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ORIGINAL RESEARCH

Efficacy Evaluation of a Topical Hyaluronic Acid Serum in Facial Photoaging

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ABSTRACT

Introduction: Hyaluronic acid (HA) acts as a biologic humectant, thus retaining water in the skin, making HA useful as a topical moisturizing ingredient. The goal of the research was to evaluate the ability of a HA facial serum to deliver skin benefits.

Methods: Forty females 30–65 years of age with Fitzpatrick skin types I–VI who exhibited photoaging used the HA facial serum twice daily with sunscreen. The dermatologist investigator evaluated smoothness, plumping, hydration, fine lines/wrinkles, and global appearance issues on a 5-point ordinal scale. The subjects assessed product tolerability in terms of stinging, itching, and burning. Corneometry was undertaken, with assessments performed at baseline, immediately after application, and at weeks 2, 4, and 6. Facial swabbing and photography were performed at the same intervals on a subset of 15 subjects.

Results: The HA serum demonstrated excellent tolerability and produced an increase in skin hydration (as measured by corneometry) immediately after application of 134% ($p < 0.001$), with a sustained increase of 55% ($p < 0.001$) at week 6. At week 6, there was also improvement ($p \leq 0.001$) in all evaluated attributes: smoothness (64%), plumping (60%), hydration (63%), fine lines (31%), wrinkles (14%), and overall global assessment (43%). Facial swabbing confirmed an increase in topical HA at week 6 ($p = 0.04$), accounting for the enhanced skin appearance, but there was no statistically significant increase in IL-1a, indicating no product irritation.

Conclusion: Topical HA in a serum formulation provides excellent skin hydration, as demonstrated through clinical, photographic, chemical, and instrumental assessments.

Keywords: Moisturizer; Facial aging; Humectant; Corneometry; Transepidermal water loss

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Key Summary Points
Topical hyaluronic acid in a serum formulation can increase skin hydration by 55%, as measured by corneometry.
Topical hyaluronic acid skin hydration is visualized as improved skin plumping, smoothness, and overall skin appearance.
Topical hyaluronic acid possesses an excellent skin tolerability profile.
Topical hyaluronic acid is suitable for all Fitzpatrick skin types.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14748876.

INTRODUCTION

Improvement in overall facial skin appearance is most rapidly achieved through enhanced moisturization. Moisturization occurs by increasing the water content of the epidermis, thereby improving skin texture and reducing the appearance of fine lines and superficial wrinkles. The skin naturally achieves hydration through dermal glycosaminoglycans (GAGs) such as hyaluronic acid [1]. Hyaluronic acid (HA), also known as hyaluronan, is a linear carbohydrate polysaccharide found in all living organisms [2]. It is a highly hydrophobic substance [3]. The human body contains 15 g of HA, with one-third residing in the skin [1]. HA is multifunctional in the skin, modulating cellular immunity, regulating epidermal cell interactions, residing in extracellular matrix molecules, and absorbing high amounts of water [4]. Six liters of water can be absorbed by 1 g of HA [5].

HA can penetrate into the stratum corneum if it is of the correct size [6]. Raman microimaging and other techniques are able to monitor the penetration of HAs of different molecular weights [7]. HA with a low molecular weight of 20–300 kDa passes through the stratum corneum, while high molecular weight (1000–1400 kDa) HA is largely impermeable [1]. This points to the importance of selecting HA of the proper molecular weight in effective skin formulations.

The ability to manufacture large quantities of HA from bacterial fermentation has led to enhanced-efficacy moisturizers that are able to mimic the natural moisturization process of the skin. The objective of this study was to evaluate the ability of a facial serum to deliver skin benefits by promoting skin plumpness and hydration while minimizing fine lines/wrinkles and improving the overall global assessment of facial appearance. The clinical study was additionally supported by in vitro work to determine if the HA serum product could increase hyaluronan expression.

METHODS

In Vivo Clinical

Forty females 30–65 years of age with Fitzpatrick skin types I–VI who were diagnosed by the dermatologist investigator as possessing poor skin plumpness and hydration along with photoaging were enrolled in this single-site study to evaluate the efficacy of a facial serum. This study was conducted in compliance with the Helsinki Declaration of 1964 and its later amendments. The study was approved by the Allendale Institutional Review Board (AIRB), Old Lyme, CT). Informed consent for participation and for photograph and article publication was received from all participants. Following this, and after meeting all inclusion criteria and none of the exclusion criteria (Table 1), subjects with a lack of skin hydration and plumping and with global photoaging were enrolled. Subjects were asked to wash their face at the research center. They were provided with a headband to pull hair off their face and a black

Table 1 Inclusion and exclusion criteria

Inclusion criteria:
1. Subjects must be diagnosed by the investigator as possessing poor skin plumpness and hydration along with photoaging.
2. Subjects must be female, 30–65 years of age, Fitzpatrick skin types I–VI, with no known medical conditions that, in the investigator's opinion, may interfere with study participation.
3. Women of childbearing potential must be willing to use a form of birth control during the study. For the purpose of this study, the following are considered acceptable methods of birth control: oral contraceptives, Norplant, Depo-Provera, double barrier methods (e.g., condom and spermicide), and abstinence. No new methods of birth control should be started during the study.
4. Subjects must be able to read, understand and provide written informed consent.
5. Individuals must agree to continue to use all regular brands of cosmetics, makeup remover, and the assigned test materials for the duration of the study. Individuals must refrain from using any new products other than the assigned test materials.
6. Willingness not to use any moisturizer, cleanser, and/or sunscreen on the face other than the provided study product and sunscreen along with their normally used facial cleanser.
7. Subjects must agree to avoid excessive sun exposure and the use of artificial tanning methods.
8. Subjects must agree to arrive at their study visits with a clean face and without any products (lotions, creams, makeup, etc.) applied to their face.
Exclusion criteria:
9. Any dermatological disorder that, in the investigator's opinion, may interfere with the accurate evaluation of the subject's face.
10. Subjects who have demonstrated a previous hypersensitivity reaction to any of the ingredients of the study products.
11. Concurrent therapy with any medication, either topical or oral, that might interfere with the study.
12. Subjects who have used a topical retinoid or other cosmeceutical preparation within 2 weeks of study enrollment, to include kojic acid, vitamin C, licorice extracts, alpha hydroxy acids, etc.
13. Subjects who are unwilling to discontinue use of all other facial moisturizers.
14. Subjects who are unwilling to leave their current oral and/or topical product medications unchanged for the duration of the study.
15. Subjects who use an indoor tanning booth.
16. Subjects who are pregnant, breastfeeding, or planning a pregnancy.
17. Subjects with clinically significant unstable medical disorders.
18. Subjects who are unwilling or unable to comply with the requirements of the protocol.
19. Individuals who are participating in any other research study.

neck drape to conceal their clothing. All visible facial jewelry was removed and the subjects were instructed to close their eyes and mouth. These procedures were undertaken to anonymize the photographs.

Subjects were provided with the study facial serum (PCA Skin Hyaluronic Acid Boosting Serum, Colgate-Palmolive Co., Piscataway, NJ and PCA Skin, Scottsdale, AZ) for twice-daily use and a sunscreen (Neutrogena Clear Face Broad Spectrum SPF 55, Johnson & Johnson, Skillman, NJ) for use as needed during the study. The use of facial sunscreen was required by the IRB and it was used by all subjects, as documented in the subject diaries. Subjects used their own self-selected cleanser and cosmetics, but these products were stable for 30 days prior to study entry and throughout the study. A compliance diary was provided to record the use of the study serum.

The dermatologist investigator evaluated smoothness, plumping, hydration, fine lines/wrinkles, and global appearance issues. The following 5-point ordinal scale was used: 0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe. Subjects assessed product tolerability in terms of stinging, itching, and burning. The following 5-point ordinal scale was used: 0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe. Corneometry (Dermalab Combo Pin Probe, Cortex Technologies, Hadsund, Denmark) of the left cheek was conducted for all subjects in triplicate after they had acclimated to the study environment for 20–30 min.

VISIA CR4.3 (Canfield Scientific, Parsippany, NJ) photography of the front, right, and left face with visible light was conducted for a subset of 15 subjects. The faces of these 15 subjects were then swabbed on the right cheek for HA levels after photos had been captured at each study visit so as not to interfere with images. Swabs were collected on clean skin, as each subject was asked to wash their face with their self-selected cleanser at the research center prior to all study assessments during their afternoon study visits (the last product application was completed in the morning of the study visit at weeks 2, 4, and 6). The swabbing technique is often used to collect skin surface microbiome samples. HydraFlock (25-3606-H, Puritan Medical Products Company LLC, Guiford, ME) was first wetted by dipping it into sterile phosphate-buffered saline (PBS). A skin surface sample was collected by covering a surface area of 2 inches by 2 inches with a swab while rotating and moving the swab. Swabs collected throughout the study were stored at − 80 °C until processing. Each swab was soaked and shaken in 1 mL of PBS with protease inhibitor cocktails for 1 h at room temperature. Freezing/thawing of the extracts to/from − 80 °C was limited to three times within 2 weeks which did not impact the ELISA results. The resulting extracts were used in interleukin-1a (IL-1a, SLA50, Human IL-1 Alpha/IL-1F1 Quantikine ELISA Kit, R&D Systems Minneapolis, MN), hyaluronan (DHYAL0, Hyaluronan Quantikine ELISA Kit, R&D Systems, Minneapolis, MN), and filaggrin (CSB-EL008712HU, Cusabio, Houston, TX) enzyme-linked immunosorbent assays (ELISAs) according to the manufacturer's protocols.

During the baseline visit only, all subjects applied the study product and sat for 10–15 min at the end of their study visit after all assessments were completed. Investigator assessments were completed for immediate plumping and hydration. Postapplication corneometry of the left cheek was conducted for all subjects in triplicate. Subjects returned for the same assessments at weeks 2, 4, and 6.

In Vitro

Full-thickness human skin equivalents from MatTek (EpiDermFT, EFT-400, Ashland, MA) were used to evaluate whether the study HA serum product could increase hyaluronan expression. After equilibration overnight after receiving EFT-400, 10 μL of the product were applied on top of the skin equivalents for further incubation at 37 °C with 5% CO_2. Triplicates were used for untreated samples and duplicates for the serum-treated samples. After 24 h of treatment, the medium was collected for IL-1a release. Tissues were rinsed with PBS three times and collected for HA expression. The epidermis and the dermis were separated from tissues for protein extraction using a TissueLyser II (85300, Qiagen, Carlsbad, CA) and RIPA lysis buffer (R0278, Sigma-Aldrich, St. Louis, MO). The protein concentration was determined using a Micro BCA Protein Assay Kit (23235, Thermo Scientific, Waltham, MA) according to the manufacturer's protocol. IL-1a release and

hyaluronan expression were determined using ELISAs (SLA50, DHYAL0, R&D Systems) according to the manufacturer's protocols. For the hyaluronan ELISA, protein lysates were diluted 1000-fold (epidermis) and 10,000-fold (dermis) and normalized to the protein concentration.

Levels of HA and other active ingredients in the PCA Skin Hyaluronic Acid Boosting Serum are kept proprietary. The serum contains HA as well as HA Pro Complex containing disodium acetyl glucosamine phosphate, hydrolyzed yeast extract, polyglucuronic acid, and sodium carrageenan.

RESULTS

In Vivo Clinical

40/40 subjects with Fitzpatrick skin types I–VI (35 Caucasians, 5 African Americans) successfully completed the 6-week study. Subjects aged 38–60 years were enrolled, with 8 on hormonal contraception and 32 postmenopausal. Statistical significance was defined as $p \leq 0.05$. Ordinal five-point nonparametric subject and investigator questionnaire data were evaluated as the change from baseline and percent change in an intragroup analysis using a Wilcoxon signed rank test. Numeric corneometry data representing the average of three facial measurements were assessed using a Student *t*-test and reported as the average for each visit and as the percent change from baseline.

The subjects noted no statistically significant stinging, itching, or burning immediately after product application or at any time during the 6-week study. The investigator assessed hydration and plumping visually immediately after product application. There was a statistically significant ($p < 0.001$) 30% improvement in plumping and a 31% improvement in skin hydration. This improvement continued into week 2 with statistically significant ($p \leq 0.003$) improvements in smoothness (29%), plumping (35%), hydration (35%), fine lines (9%), and overall global assessment (19%). Cumulative improvement was seen at week 4, with statistically significant ($p < 0.001$) improvements in smoothness (49%), plumping (48%), hydration (46%), fine lines (21%), and overall global assessment (33%). The study concluded at week 6 with continued improvement ($p < 0.001$) in all attributes: smoothness (64%), plumping (60%), hydration (63%), fine lines (31%),

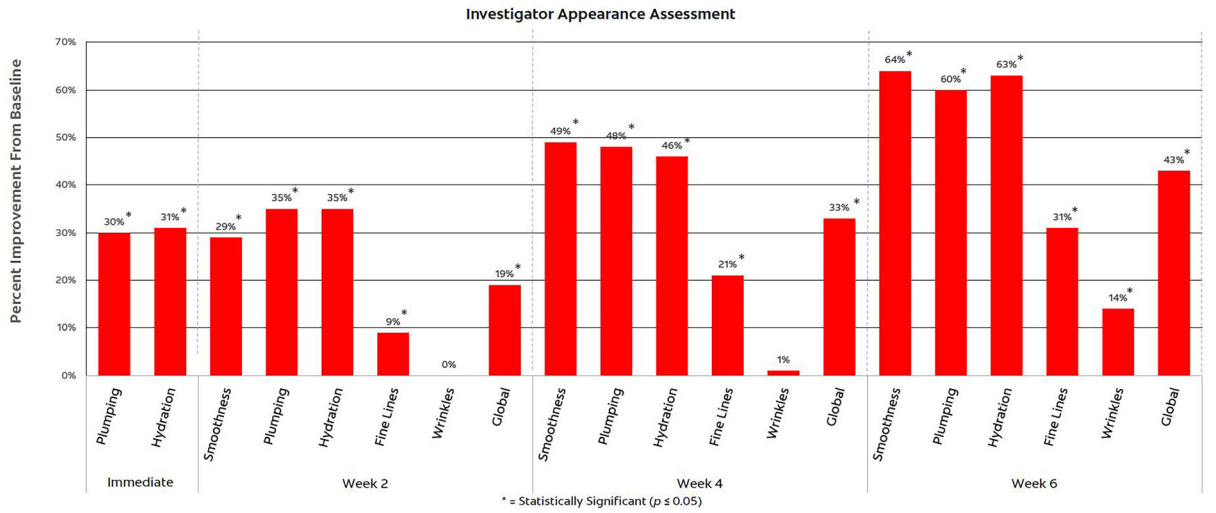

Fig. 1 Investigator assessments. Percent improvements from baseline immediately after application and at week 2, week 4, and week 6 are shown. Note the cumulative improvement over time with continued use of the product

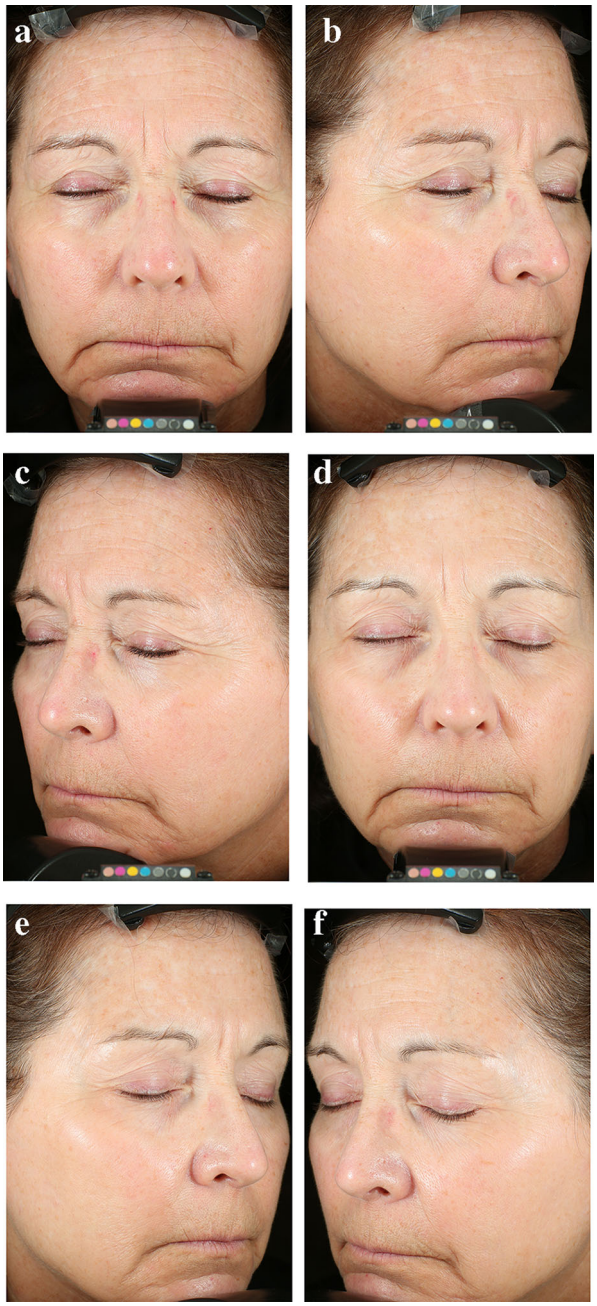

Fig. 2 Before treatment (**a** front of face, **b** right of face, **c** left of face) and after 6 weeks of treatment (**d** front of face, **e** right of face, **f** left of face) of Fitzpatrick type II skin. This Caucasian female photographically demonstrated increased light reflection from the face (seen as facial shine) after treatment. This increased light reflection is due to smoothing of the skin surface and a reduction in fine facial lines

Fig. 3 Before treatment (**a** front of face, **b** right of face, **c** left of face) and after 6 weeks of treatment (**d** front of face, **e** right of face, **f** left of face) of Fitzpatrick type V skin. This African-American female demonstrated increased light reflection from the face, especially from the medial cheeks, improving overall skin tone

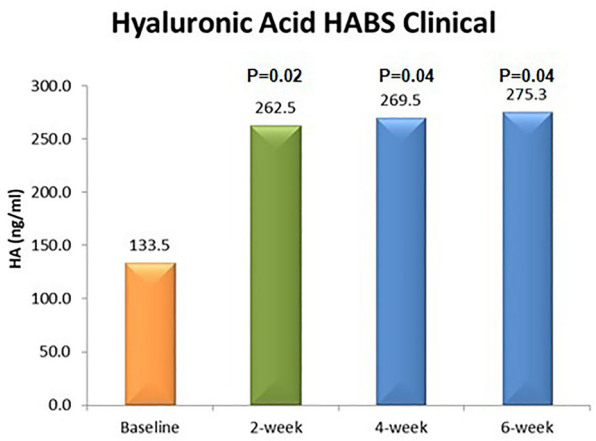

Fig. 4 In vivo clinical hyaluronic acid analysis based on skin surface swabs. Skin surface swabs were collected and extracted using PBS with protease inhibitor cocktails. HA concentrations were analyzed by ELISA for all four time points (baseline, 2 weeks, 4 weeks, and 6 weeks). Average HA concentrations from 40 subjects are shown, and statistical tests were performed for weeks 2, 4, and 6 using the baseline for comparison. The increases in HA from the skin at weeks 2, 4, and 6 are shown

wrinkles (14%), and overall global assessment (43%) (Fig. 1). Before and after photographs of representative subjects are presented in Figs. 2 and 3.

The investigator noted that the improvement was probably due to the enhanced water-holding capacity of the topically applied HA, which was effective for all Fitzpatrick skin types regardless of the degree of photodamage. Immediately after application, there was a 134% increase in skin water content ($p < 0.001$) as measured by corneometry. This is possible due to the water-holding effect of the HA when present on the skin surface. After 2 weeks of application, a 15% increase ($p = 0.025$) was seen; there was a further improvement in water content of 29% at 4 weeks ($p < 0.001$) and of 55% at 6 weeks ($p < 0.001$).

Facial swabs taken at baseline and weeks 2, 4, and 6 were analyzed. Posttreatment swabs collected at weeks 2, 4, and 6 were compared to baseline swabs (control, prior to serum treatment). IL-1a was measured to determine if the HA serum produced any irritation. Baseline swabs (before serum application) were used as a control. There was no statistically significant increase in IL-1a, indicating that there was no irritation (data not shown). Filaggrin, which is broken down into natural moisturizing factor (NMF), was also measured. There was no statistically significant change in filaggrin, indicating that the HA serum helped maintain NMF (data not shown). An examination of the HA present on the skin surface was conducted. There was a statistically significant increase in HA. The change from baseline p-values was $p = 0.02$ at week 2, $p = 0.04$ at week 4, and $p = 0.04$ at week 6 (Fig. 4).

One problem with HA-containing products is stickiness due the humectant properties of HA, which draws water from the atmosphere, which means that the serum does not dry down on the skin. The subjects were asked to assess product stickiness at week 6. Minimal stickiness was noted by the subjects. Subjects reported no application concerns.

In Vitro

After 24 h of treatment with serum, the full-thickness skin equivalents were rinsed with PBS. The epidermis and the dermis of the full-thickness skin equivalents were separated by pulling, which was followed by protein extraction. Samples were analyzed for the presence of hyaluronan by ELISA. More hyaluronan was present in the dermis compared to the epidermis, which is consistent with the literature. Serum-treated samples were compared to the untreated samples (control). While no differences in the epidermis were observed between the untreated and serum-treated samples, there was an increase in the hyaluronan in the dermis from serum-treated samples. Based on this finding, the increase in dermal hyaluronan is from the boosting effects of the HA serum, not residual hyaluronan from the study product, since there was no difference between the untreated and serum-treated epidermis (Fig. 5). The paired t-test was used as the method of statistical analysis.

	Epidermis		Dermis	
	Average	StDev	Average	StDev
Untreated	8.39	6.12	205.29	35.76
Serum	7.62	5.31	306.93	94.12

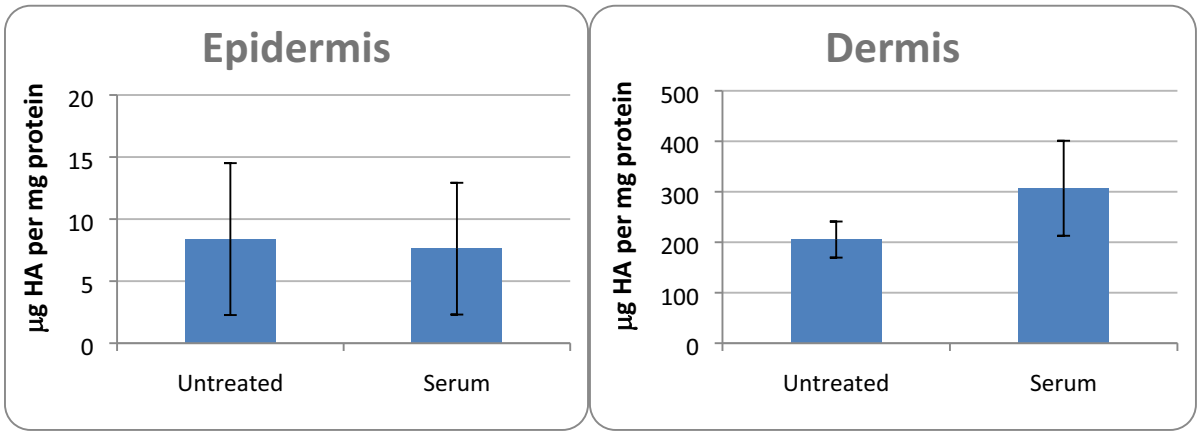

Fig. 5 In vitro hyaluronic acid analysis using EpiDermFT. EpiDermFT was treated with Hyaluronic Acid Boosting Serum (*Serum*) or left untreated (*Untreated*) for comparison. Proteins for the epidermis and the dermis were separately extracted using the RIPA lysis buffer with protease inhibitor cocktails, and ELISAs were run to evaluate the HA concentrations in these tissue samples. The HA ELISA results were normalized to the total protein concentrations in the same samples and are represented as the HA concentration per mg protein. The epidermis results and the dermis results are shown separately. Increased dermal hyaluronan was detected in these samples. The increase in dermal hyaluronan was from the boosting effects of the Hyaluronic Acid Boosting Serum (HABS)

DISCUSSION

HA is a valuable ingredient to improve facial appearance in women with poor skin plumpness, decreased skin hydration, and photoaging [8]. It has been used both topically and orally for appearance improvement [9]. HA is multifunctional, even possessing a role in immune modulation in disease [10] and as a postprocedure treatment in facial resurfacing [11]. Changes occur in HA with aging such that a HA-based moisturizer might improve facial appearance through topical application [12].

The current formulation contains hydrolyzed 50 kDa HA and 10–1000 kDa sodium hyaluronate. This size of the HA allowed it to penetrate into and through the stratum corneum [4]. These humectant ingredients produced an immediate increase in the water-holding capacity of the skin, as demonstrated by the investigator assessments and corneometry 15 min postapplication. The film-forming capabilities of the HA formulation created a smoothed skin surface with excellent humectant properties, producing appearance improvement. In addition, the improvement was cumulative, with increasing results over the 6 weeks of study product application as continued hydration occurred.

HA increased significantly after 2 weeks of product application, with slight continued increases observed through weeks 4 and 6 (Fig. 5). These results indicate there was a significant amount of HA deposited on the skin from the study serum, which may account for the cumulative improvement observed over

time. This research supported the clinical findings of increased skin hydration by documenting the increase in HA through skin swabbing. This increased skin hydration resulted in the investigator observing facial appearance improvement. This type of improvement was probably not due to the sunscreen used for photoprotection during the study, as it did not possess humectant properties.

However, there are some limitations of this study. While skin punch biopsies can definitively assess the modulation of HA in the skin after serum application, skin punch biopsies are invasive and may produce facial scarring in volunteers. In order to assess clinical subjects noninvasively, we utilized skin surface swabbing as well as in vitro assessment. Even though we were able to demonstrate modulation of HA, these changes were not assessed via biopsy. Since clinical assessments demonstrated changes in plumpness and hydration, it is likely that biomarkers related to increased skin hydration, as seen in the HA ELISA from skin surface swabbing. Another limitation of this study is the lack of a placebo to compare with the serum product. It might have been possible to compare the serum to placebo, but there are no true moisturizer placebos. Therefore, the serum was compared to baseline or no treatment instead. Finally, this study did not consider the possible preventative activity of HA in photoaging.

CONCLUSIONS

Skin hydration is one of the major concerns for skin health. Among ingredients that improve skin hydration, HA stands out with its ability to retain moisturization. With an appropriately selected HA based on efficacy, this well-formulated HA serum can visually improve skin plumping and mechanistically improve skin hydration by 55% as measured by corneometry due to an increase in dermal hyaluronan in all Fitzpatrick skin types.

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Compliance with Ethics Guidelines. This study was conducted in compliance with the Helsinki Declaration of 1964 and its later amendments. The study was approved by the Allendale Institutional Review Board (AIRB), Old Lyme, CT). Informed consent for participation, photograph and article publication was received from all participants.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution. Zoe Diana Draelos, MD, Isabel Diaz, BA, Jin Namkoong, PhD, Joanna Wu, PhD, and Thomas Boyd, PhD all contributed to the conduct of the scientific research detailed in this manuscript and the writing of the manuscript.

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