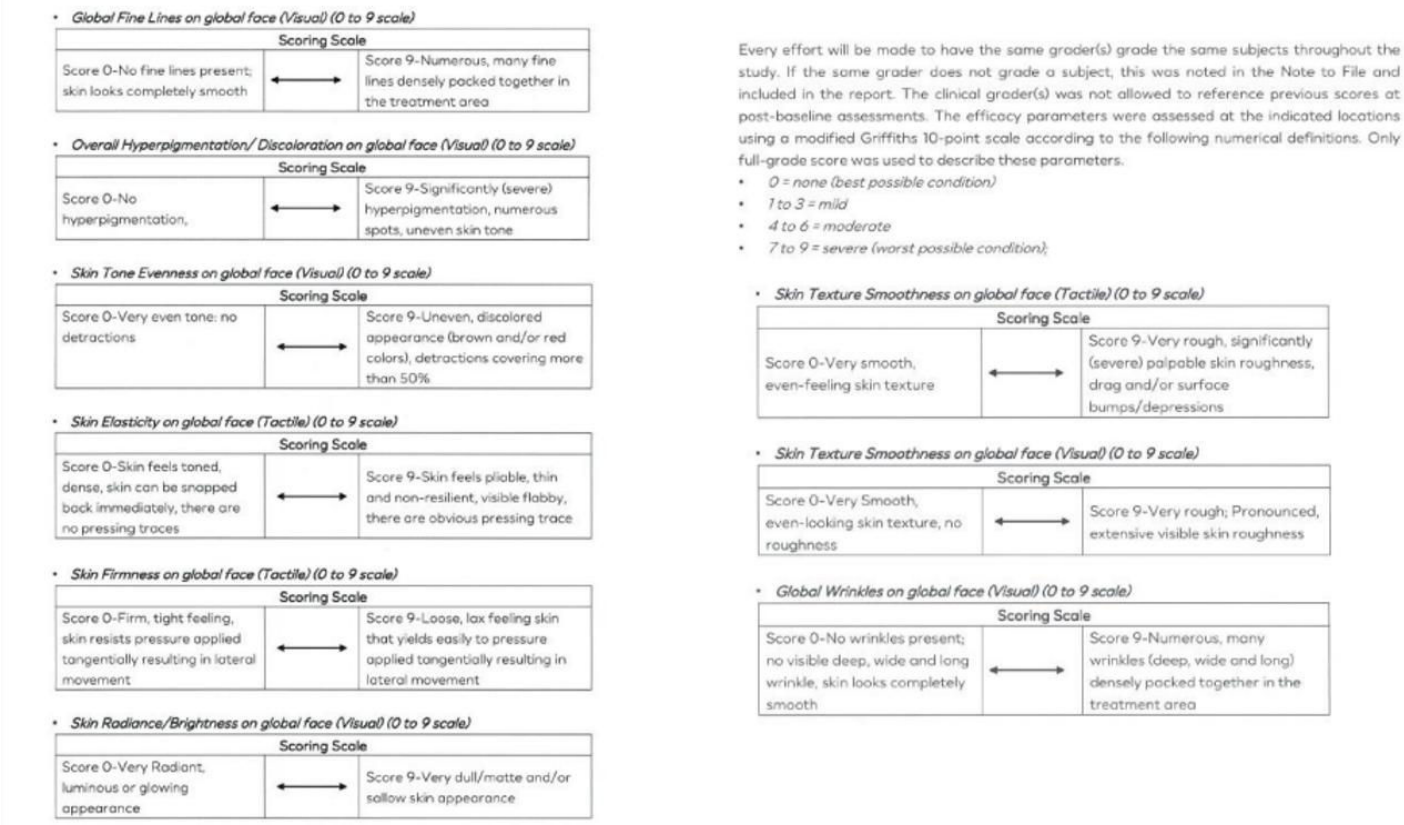
Supplementary Files



- *Global Fine Lines on global face (Visual) (0 to 9 scale)*

Scoring Scale		
Score 0-No fine lines present; skin looks completely smooth	⟷	Score 9-Numerous, many fine lines densely packed together in the treatment area

- *Overall Hyperpigmentation/ Discoloration on global face (Visual) (0 to 9 scale)*

Scoring Scale		
Score 0-No hyperpigmentation,	⟷	Score 9-Significantly (severe) hyperpigmentation, numerous spots, uneven skin tone

- *Skin Tone Evenness on global face (Visual) (0 to 9 scale)*

Scoring Scale		
Score 0-Very even tone: no detractions	⟷	Score 9-Uneven, discolored appearance (brown and/or red colors), detractions covering more than 50%

- *Skin Elasticity on global face (Tactile) (0 to 9 scale)*

Scoring Scale		
Score 0-Skin feels toned, dense, skin can be snapped back immediately, there are no pressing traces	⟷	Score 9-Skin feels pliable, thin and non-resilient, visible flabby, there are obvious pressing trace

- *Skin Firmness on global face (Tactile) (0 to 9 scale)*

Scoring Scale		
Score 0-Firm, tight feeling, skin resists pressure applied tangentially resulting in lateral movement	⟷	Score 9-Loose, lax feeling skin that yields easily to pressure applied tangentially resulting in lateral movement

- *Skin Radiance/Brightness on global face (Visual) (0 to 9 scale)*

Scoring Scale		
Score 0-Very Radiant, luminous or glowing appearance	⟷	Score 9-Very dull/matte and/or sallow skin appearance

Every effort will be made to have the same grader(s) grade the same subjects throughout the study. If the same grader does not grade a subject, this was noted in the Note to File and included in the report. The clinical grader(s) was not allowed to reference previous scores at post-baseline assessments. The efficacy parameters were assessed at the indicated locations using a modified Griffiths 10-point scale according to the following numerical definitions. Only full-grade score was used to describe these parameters.

- *0 = none (best possible condition)*
- *1 to 3 = mild*
- *4 to 6 = moderate*
- *7 to 9 = severe (worst possible condition);*

- *Skin Texture Smoothness on global face (Tactile) (0 to 9 scale)*

Scoring Scale		
Score 0-Very smooth, even-feeling skin texture	⟷	Score 9-Very rough, significantly (severe) palpable skin roughness, drag and/or surface bumps/depressions

- *Skin Texture Smoothness on global face (Visual) (0 to 9 scale)*

Scoring Scale		
Score 0-Very Smooth, even-looking skin texture, no roughness	⟷	Score 9-Very rough; Pronounced, extensive visible skin roughness

- *Global Wrinkles on global face (Visual) (0 to 9 scale)*

Scoring Scale		
Score 0-No wrinkles present; no visible deep, wide and long wrinkle, skin looks completely smooth	⟷	Score 9-Numerous, many wrinkles (deep, wide and long) densely packed together in the treatment area

Supplemental 1: Modified Griffiths 10-point scale to be used for investigator grading of cutaneous signs of photoaging on the face.

"The topical skincare regimen in pairing with the laser treatments…"	Agree strongly	Agree	Neither agree nor disagree	Disagree	Disagree strongly
1. Skin feels more comfortable					
2. Skin appears younger looking					
3. Skin appears healthier					
4. Skin looks renewed/revitalized					
5. Skin looks firmer					
6. Skin feels elastic					
7. Redness looks reduced					
8. With the product I'm more satisfied with the procedure results					
9. The product reduced the downtime of the procedure or makes the downtime more acceptable					
10. The product improves the outcome of the procedure					
11. With this product, I would feel more confident to do another procedure					
12. I would recommend this product post-procedure					
13. It's the best post-procedure care I ever used (if relevant)					
14. Is something I would use after future laser treatments					
15. The product has a pleasant texture					

Supplemental 2: Subject self-assessment questionnaire.

Stinging/Burning:

None	No stinging/burning of the treatment area
Mild	Slight, but definite burning of the treatment area
Moderate	Definite stinging/burning of the treatment area
Severe	Marked stinging/burning of the treatment area

Itching:

None	No itching of the treatment area
Mild	Slight, but definite itching of the treatment area
Moderate	Definite itching of the treatment area
Severe	Marked itching of the treatment area

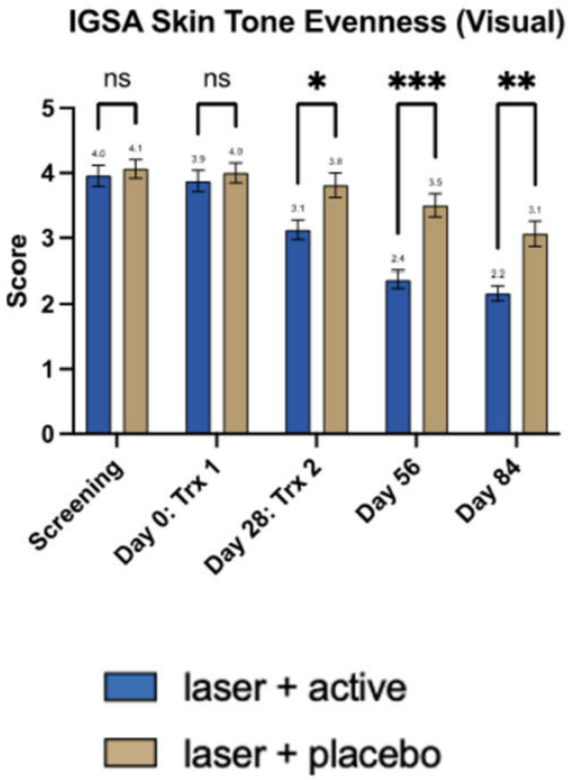
Rash:

None	No new rash over the treatment area
Mild	New rash covering some of the treatment area
Moderate	New rash covering much of the treatment area
Severe	New rash covering the entirety of the treatment area

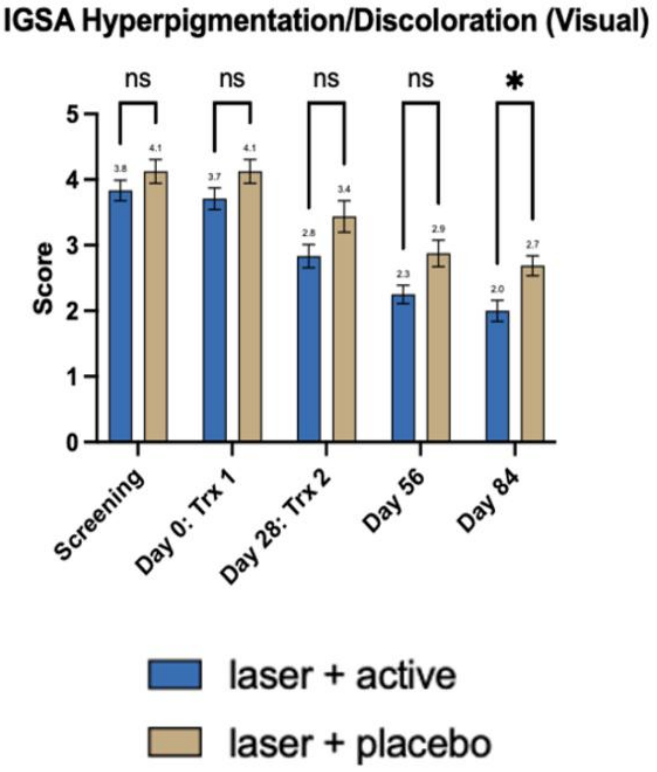
Supplemental 3: Evaluating investigator tolerability assessment.

Category	Count
Age	
Mean	49
Median	51
Fitzpatrick	
I	2
II	16
III	11
IV	8
V	2
VI	1
Gender	
Female	35
Male	5
Ethnicity	11
Hispanic or Latino	29
Not Hispanic or Latino	
Race	
White	24
Asian	4
Hispanic	5
Pacific Islander / American Indian or Alaska Native	2
Black or African American	1
Others	4

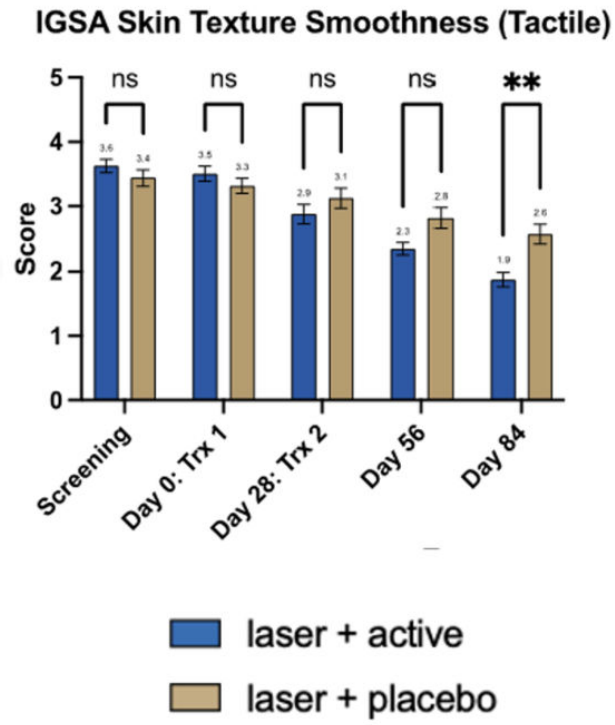
Supplemental 4: Demographics table of all subjects



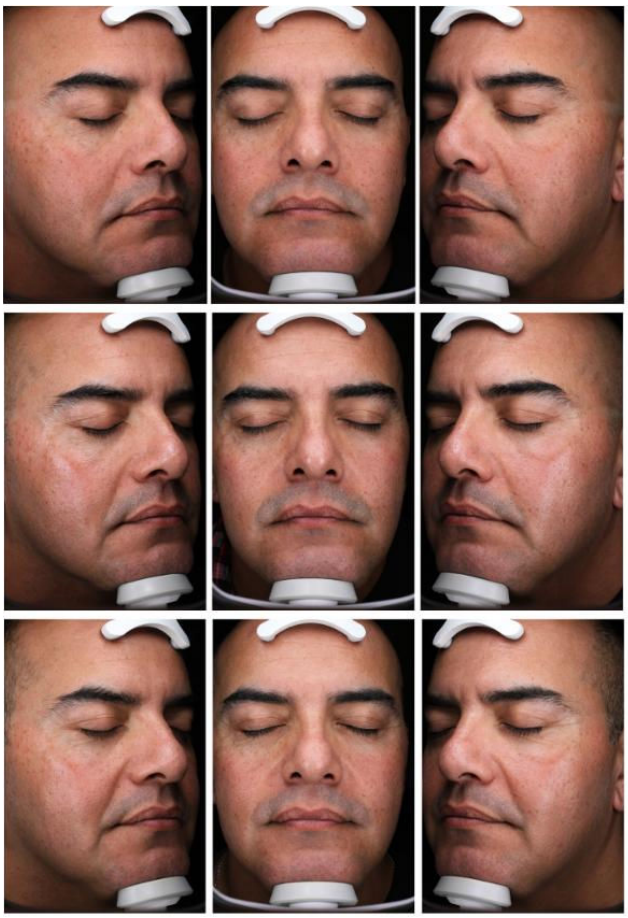
Supplemental 5: Mean IGSA visual scores for skin tone evenness over time show significantly greater improvement in laser + active group compared to laser + placebo group at Days 28, 56, and 84 (*p=0.037, ***p<0.001, **p=0.002).



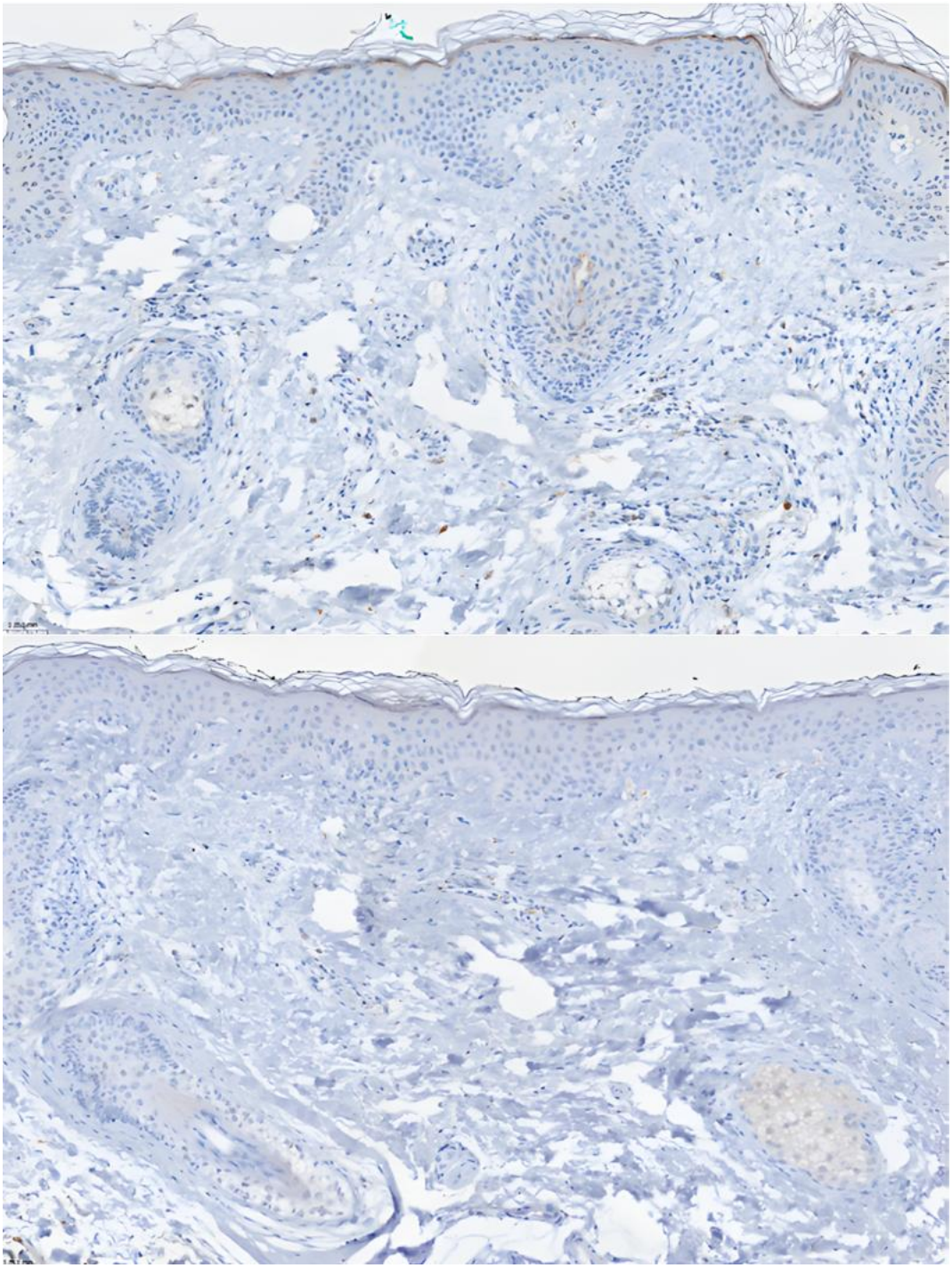
Supplemental 6: Mean IGSA scores hyperpigmentation over time show gradual improvement with statistically significant greater improvement in laser + active group compared to laser + placebo group at Day 84 *p<0.001).



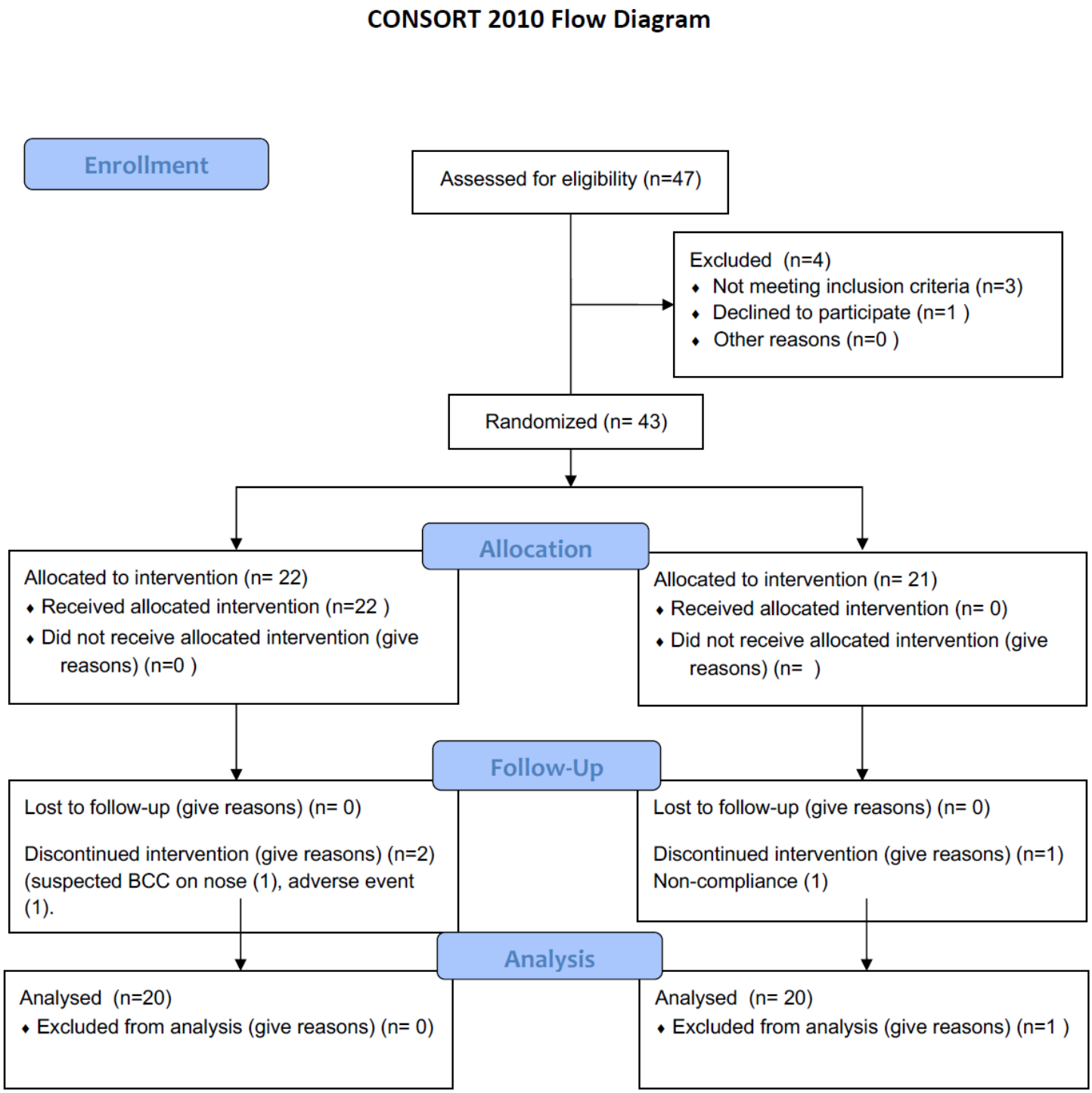
Supplemental 7: Mean IGSA tactile scores for skin texture smoothness over time show gradual improvement with statistically significant greater improvement in laser + active group compared to laser + placebo group at Day 84 (**p=0.006).



Supplemental 8: 48-year-old Fitzpatrick V male in the active group showing skin changes from baseline (Visit 1 - top row) to one-month post-treatment #1 (Visit 3 - middle row) and two months post-treatment #2 (Visit 5 - bottom row).



Supplemental 9: A. Beta-galactosidase expression prior to active regimen treatment in a 62-year-old Fitzpatrick II female, where rare fibroblasts show positivity for beta-galactosidase B. Two months following second laser treatment, there is no staining within fibroblasts for beta-galactosidase.



Supplemental 10: CONSORT flow diagram.