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# Evaluation of the efficacy and safety of hyaluronic acid and supplemented with amino acids, and glutathione or colin, for the prevention and treatment of wrinkles on the face, neck, décolleté and hands

F. SVOLACCHIA[1], L. SVOLACCHIA[2], M. MARCHETTI[3], C. PRISCO[4], F. INCHINGOLO[5], D. AMUSO[6], F. GIUZIO[7], A. SCARANO[6]

[1]Department of Anatomical, Histological, Medical and Legal Sciences and the Locomotor Equipment, Section of Human Anatomy, Laboratory of Experimental Morphology, [2]Faculty of Medicine and Surgery, University of Rome "La Sapienza", Rome, Italy
[3]School of Applied Medical-Surgical Sciences, University of Tor Vergata, Rome, Italy
[4]Department of Experimental Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy
[5]Department of Interdisciplinary Medicine, University of Bari "Aldo Moro", Bari, Italy
[6]Department of Innovative Technologies in Medicine and Dentistry, University of Chieti-Pescara, Chieti-Pescara, Italy
[7]Department of Science, University of Basilicata, Potenza, Italy

**Abstract. – OBJECTIVE: Hyaluronic acid has been used for a long time as a biorevitalizer to treat skin aging both in single formulation and in association with other compounds such as amino acids or vitamins. The purpose of this study was to evaluate the efficacy and safety of class III medical devices SKIN B, SKIN R, SKIN OX, SKIN COLIN, for the treatment of wrinkles on the face, neck, décolleté and hands. These medical devices are all based on hyaluronic acid and supplemented with amino acids (SKIN B and SKIN R) and glutathione (SKIN OX) or colin (SKIN COLIN). This gives broader possibilities to the aesthetic surgeon for personalization and pharmacological diversification based on the patient's deficits to treat.**

**PATIENTS AND METHODS: A total of 60 subjects affected by skin damage such as rhytidids, dehydration, reduced sebum production and skin hypoxia were enrolled. The patients were treated with a session of mesotherapy every 7 days for 30 days, followed by other 2 sessions every 15 days for 30 days and the follow-up on day 90. The primary efficacy endpoint was evaluated by means of a 0-10 visual analog scale at day 60; the secondary efficacy endpoint was evaluated by means of a 0-10 visual analog scale at day 90.**

**RESULTS: All patients completed the 3-month follow-up. Treatment with SKIN B, SKIN OX, SKIN COLIN and SKIN R medical devices for the prevention and treatment of wrinkles on the face, neck, décolleté and hands were associated with favorable and positive results. A clear reduction of wrinkles has been clinically observed with improvement in the texture, brightness, and turgor of the skin. No adverse events were reported.**

**CONCLUSIONS: The medical devices SKIN B, SKIN SKIN OX, SKIN COLIN produce an aesthetic improvement in patients affected by skin defects, when administered by mesotherapy technique. This study confirms the safety and efficacy of the medical devices based on hyaluronic acid supplemented with amino acids and glutathione or colin.**

*Key Words:*
Biostimulation, Hyaluronic acid, Neo-collagenogenesis, Amino acids, Colin, Glutathione.

## Introduction

An increasing number of women and men who are interested in skin rejuvenation have created a great demand for so-called anti-aging remedies to counteract photo and chrono-aging, as well as an improvement in interpersonal relationships which is combined with the extension of life expectancy and a significant increase in attention to one's appearance[1]. Environmental factors influence the skin damage associated with chronological age by increasing dehydration, causing wrinkles, skin relaxation and irregular skin pigmentation[2]. In

*Corresponding Author:* Antonio Scarano, MD; e-mail: ascarano@unich.it

particular, the reactive oxygen species determine the involution of the fibroblasts that have a limited possibility for cell division as explained by the Hayflick limit. In this case, the fibroblasts are not able to synthesize elastin and glycosaminoglycans, which are fundamental for skin physiology, causing connective tissue degeneration[2,3]. In addition, the reactive oxygen species induce a deletion in fibroblasts and an increase in the metalloprotein-1. The induction of metalloproteinases in the matrix plays an important role in the pathogenesis of photo-aging[4-6]. For these reasons, the skin, during the chrono and photo aging, shows a series of thin superficial lines of the face that lead to the formation of deep folds on the forehead and between the eyebrows, in the periorbital area, and in the nasolabial folds. The simplest procedures of contrast to chrono and photo aging involve the use of hyaluronic acid in variable concentrations in order to have a rapid dermo-epidermal remodeling and to improve the survival of fibroblasts through a suitable crosstalk with growth factors[7-11]. The more complex procedures involve the association of multiple active ingredients, such as amino acids and vitamins, with various concentrations in order to activate also cell metabolism and membranes' protection[12,13]. Hyaluronic acid (HA) is a natural linear polysaccharide widely used in the biomedical field as a biocompatible, biodegradable, non-toxic and non-immunogenic polymer with high water affinity[14-16]. HA is an important component of the extracellular matrix and helps to give elasticity to the skin. It plays a pivotal role in wound healing and tissue repair processes due to its ability to maintain a moist environment conducive to healing and stimulation of growth factors, cell constituents, and the migration of various cells essential for tissue healing[17,18]. The degradation of the injected hyaluronic acid seems to induce a production of elastin and a neocollagenogenesis as a response of the fibroblasts on the matrix[19]. Efficacy and safety of hyaluronic acids have been widely demonstrated[20]. High molecular weight HA (HMWHA) is deposited in normal tissues during homeostasis and promotes their stability while low molecular weight HA (LMWHA) fragments can result from enzymatic activity. The degradation of HMWHA fragments into LMWHA often leads to the generation of biologically active oligosaccharides with different properties[21]. The native high molecular weight HA has structural properties while the degradation products of HA (oligomers) stimulate the proliferation and migration of endothelial cells. HA oligomers modulate inflammatory processes and promote neo-angiogenesis during the different stages of wound healing. HA mediates its biological effects through binding interactions with specific cell-associated receptors (CD44 and RHAMM)[22] and promoting the biosynthesis of growth factors such as FGF2 and KGF (keratinocyte growth factor)[23] and the benefit on pathological events from photo and chrono aging have been demonstrated[24]. The purpose of this study was to evaluate the efficacy and safety of hyaluronic acid and supplemented with amino acids, glutathione or colin. This gives broader possibilities to the aesthetic surgeon for personalization and pharmacological diversification based on the patient's deficits to treat.

## Patients and Methods

The present study was approved by FMD University of Tirana, Albania and it was conducted in accordance with the principles and guidelines of the Declaration of Helsinki. The informed consent was obtained from all participants included in the study. This clinical study was conducted to test the safety and efficacy of the product in treatments of skin aging and to reduce the general appearance of fine and deep wrinkles. Prior to the study, each subject was informed about the purpose of the study and their written informed consent was obtained according to the ethics of medical device testing. No drugs or cosmetic procedures that might affect the course of the anti-aging treatment were allowed two weeks before to start and during the study.

The exclusion criteria from the clinical trial were dietary changes, pregnancy, and heavy smoker (20 cigarettes per day) contact history of allergic and/or irritating hand dermatitis, systemic illness and psychiatric illness. The main inclusion criterion was the presence of one or more signs of chrono or photo-aging affecting the face, such as fine wrinkles around the eyes, crease lines around the mouth and cheeks, wrinkles and spots on the face, back of hands, etc., corresponding to grades 3-5 on the photo digital scale described by Larnier et al[25]. The treatment for the study was carried out free of charge and the sensitive and privacy data were kept exclusively for the duration of the study and then destroyed, keeping only one case series. Patients were selected and invited to pre-arranged appointments. The class III medical devices used for the clinical-observational study were:

- SKIN B, in 5 ml bottles containing hyaluronic acid sodium salt, L-isoleucine, L-leucine, L-lysine hydrochloride, L-proline, L- valine, glycine, L-serine, L-alanine, L-cysteine, phosphate buffer system, ppi water formulated for the prevention and treatment of facial skin damage, and it was used in the following points: glabella, cheekbones, nasogenic fold, lower corner of the mouth, submental area.
- SKIN OX, in 5 ml vials and bottles containing Hyaluronic acid sodium salt, L-serine, L-alanine, L-cysteine, L-leucine, L-lysine, hydrochloride, L-proline, L-valine, glycine, glutathione reduced, sodium ascorbyl phosphate, phosphate buffer system, ppi water, and it was used in this study in the prevention and treatment of skin damage from free radicals on the face, neck, décolleté and hands.
- SKIN COLIN, in 5 ml vials and bottles containing Hyaluronic acid sodium salt, Choline bitartrate, Glycine, L-serine, L-alanine, L-proline, L-lysine hydrochloride, L-cysteine, sodium chloride, phosphate buffer system, ppi water and it has been used for the prevention and treatment of skin and epidermal damage on the face, neck, décolleté and hands.
- SKIN R, in 10 ml ampoules and in 9 ml bottles, contains hyaluronic acid, glycine, L-proline, L-Lysine hydrochloride, phosphate buffers, water for injection and was used in this study for the treatment of skin damage of the neck, décolleté or other hypotonic areas.

The sterile medical devices are supplied by Italfarmacia srl (Rome, Italy) and the lots examined in the study were for SKIN B 1923 expiring on September 2022 and bottles 2033 expiring on June 2023, for SKIN R 1924 expiring on September 2022 and bottles 2034 expiring on June 2023, for SKIN C 1925 expiring on September 2022 and 2035 bottles expiring om June 2023 and for SKIN OX 1926 expiring on September 2022 and 2036 bottles expiring on June 2023.

The contents of the vials were injected directly into the different skin areas of the patients undergoing the clinical-observational study. The technique used was based on a session of mesotherapy administration to micropomphs every 7 days for 30 days, followed by other 2 injections every 15 days for 30 days for a total personalized treatment of 60 days with a final check on day 90 (regression period). The medical treatment used was based on the mesotherapy technique, using a vial per session divided by the areas to be treated with a 5 ml syringe solution and a 30 g by 6 mm needle positioned at 45° with respect to the skin surface. The needle was inserted all the way to the middle dermis, aspiration was performed to make sure the tip was not inside a blood vessel, and the injection was then started slowly when the needle was withdrawn. The injection rate was always less than 0.3 ml/min. The firm massage, with the index finger inside the mouth and the thumb outside, was then used to remove any rare irregularities.

### Statistical Analysis

The data analysis has been performed through the statistical software package Graphpad (Prism 8, San Diego, CA, USA). The descriptive statistics have been conducted indicating the means and standard deviations. The groups comparison has been considered for $p$-value $<0.05$ applying the One-way ANOVA followed by the Tukey's post-hoc test.

## Results

The purpose of the study was to evaluate the efficacy and safety of SKIN B, SKIN R, SKIN OX, SKIN COLIN, class III medical devices based on hyaluronic acid and colin or glutathione, for prevention and the treatment of wrinkles on the face, neck, décolleté, and hands. Seventy subjects were screened and included in the study; only 60 subjects completed the study. All 60 subjects were treated at least once with the investigational device (15 with SKIN B; 15 with SKIN R; 15 with SKIN OX; 15 with SKIN Colin) and included in the safety analysis set and per-protocol (PP) analysis set. All 60 subjects enrolled were female. The median age at study entry was 49.45 years (range, 35-64 years). The Body Mass Index (BMI) median range was 25.30 (range, 21.76-30.00). Demography details are analyzed in Table I.

**Table I.** Subject demography (N = 60).

| | | |
|---|---|---|
| Male | N (%) | 0 (0) |
| Female | N (%) | 60 (100) |
| Age (years) | Median | 48.0 |
| | Range | 35-64 |
| BMI | Mean | 25.3 |
| | STD | 2.34 |

N = number of subjects, STD = standard deviation.

### Efficacy

Follow-up visits and evaluations were performed on the first day (D1, baseline) and after 60 (D60) days of treatment, with a follow-up visit to D90 (period regression). Individual signs of chrono and photo-aging symptoms, skin irritation and the degree of correction obtained for each treatment and each area were objectively assessed using a 0-10 visual analog scale with separate scores for each facial site (0 = no correction; 5 = satisfactory correction; 10 = total correction). Data obtained were analyzed in two different ways: cumulative analysis and specific independent analysis. The 0-10 clinical scale in the cumulative analysis had significantly improved at Day 60 compared with Baseline in all three parameters: for "thin lines" -3.25 (*p*-value <0.0001, -CI 3.476 to -3.024), indicating a general reduction in thin lines (Figure 1); for "wrinkles" -1.38 (*p*-value <0.0001, -CI 1.582 to -1.185), indicating a general reduction in wrinkles (Figure 1). For "pigmentation" -2.9 (*p*-value <0.0001, -CI 3.178 to -2.622), indicating a general improvement in pigmentation (Figure 1). The 0-10 clinical scale in the cumulative analysis had significantly improved at Day 90 compared with the Baseline in all three parameters. For "thin lines" -4.25 (*p*-value <0.0001, -CI 4.476 to -4.024), indicating a general reduction in thin lines (Figure 1). For "wrinkles" -2.383 (*p*-value <0.0001, -CI 2.582 to -2.185), indicating a general reduction in wrinkles (Figure 1). For "pigmentation" -3.433 (*p*-value <0.0001, -CI 3.657 to -3.209), indicating a general improvement in pigmentation (Figure 1).

### Specific Independent Analysis on Each MD

All patients completed the 3-month follow-up. Treatment with the medical device "SKIN B, SKIN OX, SKIN COLIN, and SKIN R for the prevention and treatment of wrinkles on the face, neck, décolleté and hands have been associated with favorable clinical results as indicated by an evident reduction of wrinkles. The texture, brightness, and turgor of the skin are improved. As mentioned above, the results obtained from the 3 months of follow-up were also analyzed on the efficacy of each MD. Figure 2 shows the results relative to the absolute change of 0-10 clinical scale at Day 60 and Day 90 for Skin B, Skin R, Skin Colin, and Skin Ox. For Skin B the 0-10 clinical scale in the cumulative analysis had significantly improved at Day 60 compared with the Baseline in all three parameters "thin lines" -4.2 (*p*-value <0.0001, -CI 4.723 to -3.677), indicating a general reduction in thin lines (Figure 2); "wrinkles" -2.333 (*p*-value <0.0001, -CI -2.75 to -1.916), indicating a general reduction in wrinkles (Figure 2) and "pigmentation" -3.4 (*p*-value <0.0001, -CI -3.96 to -2.84), indicating a general improvement in pigmentation (Figure 2). As well as the secondary efficacy endpoints showed significant improvements at Day 90 compared with the Baseline in all three parameters: "thin lines" -3.133 (*p*-value <0.0001, -CI -3.636 to -2.631), indicating a general reduction in thin lines (Figure 2); "wrinkles" -1.4 (*p*-value <0.0001, -CI -1.898 to -0.9021), indicating a general reduction in wrinkles (Figure 2) and "pigmentation" -3.0 (*p*-value <0.0001, -CI -3.676

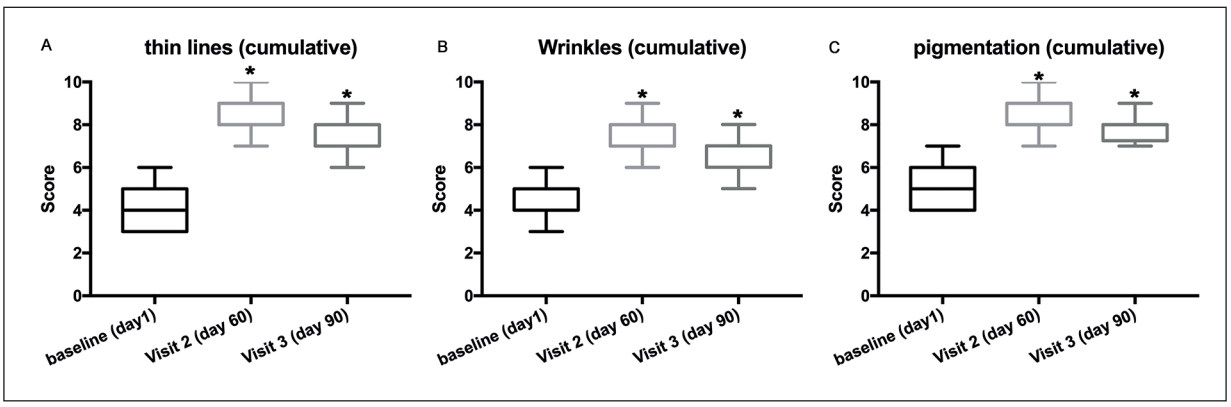


**Figure 1.** Cumulative analysis of 0-10 visual analog scale. The 0-10 clinical scale in the cumulative analysis (Skin B; Skin R; Skin Colin; Skin Ox) had significantly improved at Day 60 (primary efficacy endpoint) and day 90 (secondary efficacy endpoint) compared with Baseline in all three parameters: "thin lines", "wrinkles" and "pigmentation" (**p*-value <0,0001). **A**, thin lines scoring at baseline, after 60 days and 90 days; (**B**), wrinkles scoring at baseline, after 60 days and 90 days; (**C**), pigmentation scoring at baseline, after 60 days and 90 days.

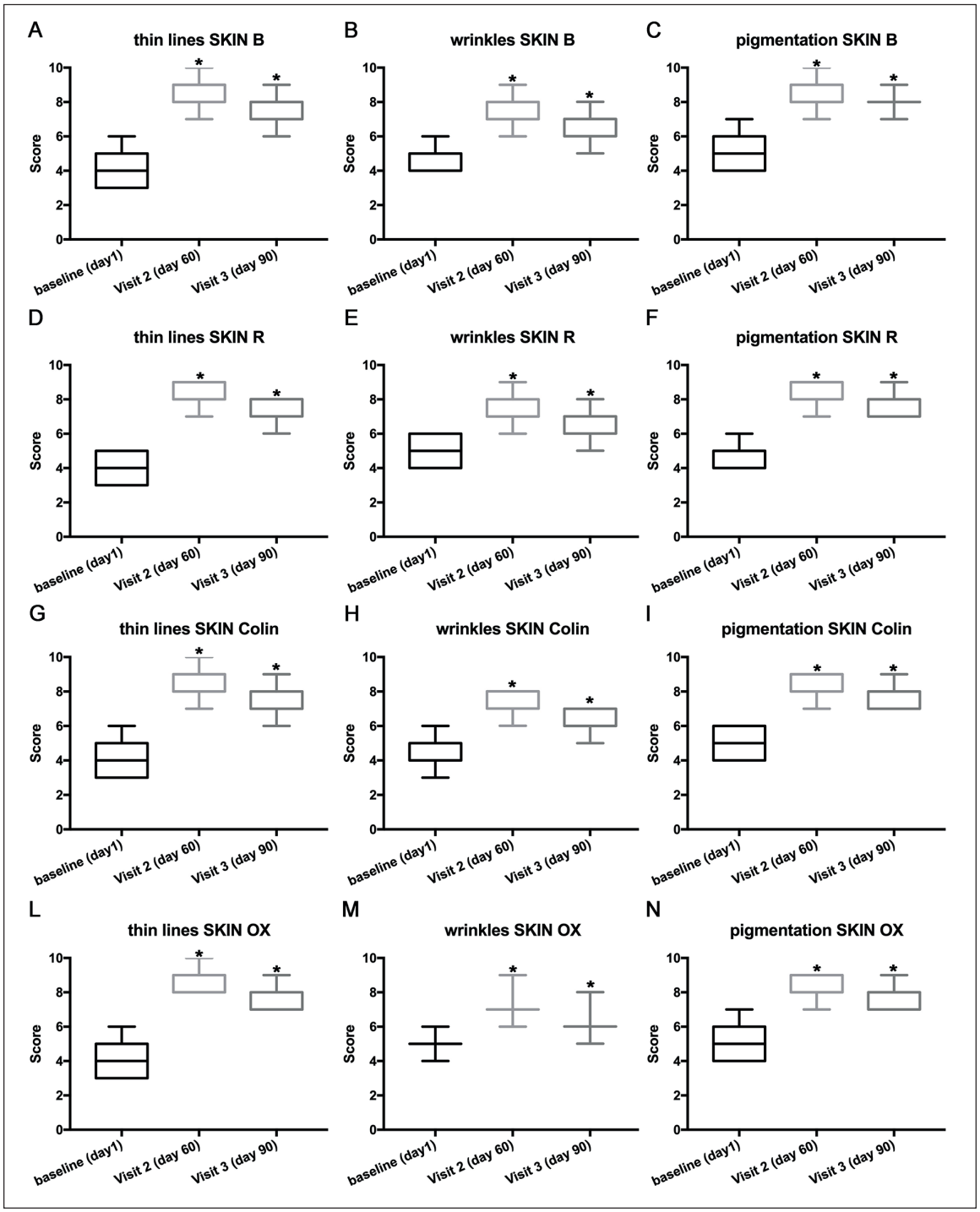


***Figure 2.*** Specific independent analysis on each MD. The 0-10 clinical scale in the single analysis of Skin B; Skin R; Skin Colin; Skin Ox, had significantly improved at Day 60 (primary efficacy endpoint) and day 90 (secondary efficacy endpoint) compared with Baseline in all three parameters: "thin lines", "wrinkles" and "pigmentation" (**p*-value <0,0001), for each medical device. **A**, thin lines scoring at baseline, after 60 days and 90 days- SKIN B; (**B**), wrinkles scoring at baseline, after 60 days and 90 days-SKIN B; (**C**), pigmentation scoring at baseline, after 60 days and 90 days-SKIN B; (**D**), thin lines scoring at baseline, after 60 days and 90 days- SKIN R; (**E**), wrinkles scoring at baseline, after 60 days and 90 days-SKIN R; (**F**), pigmentation scoring at baseline, after 60 days and 90 days-SKIN R; (**G**), thin lines scoring at baseline, after 60 days and 90 days- SKIN Colin; (**H**), wrinkles scoring at baseline, after 60 days and 90 days-SKIN Colin; (**I**), pigmentation scoring at baseline, after 60 days and 90 days-SKIN Colin; (**L**), thin lines scoring at baseline, after 60 days and 90 days- SKIN Ox; (**M**), wrinkles scoring at baseline, after 60 days and 90 days-SKIN Ox; (**N**), pigmentation scoring at baseline, after 60 days and 90 days-SKIN Ox.

to -2.324), indicating a general improvement in pigmentation (Figure 2). Primary and secondary efficacy endpoints of Skin R had significantly improved at Day 60 and 90 respectively, compared with the Baseline in all three parameters: "thin lines" -4.133 ($p$-value <0.0001, -CI -4.636 to -3.631), indicating a general reduction in thin lines (Figure 2); "wrinkles" -2.467 ($p$-value <0.0001, -CI -2.816 to -2.118), indicating a general reduction in wrinkles (Figure 2); for "pigmentation" -3.533 ($p$-value <0.0001, -CI -3.966 to -3.101), indicating a general improvement in pigmentation (Figure 2) at day 60. For "thin lines" -3.267 ($p$-value <0.0001, -CI -3.806 to -2.727), indicating a general reduction in thin lines (Figure 3); For "wrinkles" -1.467 ($p$-value <0.0001, -CI -1.816 to -1.118), indicating a general reduction in wrinkles (Figure 3); for "pigmentation" -2.867 ($p$-value <0.0001, -CI -3.299 to -2.434), indicating a general improvement in pigmentation (Figure 3) at Day 90. The 0-10 clinical scale in the cumulative analysis of Skin Colin_also showed a significant increase in all three parameters at Day 60 compared with the Baseline: lines (Figure 2); "wrinkles" -2.533 ($p$-value <0.0001, -CI -2.966 to -2.101), indicating a general reduction in wrinkles (Figure 2); "pigmentation" -3.467 ($p$-value <0.0001, -CI -3.899 to -3.034), indicating a general improvement in pigmentation (Figure 2). As well at day 90: "thin lines" -3.2 ($p$-value <0.0001, -CI -3.579 to -2.821), indicating a general reduction in thin lines (Figure 2); "wrinkles" -1.533 ($p$-value <0.0001, -CI -1.966 to -1.101), indicating a general reduction in wrinkles (Figure 2); F "pigmentation" -2.933 ($p$-value <0.0001, -CI -3.583 to -2.284), indicating a general improvement in pigmentation (Figure 2). In Skin Ox the 0-10 clinical scale in the cumulative analysis had significantly improved at Day 60 compared with the Baseline in all three parameters: "thin lines" -4.333 ($p$-value <0.0001, -CI -4.885 to -3.782), indicating a general reduction in thin lines (Figure 2); "wrinkles" -2.133 ($p$-value <0.0001, -CI -2.566 to -1.701), indicating a general reduction in wrinkles (Figure 2); "pigmentation" -3.333 ($p$-value <0.0001, -CI -3.885 to -2.782), indicating a general improvement in pigmentation (Figure 2). Also, the Secondary efficacy endpoints at Day 90 were satisfied with the 0-10 clinical scale in the cumulative analysis, and it had significantly improved at Day 90 compared with the Baseline in all three parameters: "thin lines" -3.67 ($p$-value <0.0001, -CI -3.64 to -2.669), indicating a general reduction in thin lines (Figure 2); "wrinkles" -1.133 ($p$-value <0.0001, -CI -1.566 to -0.7009), indicating a general reduction in wrinkles (Figure 2); "pigmentation" -2.8 ($p$-value <0.0001, -CI -3.485 to -2.115), indicating a general improvement in pigmentation (Figure 2).

### *Subject Satisfaction*

After the first and second months of treatment, with a third month follow-up (regression period), to assess subject's satisfaction about all medical devices Skin B, Skin R, Skin Colin, and Skin Ox subjects were asked to indicate their level of satisfaction on 0-4 points scales as follows: (4) Very much improved; (3) Much improved; (2) Slightly improved; (1) No change. The degree of satisfaction with the efficacy of the product was also obtained subjectively by asking patients if there was any itching, burning or stinging sen-

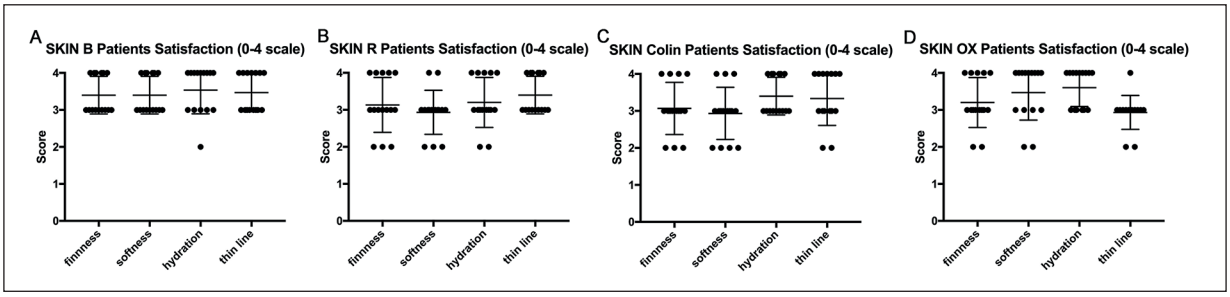


**Figure 3.** Subject satisfaction. Patients level of satisfaction on 0-4 points scales as follows: (4) Very much improved; (3) Much improved; (2) Slightly improved; (1) No change. The analysis was made for single medical device. By termination of the study on Day 90, most of the subjects still considered their appearance very much improved or much improved. **A**, Patients satisfaction scoring of treatment group with SKIN B; (**B**), Patients satisfaction scoring of treatment group with SKIN R; (**C**), Patients satisfaction scoring of treatment group with SKIN Colin; (**D**), Patients satisfaction scoring of treatment group with SKIN Ox.

**Table II.** Adverse events by system organ class and preferred term (N = 60).

| | All, N = 60 | | |
|---|---|---|---|
| | n | N′ | (%) |
| Total | 7 | 7 | (11.0) |
| General dis. and ad. site cond. | 7 | 7 | (11.0) |
| Injection site hematoma | 3 | 3 | (5.0) |
| Injection site redness | 4 | 4 | (6.0) |

n = number of events, N = number of subjects in data set, N' = number of subjects with events, SAF = safety data set.

sation. The results obtained are shown in Figure 3. The majority of subjects rated the appearance and the treatment positive and would recommend it to others. The subjects' judgment of appearance after treatment changed with time, however, by termination of the study on Day 90, most of the subjects still considered their appearance very much improved or much improved.

## Results

### *Safety*

All 60 enrolled subjects received the treatment with an investigational device for 60 days (4 injections, once a week for 4 weeks + 2 injection and one every other week for 4 weeks). The mean injected volume for each treatment was 1.2 mL for each patient. Adverse events, adverse device effects, and device deficiencies were recorded: a total of 8 subjects (32.0%) reported 14 AEs. 11 AEs reported by 8 subjects had a possible, definite, or unknown relationship to the investigational device and were classified as adverse device effects (ADEs). An overview of AEs by system organ class is provided in Table II. 'General disorders and administration site disorders' were the most frequently reported AEs. Injection site hematoma, injection site pain, and injection site swelling (reported by four, two, and two subjects, respectively) were the only AEs reported by more than one subject. The intensity of AEs is summarized in Table III. The majority of AEs were mild, and two AEs were moderate. 7 AEs were judged "possibly related" to the investigational device by the investigator and were classified as ADEs. All 7 ADEs were also judged related to the procedure ('possibly related') by the investigator. The AEs related to the procedure included injection site hematoma, and injection site redness. The majority of AEs had resolved by study completion. Six (6) ADEs were judged by the investigator as mild in severity, and one (1) were moderate in severity. All subjects who experienced an ADE had recovered by the end of the study. No device deficiencies were recorded. No deaths occurred during this investigation. This clinical observation is equivalent to a biological improvement of the tissue that becomes healthier and aesthetically more beautiful. In this clinical-observational study the objective was achieved and in particular that of demonstrating that the administration of medical devices containing hyaluronic acid and amino acids and/or vitamins through the mesotherapy administration technique produces a biological and aesthetic improvement of the patients treated and is effective in this type of treatment.

## Discussion

In the present clinical investigation, the safety and efficacy of SKIN B, SKIN R, SKIN Colin, and SKIN OX was evaluated in the treatment of

**Table III.** AEs severity.

| Grade | Number (%) of events |
|---|---|
| Number of events | 7 |
| Mild - intervention not indicated | 6 (85.7) |
| Moderate - minimal, local or noninvasive intervention indicated | 1 (14.3) |
| Severe but not immediately life-threatening | 0 (0.0) |

Percentages are based on the total number of events. N = number of subjects.

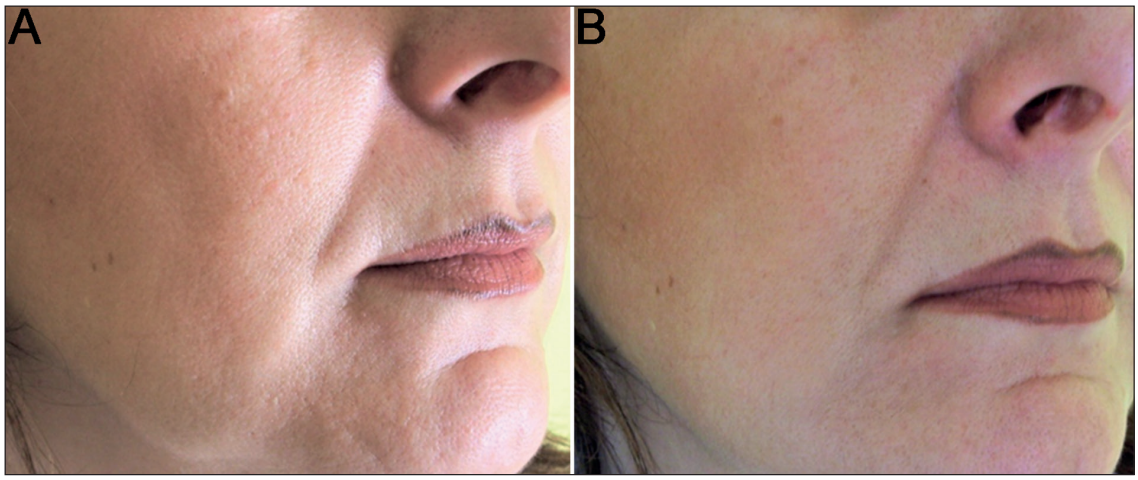


**Figure 4.** Clinical evaluation of a patient's response to mesotherapy with the treatment of facial rejuvenation. Baseline T0 (**A**), after treatment (period of regression) (**B**).

skin damages (Photoaging, dehydration etc.). The results obtained were in line with our expectations on *in vivo* evaluations for treatment efficacy as shown in Figure 4, in which it is possible to appreciate a reduction in imperfections and an evident increase in the volumes of the perioral soft tissues. The analysis of the primary efficacy endpoint, the absolute change in a 0-10 clinical evaluation scale from Day 0 to Day 90 showed a significant improvement of the clinical scores, consistent with a general reduction in thin line, wrinkle, and pigmentation. At the last visit (Day 90), the majority of subjects had improved the clinical scores by at least 1.0 grade in all three parameters analyzed. The analysis of the secondary efficacy endpoints, the absolute change in a 0-10 clinical evaluation scale from Day 0 to Day 90 showed a significant improvement of the clinical scores, consistent with a general reduction in thin line, wrinkle, and pigmentation already at 90 days of treatment. The efficacy of the investigational devices was further reflected in the positive rating by subjects (subject satisfaction; 0-4 scale). In fact, all subjects treated during the clinical observation period reported being satisfied with the general appearance of their skin, which appeared softer and more hydrated from the first month of treatment. In line with their self-assessment, the appearance of fine wrinkles was significantly reduced, and the resulting softness and firmness of the skin increased during the entire treatment period. Interestingly, this overall improvement remained throughout the regression period as well, 30 days after stopping treatment. Treatment with all the investigational devices was generally safe. Adverse events included injection site redness, which were anticipated short-term ADEs that were described in previous studies with related products and are common ADEs for mesotherapy. The most common ADE in this investigation was injection site hematoma. However, injection of any dermal filler can be associated with hematoma formation amongst other injection site reactions such as burning, itching, or pain (secondary to stretching of cutaneous nerves), erythema, edema, or bruising, even with excellent injection technique. Hematoma is generally rather uncommon but could result from the inadvertent laceration of small facial blood vessels. In the present investigation, all hematomas were mild or moderate temporary effects, hence, all the investigational devices can be considered as well-tolerated. Based on safety and efficacy data presented, SKIN B, SKIN R, SKIN Colin, and SKIN OX are likely to be valuable tools for the treatment of skin damages and an asset to counter the effects of aging. The *in vivo* results confirm the biological-scientific basis of the activity of hyaluronic acid used with signaling molecules contained in the formulations examined and it is a useful anti-aging remedy for the possibilities of aesthetic medicine.

## Conclusions

In conclusion, these bio-revitalizing / bio-stimulating class III medical devices can be used for the treatment of wrinkles of the face, periocular, neck of the hands and as an adjuvant in the increase of soft tissues.

### Conflict of Interest
The Authors declare that they have no conflict of interests.

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### Availability of Data and Materials
All data generated or analyzed during this study are included in this published article.

### Authors' Contribution
All authors were involved with the literature review and performance of the surgery. All authors read and approved the final manuscrip.

### Ethics Approval
The present study has been approved by FMD University of Tirana, Albania and it was conducted in accordance with the principles and guidelines of the Declaration of Helsinki and the additional requirements of Italian law.

### Informed Consent
Written informed consent was obtained from the patients for publication and accompanying images.

### ORCID ID
Fabiano Svolacchia: 0000-0002-0522-7584; Marco Marchetti: 0000-0002-6513-462X; Francesco Inchingol: 0000-0003-3797-5883; Domenico Amuso: 0000-0002-1841-5277; Antonio Scarano: 0000-0003-1374-6146.

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