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ORIGINAL ARTICLE

Multicenter evaluation of a topical hyaluronic acid serum

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Abstract

Background: A new hyaluronic acid (HA) formulation was developed based on high molecular weight (MW) compounds used on the surface of the skin while using peptides to stimulate the high MW HA production by fibroblasts and keratinocytes from within the skin layers. Detailed science has been submitted to this journal in a previous publication. This multicenter study aims to validate the science by demonstrating the safety and efficacy of the product in the clinical realm.

Objectives: This study evaluated the efficacy and safety of a topical HA serum in facial skin.

Methods: An open-label clinical study was undertaken over 4 months from November 2021 to March 2022. Participants applied the topical serum twice daily and were provided a gentle cleanser and an SPF 30+ to use in the morning. Follow-up visits were conducted at weeks 2, 4, and 8. At every visit, participants were measured for hydration post 15 minutes of cleansing the skin and post 15 minutes of product application for cumulative skin hydration sensor measurements. Additional procedures included participant assessments and satisfaction, investigator assessments, biopsies, and photography.

Results: At each follow-up visit, there was an increase in hydration measurements compared to baseline, in both immediate scores and cumulative long-term scores. At weeks 4 and 8, there was a statistically significant increase in hydration compared to baseline and the prior visit. Participants' assessments progressively increased over 2-, 4-, and 8-week intervals with significantly favorable ratings in all measured parameters. Similarly, investigator assessment grades were statistically significant ($p < 0.0001$) for decreased fine lines/wrinkling, crepiness, texture, erythema, and dryness, and increased ($p < 0.0001$) for moisture/hydration. Histology revealed increased CD44 staining in 6 of the 7 participants biopsied, denoting increased HA stimulation. In all of the participant biopsies, H&E staining demonstrated improvement in solar elastosis. Photography revealed remarkable improvement in erythema, tone, and texture.

Conclusions: The study results demonstrated that the formulation produced significant improvements in immediate and long-term hydration effects on the skin as measured by the skin hydration sensor, 'wearifi' technology, comparison of before and after

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biopsies, and participant and investigator assessments. This high MW HA formulation produced excellent clinical improvement in skin health and hydration.

KEYWORDS

aesthetic medicine, hyaluronic acid, rejuvenation

1 | INTRODUCTION

Skin aging is associated with a loss of skin moisture. The skin is the most abundant source of hyaluronic acid (HA) accounting for 50% of the total body HA. The HA content of the dermis is far greater than that of the epidermis and accounts for most of the 50% of total body HA present in skin. The papillary dermis has a more prominent level of HA than does the reticular dermis. The HA-bound water in both the dermis and the vital area of the epidermis is critical for skin hydration. In the basal layer, HA is predominantly intracellular and involved in mitotic events, while extracellular HA in the upper layers of the epidermis is involved in barrier disassociation and the sloughing of cells. The HA-bound water in both the dermis and the epidermis is critical for skin hydration.¹ The most predominant receptor for HA is CD44.²

Many topical preparations use combinations of high and low molecular weight (MW) HA to promote skin hydration. However, in the wound healing literature, low MW HA is known to be proinflammatory and could be problematic when treating the skin.^{3,4} Comprehensive in vitro testing identified a group of active agents that stimulated high MW HA production. This novel approach to HA topical application with exclusively high MW HA production is aimed at maximizing hydration capacity while encouraging regenerative activity within the ECM.⁵

This study evaluated the efficacy and safety of a topical HA serum on facial skin.

2 | MATERIALS AND METHODS

This open-label clinical study occurred over 4 months from November 2021 to March 2022 and was approved by the Institutional Review Board, Advarra, Inc. Eligible participants were healthy men and women of age 25–70 years, without clinically significant unstable medical conditions, who were willing to only use the topical study product and refrain from extended periods of sun exposure, topical treatments, and procedures to the facial area during the course of study participation. Exclusions to study participation included a previous hypersensitivity or known allergy to any of the ingredients in the study product, use of retinols or topicals with actives within 30 days, injectable toxins or resurfacing procedures within 3 months, and injectable fillers and oral isotretinoin within 6 months. Additionally, pregnancy, breastfeeding, and participants planning on becoming pregnant during the study duration were excluded.

Eligible, enrolled participants were given the topical HA serum, HA Immerse (Alastin® Skincare Inc.) to apply twice daily and return to the office for follow-up visits at weeks 2, 4 and 8. All participants were supplied with a gentle cleanser (Alastin® Skincare Inc.) for

am and pm use and a Mineral Broad Spectrum Sunscreen SPF 30+ (Alastin® Skincare Inc.) to use in the am. A small subset of participants were supplied with an ultralight moisturizer (Alastin® Skincare Inc.) due to weather changes during the winter months. At every visit, participants cleansed their facial skin and acclimated for 15 min prior to assessments, photography, and measurements. Participants then applied the topical serum and acclimated for 15 min prior to the second set of assessments, photography, and measurements.

2.1 | Skin hydration sensor measurements (Wearifi, Chicago, IL)

At every visit, participants had 3 measurements on the right and left sides of the face, 15 min post cleansing the facial skin and 15 min post application of the topical study product. Measurements were performed in the same area at every visit. The measurement depth of the sensor is optimized to 50 μm , capturing the water content across stratum corneum and upper epidermis. The measurement is a quantitative result of volumetric ratio of water in skin tissue, which represents an absolute value with direct relevance to the effective hydration.

2.2 | Participant assessments and satisfaction

At all follow-up visits, post 15 min of cleansing the skin, participants completed an assessment of their facial skin (using a 5-point scale) and overall satisfaction with the topical study product (using a 7-point scale) compared to baseline. Additionally, at every visit, post 15 min of applying the topical serum, participants completed an assessment of their facial skin (using a 5-point scale). Assessments and scales are available in the appendix.

2.3 | Investigator Assessments

At baseline and week 8, post 15 min of cleansing, investigators completed an assessment of the facial skin. A 10-point scale was used to assess fine lines/wrinkling, crepiness, texture, erythema, dryness, and moisture/hydration. Scale parameters were 0 absent, 1–3 mild, 4–6 moderate, and 7–9 severe.

2.4 | Biopsies

A 3-mm punch biopsy was performed periauricular at baseline, and post application at week 2, 4, or 8. Participants who elected to undergo

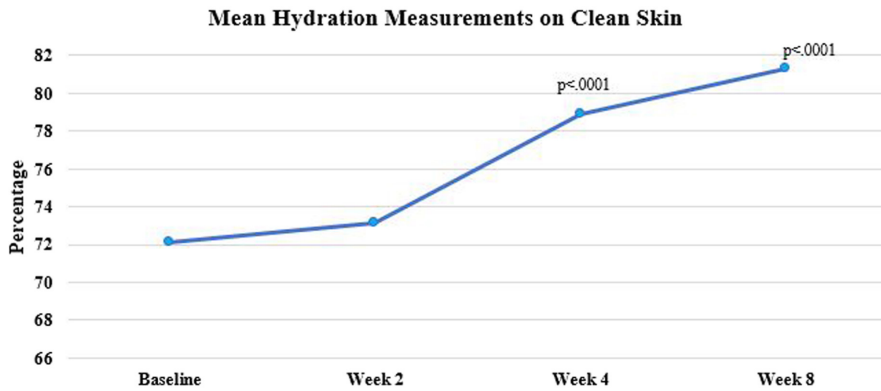


FIGURE 1 Mean hydration measurements on clean skin.

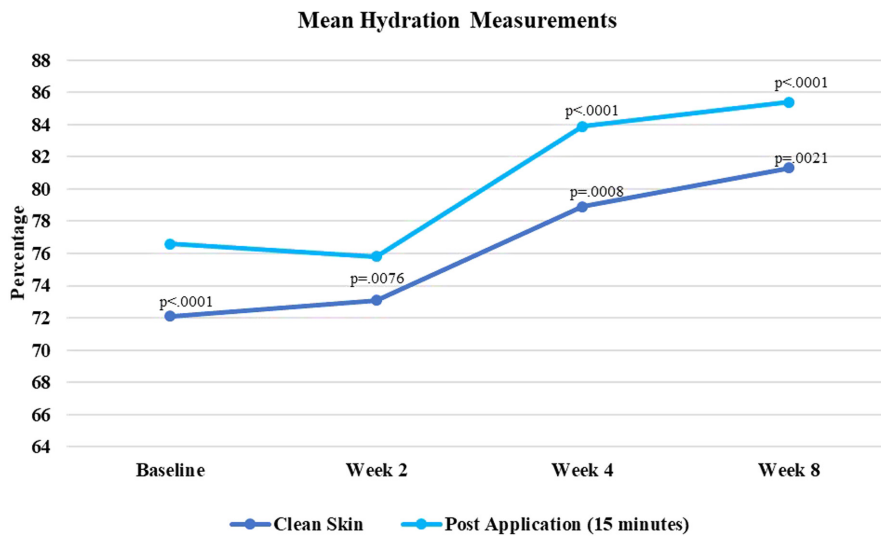


FIGURE 2 Mean hydration measurements – Clean skin and 15 minutes post study product application.

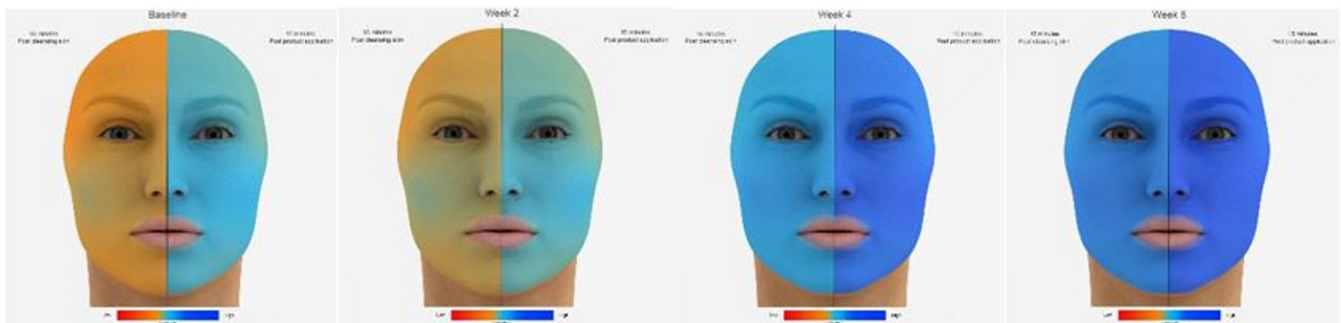


FIGURE 3 Facial hydration mapping demonstrates the mean hydration measurements pre and post application at all time points.

biopsies were instructed to apply the topical serum periauricular twice a day for the duration of the study. An independent dermatopathologist evaluated the tissue pre and post application of the study product.

2.5 | Photography

At every visit, photos were taken 15 min post cleansing the skin and 15 min post application of the study product. There were three different camera systems utilized in this study: VISIA® Skin Analysis

System (Canfield Scientific, Inc.), LifeViz® Infinity, and LifeViz® Micro (Quantificare, Inc.).

2.6 | Statistical methods

Statistical analyses were performed by an independent statistician at the Biostatistics, Institute for Clinical and Translational Science, University of California, Irvine, CA. Descriptive statistics including mean and standard deviation were computed for subject

FIGURE 4 The percentage of participants who strongly agreed or agreed with the assessment of their skin.

Grading: % of Strongly Agree or Agree	Week 2	Week 4	Week 8
Replenished the moisture in my skin	84%	91%	94%
Made my skin look more youthful	71%	87%	90%
Improved the appearance of my facial fine lines and wrinkles	50%	67%	78%
My skin looks more hydrated	77%	87%	96%
My skin feels more hydrated	84%	87%	88%
My skin feels softer and smoother	89%	96%	96%
Visibly improved my skin texture	68%	80%	90%
Increased the radiance and clarity of my skin	64%	83%	92%
Made me feel more confident in the way my skin looks	68%	74%	81%
Improved the overall appearance of my skin	79%	91%	89%
I would continue using this product	91%	91%	92%
I would recommend this product to others	86%	91%	92%

FIGURE 5 The percentage of participants who strongly agreed or agreed with the assessment of their skin post 15 minutes of application.

Grading: % of Strongly Agree or Agree	Baseline (post 15 minutes)	Week 2 (post 15 minutes)	Week 4 (post 15 minutes)	Week 8 (post 15 minutes)
Made my skin visibly more radiant	55%	73%	89%	90%
Made my skin look and feel more moisturized	81%	84%	91%	92%
Made my skin feel smooth	98%	96%	98%	96%
Made my skin visibly more hydrated	72%	75%	76%	92%

Week	% Favorable rating Grades 4, 5, and 6 Mildly, Moderately or Extremely Satisfied	P-value
2	91%	0.0061
4	98%	
8	98%	

FIGURE 6 The percentage of participants who were satisfied with their outcomes.

satisfaction, assessment scores, and hydration data. Parametric and nonparametric tests were used to determine if the scores were significantly increased from baseline through week 8. Additionally,

the percentage of subjects whose satisfaction/assessment scores were greater than three defined as ' % favorable rating ' was computed.

3 | RESULTS

Forty-six participants completed the study, and two participants terminated early due to excess sun exposure. The mean participant age was 43.6 years, with the age range of 27–69 years, and 11 were males and 35 were females with Fitzpatrick skin types I–V.

An independent statistician completed the analyses using descriptive statistics and parametric and nonparametric tests.

3.1 | Skin hydration sensor measurements

Two analyses were completed on clean skin between baseline and follow-up visits and between clean skin and post application of the study

product at each visit. A pairwise comparison between each timepoint was also computed.

15 min post cleansing facial skin, at each follow-up visit, there was an increase in the hydration measurements compared to baseline. At weeks 4 and 8, there was a statistically significant increase in hydration compared to baseline and also when compared to the prior visit (Figure 1).

At every visit, hydration measurements were statistically significant higher compared to clean skin. At weeks 4 and 8, post

application measurements were also significantly higher than post application measurements at baseline and week 2 (Figures 2 and 3).

3.2 | Participant assessments and satisfaction

Fifteen minutes post cleansing the skin, at weeks 2, 4, and 8, participants that gave a favorable rating, of either strongly agree or agree,

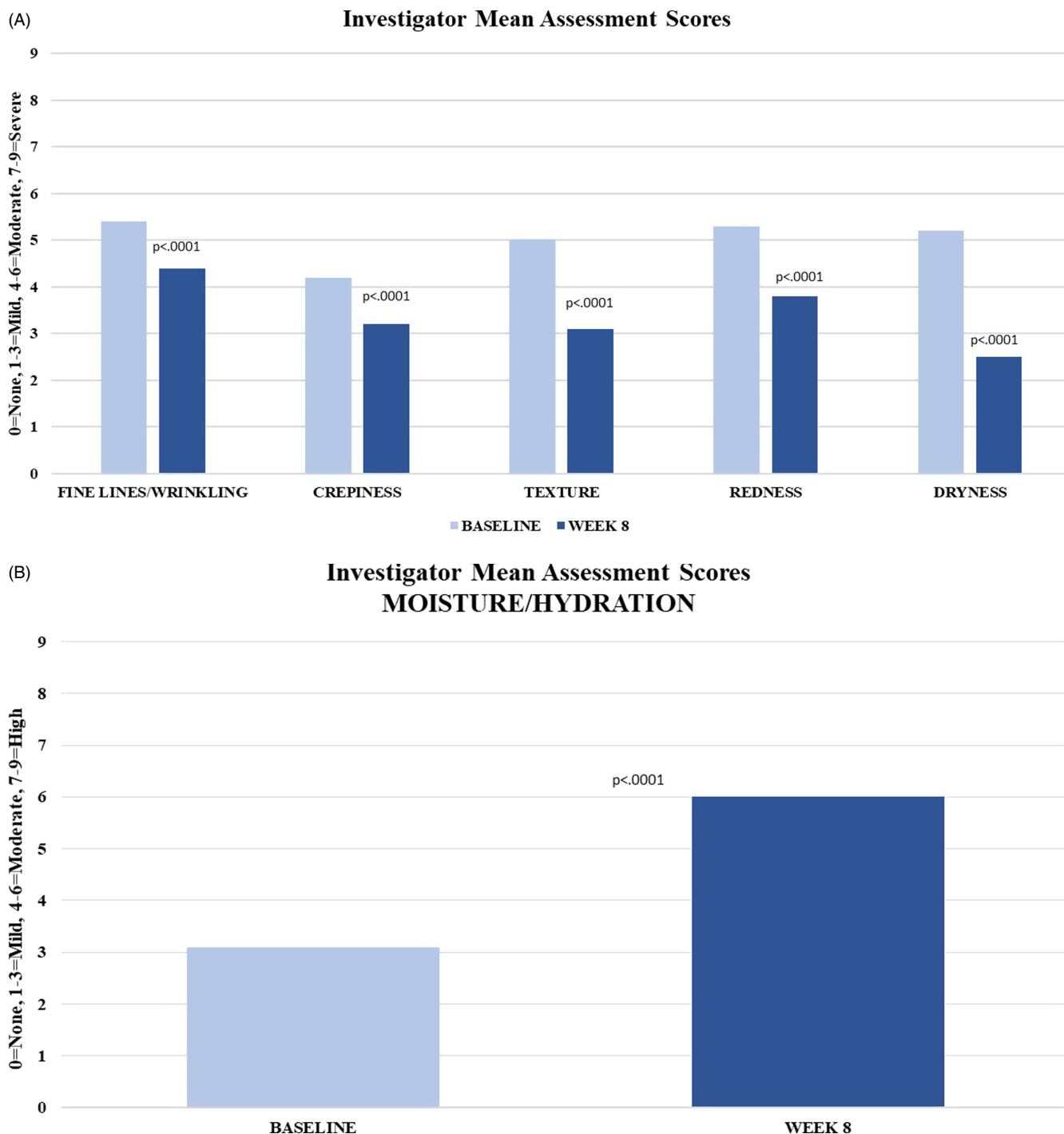


FIGURE 7 (A) Mean investigator assessment scores from baseline to week 8. (B) Moisture/hydration was graded significantly higher compared to baseline. Mean investigator assessment scores from baseline to week 8.

FIGURE 8 (A–D). Decreased erythema, red channel. (A) Female age 33. Left Baseline, Right Week 2. (B) Female age 34. Left Baseline, Right Week 4. (C) Female age 53. Left Baseline, Right Week 8. (D) Female age 35. Left Baseline, Right Week 8.

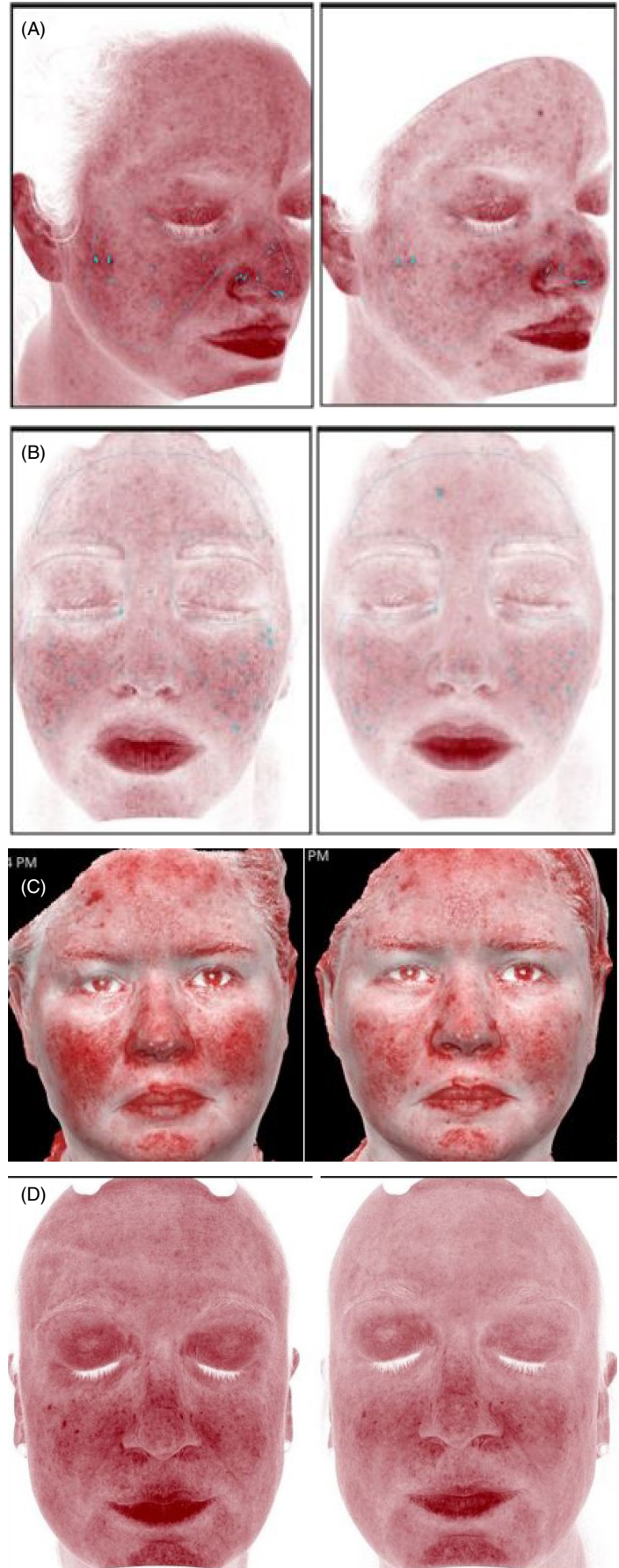




FIGURE 9 Female age 38. Left Baseline, Right Week 8



FIGURE 10 Female age 35. Left Baseline, Right Week 8.



FIGURE 11 Male age 34. Left Baseline, Center Week 2, Right Week 8.

FIGURE 12 Female age 56. Left Baseline, Right Week 8.



FIGURE 13 Female age 67. Left Baseline, Right Week 4



were statistically significant compared to week 2 for the following assessments (Figures 4 and 5).

Fifteen minutes post application of the study product, the percentage of participants who rated favorably continued to increase at each visit.

Participant satisfaction was rated favorably, 4–6 on the scale, and statistically significant: 90.9% at week 2, increased to 97.8% at week 4, and 97.9% at week 8 ($p = 0.0061$) (Figure 6).

3.3 | Investigator assessments

Compared to baseline, all assessment grades were significantly improved ($p < 0.0001$): grades for decreased fine lines/wrinkling, crepiness, texture, erythema, and dryness decreased, and increased moisture/hydration ($p < 0.0001$) (Figure 7).

3.4 | Photography

Figures 8–13 Participant photos demonstrating a decrease in erythema and improvements in texture, tone, and skin quality.

3.5 | Biopsies

Three males and four females, mean age 51.3, elected to have a 3-mm punch biopsy periauricular at baseline and post twice daily application of the product at either week 2, 4, or 8. As anticipated, CD44 staining was increased in six of the seven participants biopsied, denoting increased HA stimulation (Figure 14). What was of note, and unexpected, is when evaluating H&E staining all of the participants demonstrated remarkable improvement in solar elastosis with suggestions of significant reversal remarked by the dermatopathologist in most of the cases (Figure 15).

4 | DISCUSSION

Hyaluronic acid is ubiquitous throughout the body both within the cellular compartments and extracellular matrix, as well as in joints and synovial cavities. As such, it plays an extremely important role in lubrication, cellular motility, and general tissue homeostasis. This is especially evident in the epidermal and dermal skin layers where HA is constantly involved in maintaining skin health.⁶ As such, it has become apparent, particularly in the wound healing arena, that low

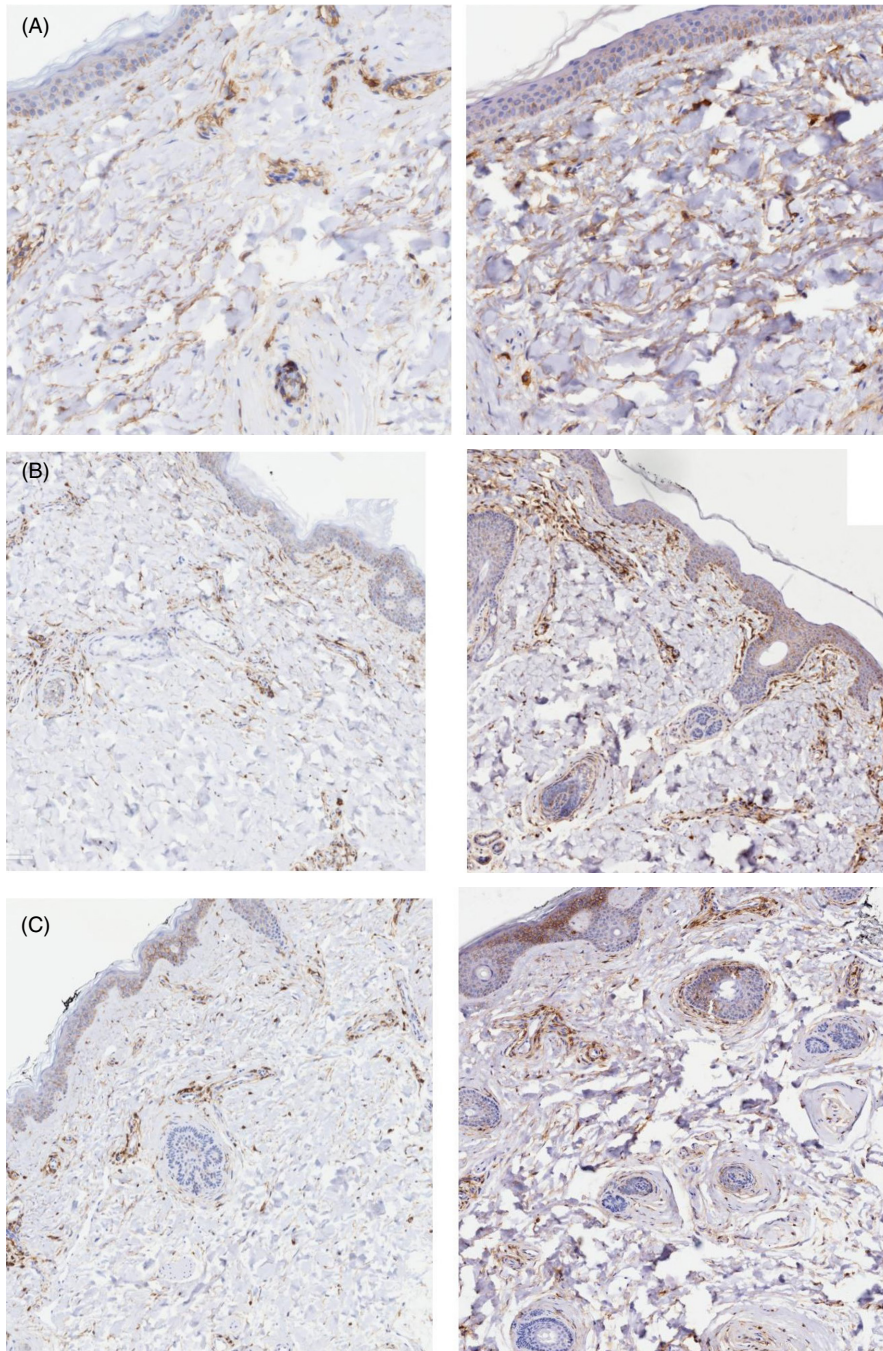


FIGURE 14 CD44 stain – pre (left) and post 8 weeks of application (right) – example of three participant biopsies. (A) Female age 55. (B) Male age 33. (C) Male age 48.

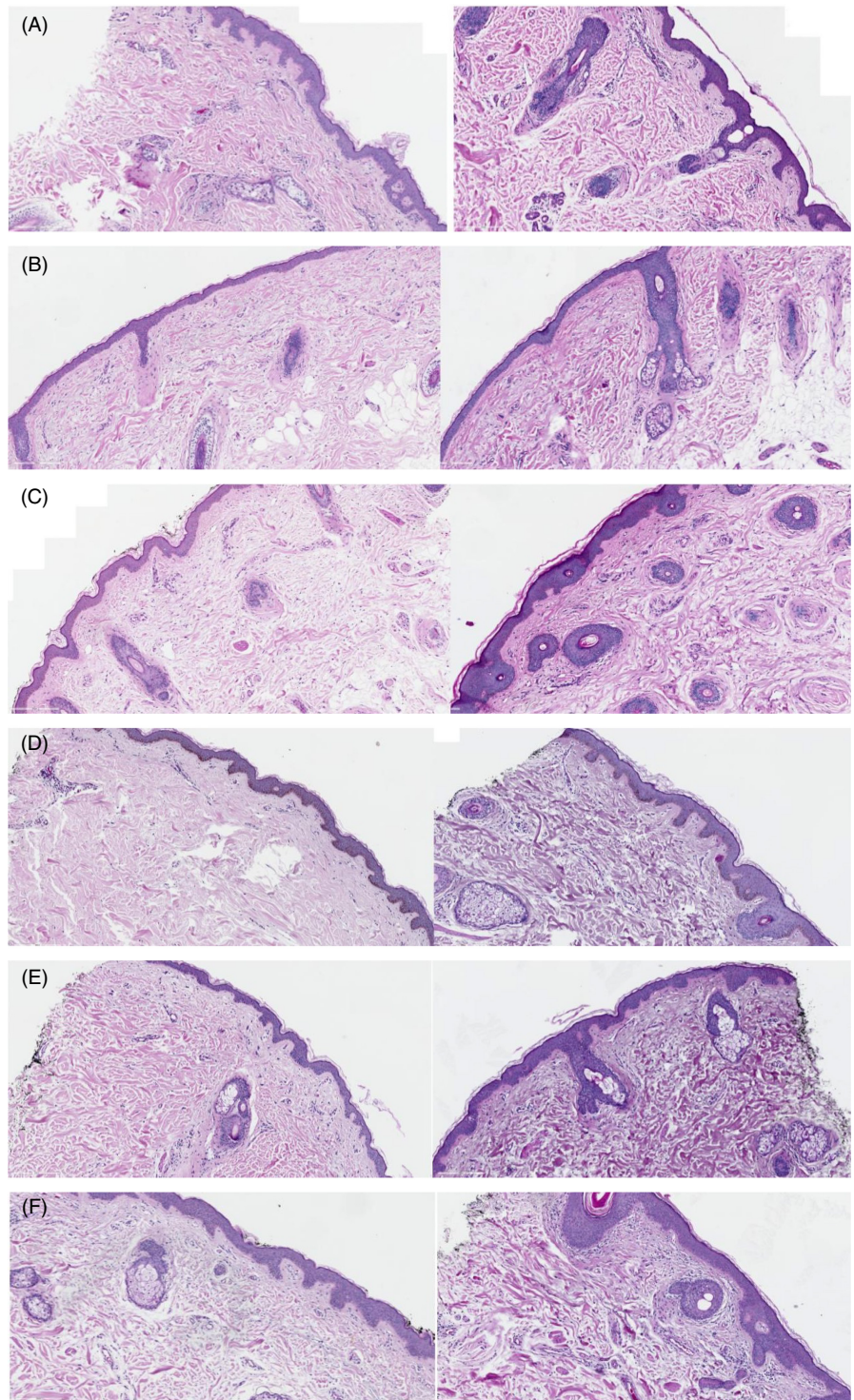
MW HA is produced from healthy high MW HA as a stress response employed as a wound healing mechanism during the highly inflammatory process of wound healing.³ For tissue maintenance, health, and regeneration, high MW HA plays an extremely important role in controlling inflammation and promoting regeneration.³ Thus, the formulation tested here, novel in its design for high MW HA output, was assessed not only in its capacity to increase hydration but also to glean evidence of resolution of redness and skin reactivity, representative of a possible background inflammatory milieu. This trial showed successful results in both areas.

From a hydration inducing perspective, the formulation was designed to produce a 'sandwich' effect of hydration both outside

and inside. Large MW HA components within the formulation work on the surface of the skin providing immediate hydration, while active components, including a proprietary peptide (Octapeptide-45), stimulate fibroblastic formation of high MW HA in depths of the skin over a longer time course.⁵

Using the skin hydration sensor (Wearifi Technology) aided not only in assessment of long-term hydration but also in immediate effect of the product and in assessment of comparisons of that immediate effect after cumulative hydration over weeks. Thus, over time, when measured 15 min post cleansing facial skin, there was an increase in the hydration measurements compared to baseline with a statistically significant increase in

FIGURE 15 H&E stain – pre (left) and post 8 weeks of application (right) – 6 participant biopsies demonstrating solar elastosis reversal. (A) Male age 33. (B) Female age 55. (C) Male age 48. (D) Female age 59. (E) Female age 53. (F) Female age 56.



hydration at 4 and 8 weeks compared to baseline. This would indicate that at a molecular level in the depths of the dermis, changes were taking place that increased the hydration of the skin, very likely related to the stimulation of HA. This was confirmed by biopsy specimens that demonstrated that after the 2-week period CD44 (surface marker reference to HA stimulation) levels were stimulated indicating HA production stimulation. Thus, at deeper levels, after 2 weeks, the effect of the topical formulation was evident on analytical measurement,

histological observation, patient satisfaction parameters, and investigator observation.

From an immediate hydration perspective, at every visit, hydration measurements were statistically significant higher compared to clean skin. At weeks 4 and 8, post application measurements were also significantly higher than post application measurements at baseline and week 2, showing a progressive improvement in depth stimulation of HA started to contribute toward immediate hydration results. An unanticipated finding also

became evident within the trial, as investigators began to observe clearing of redness and reactivity of the skin. This was very evident from clinical photographs but was validated when observing the 'red area' visual improvements (VISIA® Skin Analysis System, Canfield Scientific, Inc.). One would hypothesize that this is a reflection of the anti-inflammatory milieu created by the summation of superficial and deep high MW HA. In addition, one center reported that many of their patients who struggled with redness, especially as the weather changed, reported less or no instances of eruptive pustular rosacea that they normally experienced seasonally. Of course, we cannot rule out the possibility of the decreased redness being the adoption of a new calming skin routine and the cessation of a previously undisclosed inflammatory provoking regimen. However, patients were carefully selected following a 'wash-out' period and individual histories did not reveal any such products, making this possibility unlikely.

5 | CONCLUSION

This multicenter trial was conducted to investigate the effect on the skin of a formulation designed to utilize high MW HA on the surface of the skin and to stimulate fibroblast production of high MW HA in the depths of the skin. Trial results demonstrated that the formulation produced significant improvements in immediate and long-term hydration effects on the skin. This was validated using the skin hydration sensor, 'wearifi' technology, providing instant objective evidence, as well as using biopsies and patient and investigator assessments. An overall increase in radiance, decreased redness and improvement in skin hydration, both immediately (15 min) after application and in the long term over an 8-week period, was demonstrated. It appears to be the strategy of applying and producing high MW HA to various skin layers manifests as excellent clinical improvements in skin health and hydration.

AUTHOR CONTRIBUTIONS

D.M.R., J.V., M.D.P., and A.G. performed the research and assisted with editorial content. M.B. and A.D.W. designed the study and wrote the paper. All authors have read and approved the final manuscript.

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FUNDING INFORMATION

Alastin Skincare, Inc., provided funding for the study.

CONFLICT OF INTEREST

Drs. Robinson, Vega, and Palm are consultants for Alastin Skincare, Inc. Ms. Bell is the Director of Clinical Research at Alastin Skincare, Inc., and Dr. Widgerow is the Chief Scientific Officer, Galderma.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

This study was approved by the Advarra Institutional Review Board and followed the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects.

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