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# A hyaluronic acid-based micro-filler improves superficial wrinkles and skin quality: a randomized prospective controlled multicenter study

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**ABSTRACT**

**Background:** NCTF®135HA is a bio-revitalizing solution containing hyaluronic acid designed to compensate for skin dehydration, fatigue, and fine wrinkles associated with endogenous and environmental aging.

**Methods:** We conducted a randomized, active-controlled study to evaluate the efficacy and tolerability of NCTF®135HA injections on the face (crow's feet), neck, and décolleté regions. Subjects were randomly assigned (3:1) to receive three NCTF®135HA treatment sessions plus twice-daily anti-aging moisturizer cream or cream alone (control). The primary outcome was the reduction in superficial wrinkles between baseline and Day (D)75 in the three areas, assessed by profilometric measures, clinical scoring, subjective changes, and tolerability.

**Results:** 146 subjects were randomized to NCTF®135HA ($n = 107$) or control ($n = 38$). At D75 and D120, NCTF®135HA significantly reduced wrinkles in all three areas and improved facial radiance scores compared with the control. Skin hydration significantly increased 7 d after the last NCTF®135HA injection. Self-esteem scales showed statistically significant improvements at D75 and D120 in subjects treated with NCTF®135HA versus baseline. Most adverse events were mild, resolved within 48 h, and were related to the injection procedure.

**Conclusion:** NCTF®135HA is an effective and well-tolerated treatment to reduce the skin signs of aging. The results are significantly superior to a routine anti-aging cream alone.

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Skin rejuvenation; filler; non-crosslinked hyaluronic acid; biorevitalization; mesotherapy; neck rejuvenation; décolleté rejuvenation

## Introduction

Skin aging arises from the combination of numerous endogenous biological changes, which are mainly genetically determined, and extrinsic aging caused by environmental factors including ultraviolet radiation and pollution (1,2). The cumulative effects of these age-related changes can lead to significant alterations in facial appearance, due to loss of volume and segmentation of the facial compartments, as well as dermatological changes including loss of skin elasticity, increased skin roughness, and xerosis (3–5). Together, these changes can impact a person's self-esteem, confidence, and body image (3).

The processes involved in skin aging are diverse and include a range of physiological, structural, and biochemical changes (6). Injectable hyaluronic acid (HA) fillers are a popular approach used to restore facial volume, improving the appearance of sagging skin and skin folds (3). However, new therapies are increasingly taking a multi-targeted approach, with novel formulations that are designed to compensate for other negative effects of skin aging, such as dehydration and fine wrinkles, and to counter oxidative stress, in addition to volume loss (6–11). In addition to HA, these formulations can contain vitamins, minerals, nucleic acids, amino acids, and coenzymes and antioxidants which support adequate fibroblast functioning and corneocyte hydration to reduce skin aging (6–12).

The aim of this study was to assess the efficacy and tolerability of a novel bio-revitalizing solution containing hyaluronic acid, NCTF®135HA, with a new protocol of 3 injection sessions in comparison to an anti-aging hydrating cream with proven anti-aging effects. Previous *in vivo* and *in vitro* studies have shown that NCTF®135HA is effective and well tolerated when administered over 5 sessions spaced over 2–4 weeks, but these studies were not randomized controlled trials (6–11). This paper reports results from a randomized, active-controlled study that evaluated the efficacy and tolerability of NCTF®135HA, using a new protocol of 3 sessions for skin revitalization to improve superficial wrinkles and skin quality, compared with a control (an anti-aging hydrating cream alone. The primary outcome was the reduction in superficial

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wrinkles between baseline and Day 75 (D75, one month after the 3rd injection) on three areas: crow's feet wrinkles volume by profilometric measures (LifeViz Micro, Quantificare, France); neck wrinkles assessed using the Bazin Neck Scale (13); and décolleté wrinkles assessed using the Landau Decolleté score (14).

## Materials and methods

### Subjects

Eligible subjects were male or female, aged ≥19 years old, with a Fitzpatrick phototype of I, II, III or IV. Their photoaging grade was homogenous based on the Glogau photoaging grade of 2 or 3 (15). In addition, subjects' periorbital lines had to be level 2–4, assessed by the Lemperle scale (16), at baseline before enrollment. Subjects could also have neck wrinkles of 1–4 on the Bazin neck scale (13) or, in women only, décolleté wrinkles of at least grade 2 or 3 on the Landau décolleté scale (14).

The main non-inclusion criteria were: subjects who had received an injection or facial implantation of any non-absorbable filling agent at any time; or who had laser sessions for skin rejuvenation or a laser facelift in the previous year; or a surgical facelift in the 2 years before the study. Subjects who had received HA filler injections in the last year, botulinum toxin in the last 6 months, or injectable semi-permanent fillers in the last two years were excluded. Other non-inclusion criteria included: subjects with a skin support device (wire mesh, gold wire, liquid silicone, or other particulate material) at the study zones; subjects who underwent moderate to deep peeling or noninvasive rejuvenation techniques in the previous 6 months; those with a history of multiple severe allergies or anaphylactic shock or a known hypersensitivity to HA or another component of the NCTF® 135HA.

### Ethical approval

The study was conducted in accordance with the Helsinki declaration and obtained ethical committee authorization on 5th June 2019 (ID-RCB number: 2018-A03167-48; clinicaltrials.gov number: NCT05609617). The study was performed according to the NF EN ISO 14155 May 2012 (Clinical investigation of medical devices for human subjects – Good clinical practice). All subjects provided written informed consent.

### Treatments

New Cellular Treatment Factor (NCTF®) 135HA (Laboratoires FILLMED, France) is a viscoelastic injectable solution containing 5 mg/mL of non-crosslinked hyaluronic acid (HA) of non-animal origin in a formulation designed to compensate for the negative effects of skin aging and to counter oxidative stress (6–11). In addition to HA, NCTF®135HA contains vitamins, minerals, nucleic acids, amino acids and coenzymes and antioxidants (6–12). Subjects in the control group applied an anti-aging hydrating cream, HYDRA-FILLER® (Laboratoires FILORGA, France) with proven anti-aging effects, as an active control (17).

### Trial design

Subjects were recruited from 10 centers across Paris, France. Enrolled subjects were randomly assigned in a 3:1 ratio to receive NCTF®135HA plus an anti-aging hydrating cream, HYDRA-FILLER® (Laboratoires FILORGA, France) or the anti-aging cream alone as an active control (17). All subjects applied the anti-aging cream to thoroughly cleansed skin in the morning and evening from baseline to Day (D)120. Subjects randomized to NCTF®135HA injections received three treatments, at three-weekly intervals. After disinfection with chlorhexidine, physicians performed multiple intradermal injections of 0.05 ml NCTF®135HA using a 32 G × 4 mm needle spaced every 1–1.5 cm. Two vials, each containing 3 ml NCTF®135HA, were injected to treat the whole face. One 3 ml vial was used to treat the neck or décolleté. Local anesthesia was used at the investigator's discretion. Subjects received three injections spaced three weeks apart on D0 ± 3 d, D21 ± 3 d and D42 ± 3 d. They returned for three follow-up visits: 7 d after being injected (D49), 1 month after the last injection (D75) and 4 months after the beginning of the study (D120). Subjects in the active control croup were assessed at baseline and on D75 and D120.

### Objectives and assessments

The primary objective was to assess changes in superficial wrinkles between baseline and D75, comparing NCTF®135HA + anti-aging cream with anti-aging cream alone, based on three outcomes. Firstly, the mean volume of crow's feet wrinkles assessed using profilometric measures (18). Secondly, dermatologist-assessed neck wrinkles using the Bazin scale (13), and thirdly, wrinkles on the décolleté using the Landau scale (14) (Figure 1). The secondary objectives were to assess changes in a range of additional parameters and times, detailed below (Figure 1).

### Objective measures

Objective measures were taken at baseline, 7 d after the injection on D42 (D49; injection group only), and D75 ± 4 d and D120 ± 7 for both groups (Figure 2). As the results of the biorevitalizing solutions stabilize around one month after the last injection (10), the main comparative criteria is appointed to be measured at day 75. The mean volume and depth of crow's feet wrinkles were measured using 3D photographs taken with LifeViz 3D Micro (Quantificare Valbonne, France) on the side of the face which had the deepest wrinkle. At these times, the injecting physician assessed: cheek folds and crow's feet wrinkle scores using the Lemperle scale (14); skin radiance (face only) using a five-point scale from 0 (very dull skin) to 4 (very radiant skin); neck wrinkle scores using the Bazin photographic scale (11); and wrinkles on the décolleté using the Landau photographic scale (14). Skin hydration was measured on the cheek using the MoistureMeter® EpiD (Delfin Technologies, Kuopio, Finland) as well as, when treated, the neck, décolleté or both. Facial skin elasticity and firmness on the periorbital area and cheek was assessed using the Cutometer Dual MPA 580 (Courage and Khazaka, Köln, Germany) and density assessed on crow's feet and cheeks using High-Frequency (20 MHz) ultrasound imaging (Dermascan®, Cortex Technology, Hadsund, Denmark). The number and diameter of pores on the cheekbone was assessed with the ProScope® Micro Mobile (Lake Oswego, USA).

### Subjective assessments

The injecting physician (at D21 and D42) and an independent physician, who was unaware of randomization, (at D49, D75, and D120) assessed changes from baseline on the 7-level Global Esthetic Improvement Scale (investigator GAIS). Subjects

| *Assessment* | Baseline (& 1st treatment) | D21‡ (2nd treatment) | D42‡ (3rd treatment) | D49‡ | D75 | D120 |
|---|---|---|---|---|---|---|
| ***Primary assessments*** | | | | | | |
| *Profilometric imaging of CF wrinkles* | X | | | X | X | X |
| *Glogau aging scoring of cheek folds and CF* | X | | | X | X | X |
| *Lamperlé wrinkle scoring of cheek folds and CF* | X | | | X | X | X |
| *Bazin Wrinkle Scale on the neck* | X | | | X | X | X |
| *Landau Clinical scoring on Décolleté wrinkling* | X | | | X | X | X |
| ***Secondary assessments*** | | | | | | |
| *Standard 2D photograph* | X | | | X | X | X |
| *Skin radiance clinical scoring†* | X | | | X | X | X |
| *Skin hydration* | X | | | X | X | X |
| *Skin elasticity and firmness†* | X | | | X | X | X |
| *Pore size†* | X | | | X | X | X |
| *Skin density†* | X | | | X | X | X |
| *Pain questionnaire* | X | X | X | | | |
| *Investigator GAIS scoring* | | X* | X* | X** | X** | X** |
| *Subject GAIS scoring* | | | | X | X | X |
| *Rosenberg Self-Esteem Scale* | X | | | | X | X |
| *Subject Self-Assessment of injection‡* | | | | X | X | X |
| *Evaluation of side effects* | X | X | X | X | X | X |

*Assessed by injectors; **Assessed by independent evaluators; †Assessed on the face only; ‡Only for the injection group.
CF: Crow's feet; GAIS: Global Aesthetic Improvement Scale

**Figure 1.** Study treatments and assessments.

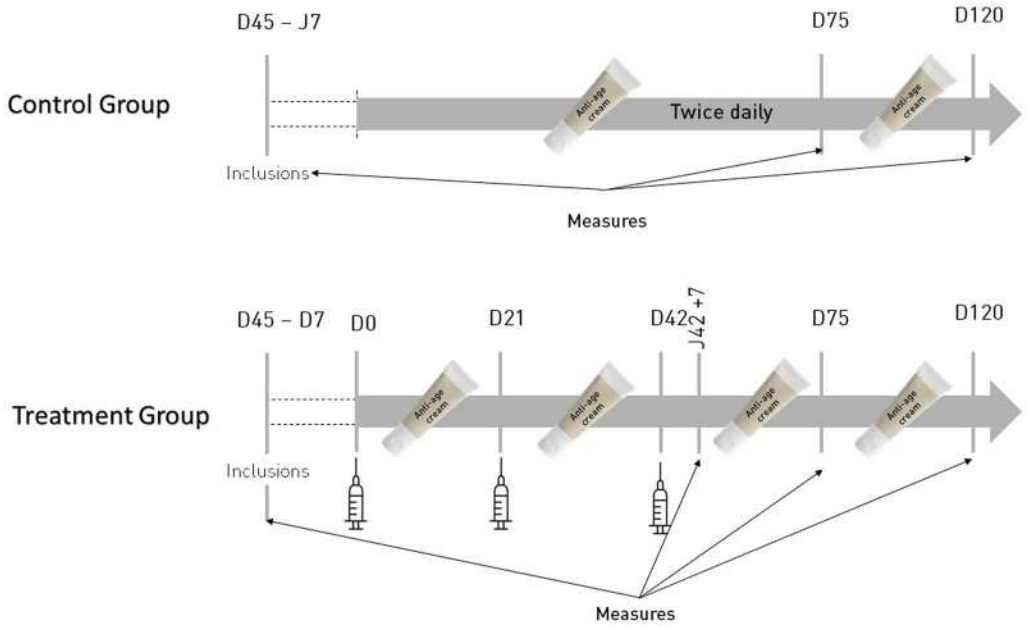


**Figure 2.** Study organogram with all time points.

also self-assessed the changes using the GAIS questionnaire (subject GAIS) at D49, D75 and D120. Subjects completed the 4-point ten-item Rosenberg Self-Esteem Scale (RSE) (16,19) at D0, D75 and D120. In addition, the subjects in the injection group completed a self-assessment questionnaire about the NCTF®135HA injections at D49, D75 and D120. The investigator assessed tolerability and safety at each visit, focusing especially on erythema, ecchymosis, hematoma, edema, dyschromia, irregularities, necrosis, Tyndall effect (bluish hue caused by superficial placement of HA filler) (17), overcorrection and pain during and after the injection.

### *Statistical analysis*

The aim of this study was the post-market follow-up of NCTF®135HA. The primary outcome was the volume of crow's feet wrinkles, assessed by 3D imaging, and based on internal assessments the anti-aging cream was expected to reduce the volume by one unit. Therefore, a 3:1 randomization included 105 subjects in the injection group (110 including expected drop off) and 35 control subjects who received anti-aging cream alone (37 including expected drop off); a total of 147 subjects. Due to a lack of previous data, comparisons of the severity of neck and décolleté wrinkles were designed for exploratory analyses.

Statistical analyses were conducted with Statistica Version 12, Graphpad Instat, and Excel 2016 or later.

Descriptive statistics were provided for each parameter. Analyses were performed by area and by treatment using intention-to-treat analyses without imputation of missing data. The volume of the crow's feet wrinkles given by the 3D imaging or the clinical score of neck wrinkles or décolleté wrinkles on D0 and D75 were calculated. The Shapiro-Wilk test verified the normality of the distribution of the difference. Statistical significance was calculated using a one-sided Student's Test or Mann-Whitney Test. Analysis was repeated on the per-protocol population.

The mean and median changes of the studied parameters (hydration, elasticity, firmness, density, pore size) between D0 and other time points were calculated for each group and each area. Statistical significance was calculated by a Student's Test for paired series or the Wilcoxon Test. Additional analyzes were conducted for each scale by target area and group. A decrease of one grade was considered a satisfactory esthetic improvement. Self-assessment results were summarized. Adverse events were described using the clinician's terms. For each event, intensity, severity, duration, consequences (therapeutic or other) and relationship (according to the clinician) with the esthetic procedure was reported.

## Results

### *Randomization and baseline characteristics*

The study included 146 subjects enrolled between June and July 2019. One subject failed the screening. Subjects were randomized 3:1 to receive either NCTF®135HA plus anti-aging cream ($n = 107$) or anti-aging cream alone ($n = 38$). Of these, 107 patients received whole-face treatment, 55 were also injected on the neck, and 49 also on the décolleté. Three subjects were injected on the neck by mistake and, since they were only evaluated on the face and décolleté at baseline, these neck treatments were not included in analyses. Four subjects missed at least one treatment session and were withdrawn from the study. All 38 subjects in the control group were assessed on the face and neck, of which 34 were also assessed on the décolleté. Table 1 summarizes the demographics and baseline characteristics.

### *Wrinkle volume and depth*

The mean volume and depth of crow's feet showed statistically significant reductions at D75 and D120 compared with baseline in subjects who received NCTF®135HA (Figure 3(A,B)). Anti-aging cream alone did not produce statistically significant differences in crow's feet depth or volume at D75 compared with baseline, but a significant reduction at D120 (Figure 3). At D75 and D120, the reduction in the mean volume and depth of crow's feet was significantly greater in the NCTF®135HA group compared with the anti-aging cream alone ($p = .0005$ (volume) and $p < .0001$ (depth) on D75 respectively, and $p = .0005$ (volume) and $p = .0012$ (depth) on D120, respectively). This effect was confirmed by clinical scoring: Crow's feet Lemperle scores showed statistically significant improvements at D75 and D120 compared with baseline in both groups (control group $p = .0006$ on D75 and $p = .0004$ on D120; NCTF®135HA group $p < .0001$ at both timepoints). At D75 and D120, the improvement in these scores was significantly greater in the NCTF®135HA group than with the anti-aging cream alone ($p < .0001$ at both timepoints).

Bazin scores for neck wrinkles showed statistically significant improvements at D75 and D120 compared with baseline in the NCTF®135HA group. The control group showed no statistically significant differences at either time compared with baseline. At D75 and D120, the improvement in neck wrinkle scores was significantly greater with NCTF®135HA than with the anti-aging cream alone (Figure 3(C)). Landau scores for décolleté wrinkles showed statistically significant improvements at D75 and D120 compared with baseline in both groups (Figure 3(D)). At both timepoints, the improvement in décolleté scores was significantly greater in the NCTF®135HA group compared with the Anti-aging cream alone.

### *Radiance scores*

Facial radiance clinical scores showed statistically significant improvements at D75 and D120 compared with baseline in both groups. At D75 and D120, the improvement in these scores was significantly greater in the NCTF®135HA group than with the anti-aging cream alone (Table 2).

### *Skin hydration*

Hydration of the facial skin, measured by Moistermeter® Epi-D one week after the final treatment session, showed a significant increase at Day 49 in the NCTF®135HA group ($p < .0001$; skin hydration was not measured in the control group at this timepoint). It also significantly improved in both groups at D120 without any difference between the groups ($p = .0002$ for NCTF®135HA; $p = .012$ for anti-aging cream alone). Skin on the neck showed an important, but non-significant, tendency to improved hydration at Day 49 and D120 in the NCTF®135HA group ($p = .06$ for both time points) but not with anti-aging cream alone. Hydration of décolleté skin did not change significantly in either group.

### *Skin elasticity, density and pore size*

Skin elasticity was not significantly different in either group.

**Table 1.** Demographics and baseline characteristics (ITT population).

| | | Face | | Neck | | Décolleté | |
|---|---|---|---|---|---|---|---|
| | | Anti-aging cream alone | NCTF®135HA + anti-aging cream | Anti-aging cream alone | NCTF®135HA + anti-aging cream | Anti-aging cream alone | NCTF®135HA + anti-aging cream |
| Female, *n* (%) | | 34 (89) | 97 (91) | 34 (89) | 45 (82) | 34 (100) | 49 (100) |
| Phototype, *n* (%) | I | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| | II | 2 (5) | 6 (6) | 2 (5) | 3 (5) | 2 (6) | 3 (6) |
| | III | 33 (87) | 86 (80) | 33 (87) | 40 (73) | 30 (88) | 43 (88) |
| | IV | 3 (8) | 15 (14) | 3 (8) | 12 (22) | 2 (6) | 3 (6) |
| Age, years | Mean ± SD | 54.0 ± 10.0 | 53.6 ± 10.2 | 53.9 ± 10.1 | 51.9 ± 9.5 | 54.4 ± 10.4 | 55.5 ± 10.9 |
| | Median (range) | 53 (32–76) | 53 (31–77) | 53 (32–76) | 52 (31–77) | 53 (32–76) | 55 (33–77) |
| Body mass index, kg/m$^2$ | Median | 24.1 | 22.9 | 24.1 | 23.2 | 23.8 | 22.1 |
| | Range | 16.5–38.5 | 16.6–42.3 | 16.5–38.5 | 17.6–36.5 | 16.5–37.0 | 16.6–42.3 |

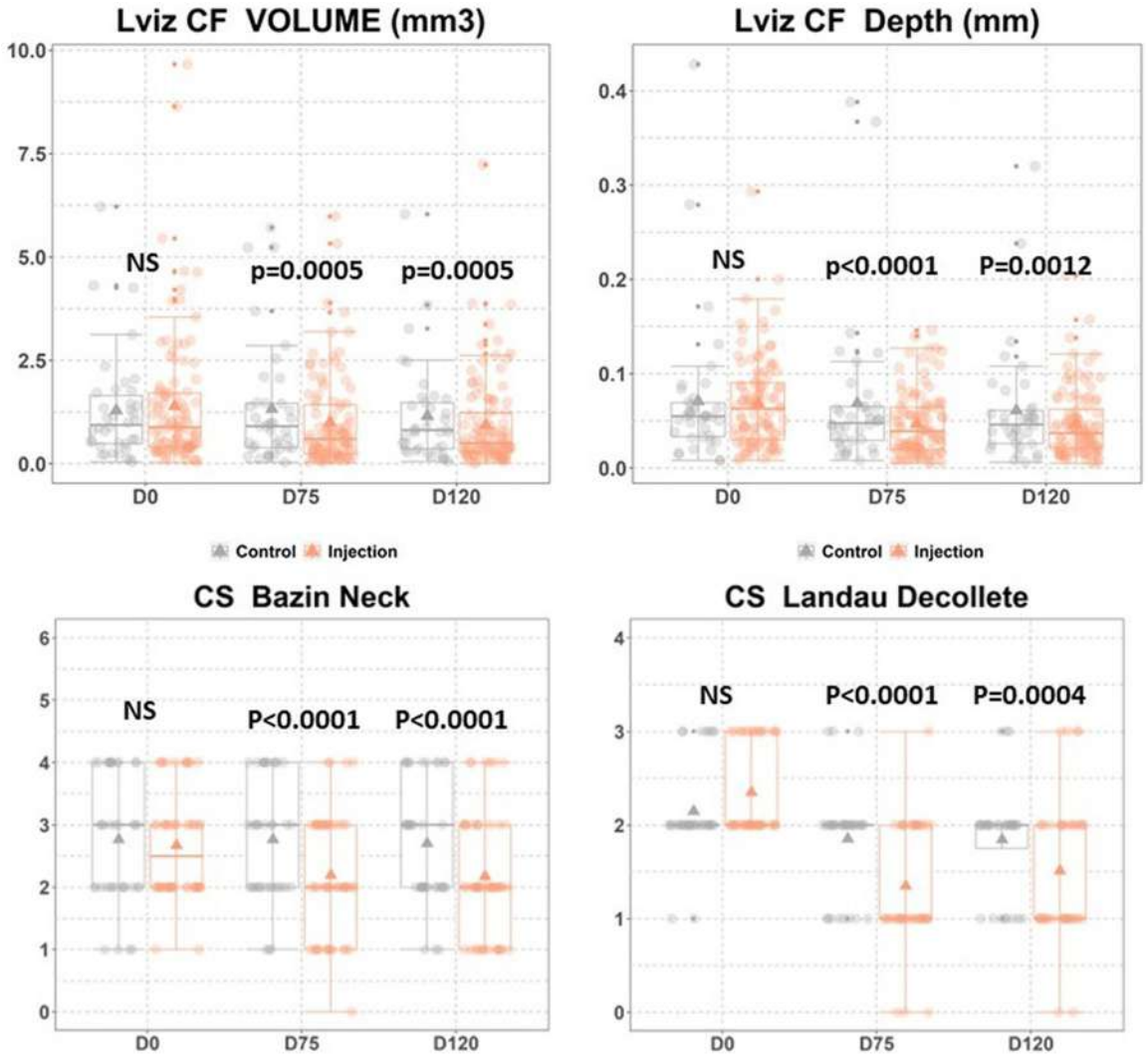


**Figure 3.** Evolution of Crow's feet and wrinkles (a) Crow's feet volume; (b) Crow's feet depth; (c) Clinical score of neck wrinkles; (d) clinical score of décolleté wrinkles.

**Table 2.** Summary of clinical radiance scores, skin hydration, elasticity, dermal density, and pore size.

| | Anti-aging cream alone | | | | | NCTF®135HA + Anti-aging cream | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | D0 | D75 | | D120 | | D0 | D75 | | D120 | |
| | Mean ± SD | Mean ± SD | *p* value | Mean ± SD | *p* value | Mean ± SD | Mean ± SD | *p* value | Mean ± SD | *p* value |
| Radiance (CS) | 1.2 ± 0.4 | 2.2 ± 0.6 | <.0001 | 2.0 ± 0.7 | <.0001 | 1.3 ± 0.5 | 2.7 ± 0.6 | <.0001 | 2.4 ± 0.6 | <.0001 |
| Hydration | 47.8 ± 7.3 | 48.6 ± 4.9 | .4340 | 50.5 ± 4.7 | .0121 | 48.6 ± 6.0 | 49.2 ± 4.9 | .2455 | 51.2 ± 5.0 | .0002 |
| Elasticity (R5-Ur/Ue) | 0.4230 ± 0.0854 | 0.4271 ± 0.1182 | NS | 0.4217 ± 0.0985 | NS | 0.4001 ± 0.0782 | 0.4378 ± 0.1624 | .0048 | 0.4092 ± 0.0892 | NS |
| Density (%) | 28.3 ± 6.8 | 33.7 ± 10.2 | .0022 | 36.2 ± 8.9 | <.0001 | 32.5 ± 9.3 | 49.9 ± 11.5 | <.0001 | 45.3 ± 10.2 | <.0001 |
| Pore size (µm) | 138.2 ± 26.7 | 115.7 ± 21.7 | .0003 | 106.0 ± 25.1 | <.0001 | 138.1 ± 29.9 | 104.0 ± 27.8 | <.0001 | 101.8 ± 23.7 | <.0001 |

CS: clinical score; SD: Standard deviation; P value versus D0; NS: Not significant.

Facial skin density assessed on the crow's feet and the cheeks using high-frequency ultrasound imaging (Dermascan® from Cortex) showed statistically significant improvements at D75 and D120 compared with baseline in both groups (Figure 4). However, the improvement in skin density was significantly greater in the NCTF®135HA group than in those who applied anti-aging cream alone ($p < 0.0001$ at D75 and $p = .0051$ at D120).

Pore size showed statistically significant improvements as soon as D49 for NCTF®135HA ($p < .0001$) and at D75 and D120 for both groups ($p < .0001$ NCTF®135HA and $p = .0003$ control at D75 and $p < .0001$ for both at D120). An important but non-significant tendency was observed between the two groups, favoring NCTF®135HA only at D75 ($p = .09$).

### *Investigator and subject satisfaction rates and self-esteem scores*

Physicians and subjects reported improved overall esthetic impressions based on the Global Esthetic Improvement Scale (GAIS) (Figure 5). The satisfaction rate was confirmed between the evaluator and subjects. Subjects also had positive experiences of the

injection procedure according to the self-assessment questionnaire (Table 3).

Scores on the RSE scales showed statistically significant improvements on D120 in subjects treated with NCTF®135HA compared with baseline (Figure 6). The control group did not show any improvement from the baseline.

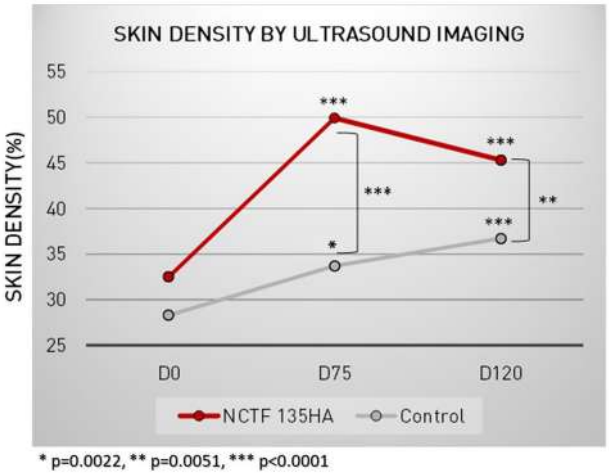


**Figure 4.** Skin density assessed on the crow's feet and the cheeks using high-frequency ultrasound imaging.

### *Tolerability and safety*

Most (95%) of the 619 adverse events reported were expected and due to the injection procedure, such as bruising (36%) or redness (23%), and not related to the product itself. Most of them (56%) were mild. Half (48%) of the adverse events resolved within 48 h and all of them resolved in a few days after the injection (Table 4). One serious adverse event reported (accidental death) which was unrelated to the study product or procedure.

## Discussion

The visible signs of skin aging arise from the interaction of endogenous biological changes and environmental factors (1, 2). Therefore, a multi-faceted approach is important to address the diverse contributory factors, including increasing moisture, reducing oxidative stress, and restoring volume. This study suggests that NCTF®135HA, which contains HA, could compensate the loss of moisture and reduce the signs of skin aging due to oxidative stress and photoaging.

At D75 and D120, NCTF®135HA significantly reduced the volume, depth, and severity of crow's feet, neck, and décolleté wrinkles, and improved facial radiance scores compared with baseline and an anti-aging cream alone. Anti-aging cream alone did not significantly reduce the volume or depth of crow's feet and neck wrinkle scores at D75 although, a significant difference in crow's

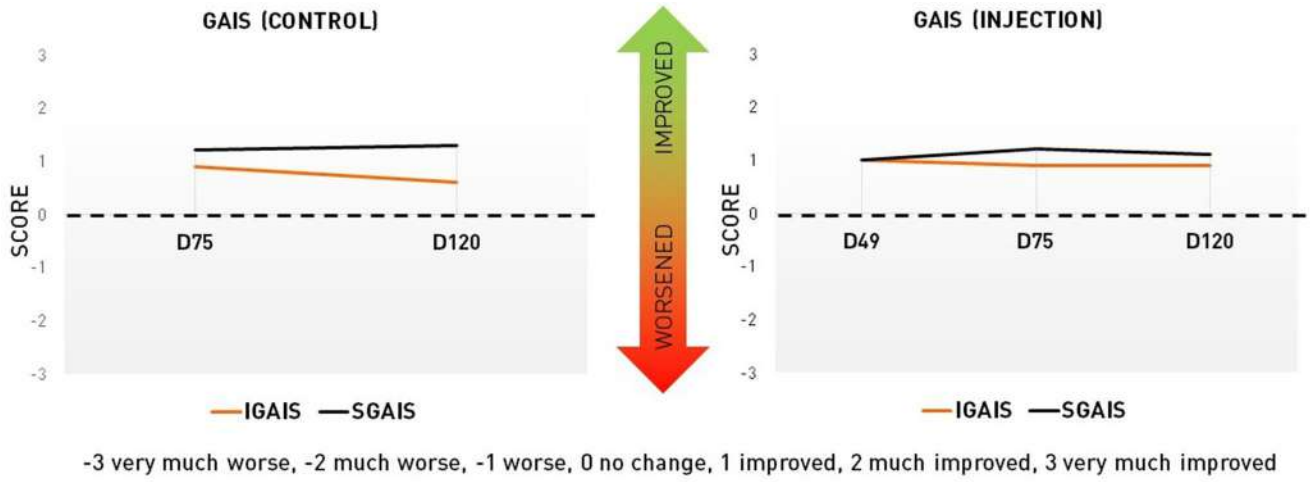


**Figure 5.** Changes in physicians' and subjects' GAIS compared with baseline in the face.

**Table 3.** Subjects' impressions of injection procedure and efficacy.

| | Proportion (%) | | | | |
|---|---|---|---|---|---|
| | Do not agree at all | Do not agree | Neither agree nor disagree | Agree | Totally agree |
| The protocol with 3 sessions is not painful | 27 | 35 | 6 | 18 | 12 |
| The number of sessions is an important criterion for the choice of treatment | 2 | 3 | 29 | 38 | 25 |
| The protocol with 3 sessions is much more comfortable than a 5 sessions injection protocol | 6 | 11 | 33 | 24 | 23 |
| The protocol with 3 sessions is rather a disadvantage for you | 49 | 26 | 9 | 10 | 3 |
| The protocol with 3 sessions is tedious | 46 | 32 | 7 | 9 | 4 |
| You are ready to make 3 consecutive doctor's visits, 3 weeks apart to perform the injection protocol | 6 | 7 | 4 | 29 | 52 |
| You are ready to make 5 consecutive doctor's visits, 2 weeks apart to perform the injection protocol | 15 | 21 | 9 | 21 | 31 |
| The protocol with 3 sessions is a sufficient reason not to return to the doctor | 32 | 34 | 18 | 11 | 3 |
| The protocol with 3 sessions is sufficient for a whole year | 12 | 23 | 46 | 9 | 7 |
| You would rather choose 2 injection protocols with 3 sessions per year for better results | 6 | 7 | 20 | 30 | 36 |

Data was missing for one person.

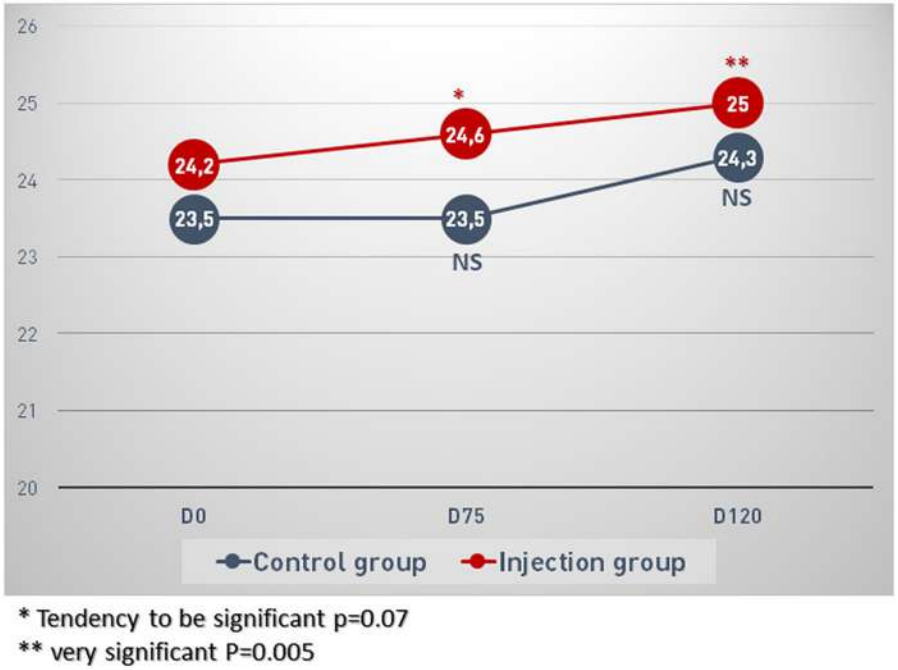


**Figure 6.** Changes in Rosenberg self-esteem scale. NS: not significant.

**Table 4.** Summary of adverse events.

| | Face ($n=107$) | Neck ($n=55$) | Décolleté ($n=49$) | Total |
|---|---|---|---|---|
| Number of adverse events, *n* (% by area) | 329 (56) | 127 (22) | 129 (22) | 585 (100) |
| Number of subjects experiencing adverse event, *n* (%) | 82 (77) | 44 (80) | 38 (78) | 93 (87) |
| Mean duration, days; *n* ± standard deviation | 4 ± 5 | 3 ± 3 | 5 ± 9 | 4 ± 2 |
| Maximum duration, days | 39 | 17 | 35 | 39 |
| Intensity: Mild, *n* (%) | 188 (57) | 63 (50) | 74 (57) | 325 (56) |
| Moderate, *n* (%) | 98 (30) | 44 (35) | 41 (32) | 183 (31) |
| Severe, *n* (%) | 43 (13) | 20 (16) | 14 (11) | 77 (13) |
| Main adverse events, *n* (%) | | | | |
| Bruising | 121 (37) | 47 (37) | 41 (32) | 209 (36) |
| Redness | 71 (22) | 25 (20) | 41 (32) | 137 (23) |
| Irregularities | 46 (14) | 21 (17) | 27 (21) | 94 (16%) |
| Swelling | 29 (9) | 13 (10) | 7 (5) | 49 (8) |
| Stinging | 17 (5) | 3 (2) | 8 (6) | 28 (5) |
| Pain | 17 (5) | 4 (3) | 2 (2) | 23 (4) |
| Itching | 5 (2) | 5 (4) | 1 (1) | 11 (2) |
| Hematoma | 6 (2) | 5 (4) | 1 (1) | 12 (2) |
| Edema | 8 (2) | 4 (3) | 0 (0) | 12 (2) |
| Pigmentation changes | 4 (1) | 0 (0) | 1 (1) | 5 (1) |

feet depth and volume was apparent at D120. This difference showed that the intradermal injection of NCTF®135HA could compensate for the signs of aging as early as 1 month after the series of injections. The results also show that instrumental measures of the skin correlate with the visible clinical scoring, as well as with the patient satisfaction scores by GAIS and Subject Self-Assessment.

Skin hydration significantly increased as early as 7 d after the last NCTF®135HA injection. The improved hydration was not apparent at D75 but became significant again at D120. This may suggest a two-phase improvement in skin hydration after the injection of non-cross-linked HA injection; an early phase within days following the treatment could reflect the product's actions due to the presence of the HA molecule in extra-cellular matrix while a later phase could reflect changes in cellular activity. The effect on skin hydration was less marked on the neck than the face and no significant effect was seen on the décolleté. This likely reflects the limited number of the subjects for the neck and décolleté compared with the face or more time or more injection sessions may be required.

Biological aging is associated with reduced skin elasticity (20) and can be targeted by moisturizers which support corneocyte hydration, which is known to contribute to improved elasticity (17). Nevertheless, skin elasticity did not significantly improve in either group. The short duration of the study (4 months) may account for this as the skin's mechanical properties need more time to show a measurable improvement (at least 6 months for collagen remodeling) (21).

Increased dermal density is associated with improved skin quality (22). Facial skin density showed significant improvements at D75 and D120 compared with baseline in both groups. However, this improvement was significantly greater in the NCTF®135HA group than with anti-aging cream alone. This result is interesting

because most of the previous publications only show the non-controlled before-and-after data whereas this study revealed a superiority of a biorevitalization treatment versus a daily ani-aging routine.

Both physicians and subjects reported improved overall esthetic impression and subjects generally had positive experiences of the injection procedure. Self-esteem scores also significantly improved in subjects treated with NCTF®135HA compared with baseline. However, culture and age as well as appearance can influence self-esteem (23), which may limit the relevance of these findings to groups other than those in this study.

Treatment was well tolerated. Most adverse events were mild, resolved within 48 h and were related to the injection procedure rather than the product.

Interestingly, the anti-aging cream used as an active control in this study also showed improvements in several assessments, showing that dehydration has a significant role in producing the visible signs of aging.

Taken together, the consistency of results across multiple anatomical sites, the concordance between subjective and objective measures, clinical scoring and instrumental measures and the size of the difference compared with anti-aging cream alone suggests that the improvements from baseline and the difference between NCTF®135HA and active control group are clinically significant. In addition, the findings concur with previous *ex vivo* and *in vitro* studies and also published clinical trials support the efficacy and tolerability of NCTF®135HA (6–11) including in people with dermatological diseases such as vitiligo (24) and alopecia (25). A previous study published in 2017 showed that NCTF®135HA, with a five session protocol, significantly reduced the depth of crow's-feet wrinkles (43.3%), decreased pore size (58.5%) and produced a brighter skin tone, as well as increasing dermis thickness (20%) and density (24%), which suggests synthesis of neo-collagen (10), correlating with the findings of this larger study with only 3 injection sessions spaced 3 weeks. NCTF®135HA can also be combined with other esthetic interventions (26) and skin care products, such as the anti-aging cream in this study.

This study has several limitations. This was an open-label study due to the fact that a split-face placebo-control injection would be unethical. Adherence with the anti-aging cream was also not assessed, although there is no reason to suppose that adherence differed between the groups. Further studies could enroll more men and also subjects from non-Caucasian ethnic backgrounds. There is, however, no reason to believe that the results will differ by gender or race.

## Conclusion

Anti-aging creams are the first line anti-aging treatment for most patients before attending esthetic clinics. As shown in previous studies, non-cross-linked HA fillers which are boosted by a complex of nutrients such as vitamins, antioxidants and amino acids, have an increasing role in preventing the signs of skin aging. These additional components could provide a suitable environment for HA molecules to support adequate fibroblast function and address the signs of aging from another angle. The results of this randomized controlled study showed that NCTF®135HA was more effective than an active control (anti-aging cream) for reducing the volume and depth of crow's feet and wrinkles on the neck and décolleté; the benefits of NCTF®135HA are in addition to improvements produced by anti-aging creams alone. Therefore, NCTF®135HA offers a new approach to address several aspects of biological and endogenous causes of skin aging.

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## Data availability statement

There is no associated data available.

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