Esperienze Dermatologiche 2019 December;21(2-4):47-53
DOI: 10.23736/S1128-9155.19.00492-8

ORIGINAL ARTICLE

# Hybrid cooperative complexes of H-HA and L-HA (Profhilo®) and the BAP technique for facial skin bioremodeling: a clinical experience at the NEO-Clinic (Tyumen, Russia)

## *Complessi ibridi stabilizzati cooperativi di acido ialuronico ad alto e basso peso molecolare (Profhilo®) e tecnica BAP per il rimodellamento della pelle del viso: esperienza clinica alla NEO-Clinic (Tyumen, Russia)*

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**Abstract - Riassunto**

BACKGROUND: Hyaluronic acid (HA) is increasingly in demand as a dermal agent for the correction of age-related soft tissue defects, such as skin laxity, loss of hydration, wrinkle formation and roughening of skin texture. IBSA Pharmaceuticals' Profhilo® is the first BDDE-free injectable formulation of thermally-stabilized, cooperative hybrid HA complexes which efficacy has been proven both *in vitro* and in several independent published clinical studies. This monocentric retrospective observational study tests the efficacy and tolerability of the clinical use of Profhilo according to the specifically-developed 5-injection point Bio-Aesthetic Points (BAP) technique for facial skin bioremodeling and treatment of laxity of the malar and submalar areas.
METHODS: Ten female patients with visible signs of facial skin aging were treated with injections of Profhilo® in 3 sittings at 4-week intervals. Photographical evidence, 3D microstructure capture and quantitative data on skin hydration levels and elasticity were collected at the time of treatment and 1 month after its completion. Patients' and doctors' subjective evaluations of the treatment's aesthetic result were recorded according to the GAIS scale.
RESULTS: At 1 month after treatment, photographical evidence and 3D Complexion analysis highlighted a clear reduction in wrinkle depth and smoothing of skin texture. Corneometry analysis showed a statistically significant 29% improvement in skin hydration, and cutometry analysis recorded a statistically significant 25.1% increase in skin compliance (R0) and 47.4% increase in skin elasticity. Both patient and doctor satisfaction levels were high, with average GAIS scores of 2.6 and 2.8, respectively.
CONCLUSIONS: Overall the treatment was well tolerated, and no notable side effects were recorded.

(*Cite this article as:* Goltsova EN, Shemonaeva OA. Hybrid cooperative complexes of H-HA and L-HA (Profhilo®) and the BAP technique for facial skin bioremodeling: a clinical experience at the NEO-Clinic (Tyumen, Russia). Esperienze Dermatol 2019;21:47-53. DOI: 10.23736/S1128-9155.19.00492-8)

KEY WORDS: Hyaluronic acid; Skin aging; Injections.

*OBIETTIVO: L'acido ialuronico (HA) è sempre più richiesto come trattamento estetico per la correzione di difetti dei tessuti molli legati all'invecchiamento, come lassità cutanea, perdita di idratazione, formazione di rughe e irritazione della cute. Profhilo® (IBSA Farmaceutici Italia Srl) è la prima formulazione iniettabile di complessi ibridi stabilizzati termicamente di HA che ha dimostrata un'efficacia di trattamento sia in vitro che in numerosi studi clinici indipendenti. Questo studio osservazionale, retrospettivo e monocentrico conferma l'efficacia della tecnica BAP (Bio-Aesthetic Points) per il biorimodellamento del volto.*
*METODI: Dieci pazienti con segni visibili di invecchiamento cutaneo sono stati trattati con iniezioni di Profhilo® in 3 sedute di trattamento a intervalli di 4 settimane. Sono state raccolti i seguenti dati: evidenze fotografiche, acquisizione di immagini 3D e dati quantitativi sui livelli di idratazione della pelle ed elasticità. È stata utilizzata la scala GAIS per le valutazioni soggettive dei pazienti e dei medici sul risultato estetico.*
*RISULTATI: A 1 mese dall'ultimo trattamento, le prove fotografiche e l'analisi 3D hanno evidenziato una chiara riduzione della profondità delle rughe e un miglioramento della microrugosità della cute. L'analisi corneometrica ha mostrato un miglioramento statisticamente significativo del 29% nell'idratazione della pelle e l'analisi cutometrica ha registrato un aumento statisticamente significativo del 25,1% della "compliance" cutanea (R0) e un aumento del 47,4% dell'elasticità della pelle.*
*CONCLUSIONI: I livelli di soddisfazione del paziente e del medico sono risultati elevati, con punteggi GAIS medi rispettivamente di 2,6 e 2,8. Il trattamento complessivo è stato ben tollerato e non sono stati registrati effetti collaterali.*

The demand for nonoperative, less invasive facial rejuvenation procedures is increasing thanks to the parallel trends of an aging population and mass media-driven demand for beauty.[1] Facial aging is due to alterations in all the face's structural layers and tissues, including skin, fat, muscle and bone. Skin specifically undergoes a plethora of metabolic changes known as chrono-aging or intrinsic aging.[2] With time, the amount of extracellular matrix proteins such as collagen and elastin and hyaluronic acid (HA) synthesis decreases, causing skin laxity and dermal thinning.[3]

HA, also called hyaluronan, is an anionic nonsulfated glycosaminoglycan widely distributed in epithelial and connective tissues. It is a main component of the extracellular matrix, where it contributes to tissue hydrodynamics and viscoelasticity and is a key player in tissue repair and in the protection from oxidative stress.[4-8] HA possesses intrinsic anti-inflammatory and bio-stimulating properties, which contribute to tissue remodeling via the stimulation of fibroblast proliferation and collagen production.[8-10] Additionally thanks to its versatility and biocompatibility, HA is increasingly being employed in aesthetic medicine as a dermal agent for the correction of soft tissue defects.[11]

The main limitation employing HA in its free form for dermal injections is its reduced *in situ* durability due its rapid degradation by hyaluronidase.[12] In order to increase its *in situ* permanence and reduce its susceptibility to enzymatic degradation, chemical stabilization via cross-linking was developed. Cross-linking increases the molecule's stability, rigidity and elasticity, but at the price of chemically altering hyaluronan's natural molecular structure.[13]

IBSA Pharmaceuticals' Profhilo® is the first BDDE-free stabilized injectable HA-based product.[14] A mixture of 32 mg high molecular weight HA (110-1400 kDa) and 32 mg low molecular weight HA (80-110 kDa), totaling with one of the highest hyaluronan concentrations on the market, the product's patented thermal production process, consisting of a first high-temperature and a second low-temperature step, yields stable, cooperative hybrid HA complexes without employing chemical agents. Among its many unique characteristics are the product's excellent manageability, low viscosity and optimal tissue diffusion, its low tissue inflammatory response despite its high HA concentration, and a duration similar to that of weakly cross-linked gel.[7, 14-16]

Several studies have tested the *in vitro* effectiveness of the studied product: D'Agostino *et al.*[7] proved tissue repair enhancement, while in studies by Stellavato *et al.*[16, 17] the product was shown to favor extracellular matrix remodeling in terms of elasticity and support and to maintain optimal conditions for fibroblast, keratinocyte and adipocyte vitality, displaying neofibrogenic and adipogenic properties.

The product's intended use in aesthetic medicine is in the tissue remodeling and improvement in skin laxity of the face, neck and body: its clinical indications include physiologically aged skin, dermal repair processes such as acne or scars, and adipose tissue damage. The product's *in vivo* efficacy has been evaluated over the course of 4 independent published studies[18-21] in a total of over 120 patients. These gave highly satisfactory quantitative results in skin hydration, elasticity, trans-epidermal water loss, validated clinical scales (WSRS, FVLS and Beagley and Gibson Scale) and patient and doctor satisfaction rates, and no relevant side effects.

Thanks to the product's favorable rheological characteristics, 2 sittings with a 4-week interval are sufficient to obtain satisfactory tissue remodeling. In particular, IBSA's specifically developed BAP (Bio Aesthetic Point) technique is the most widespread, efficient and recommended protocol for the bioremodeling of the malar and submalar areas. Due to the predisposition of the lower third of the face to age-related dermal atrophy, the BAP technique was developed with a view to maximizing the product's diffusion while minimizing the procedure's risks. This is achieved by the injection of 0.2 mL boluses with a 29G needle in the superficial layer of 5 anatomically receptive areas in each hemiface, identified by the absence of large vessels and nerve branches:[22] the zygomatic protrusion, the nasal base, the tragus, the chin and mandibular angle (Figure 1).[19] Positive visual and quantitative results, together with reduced pain and chance of bruising and a low number of sittings (only 2 treatments performed 4 weeks apart), all result in excellent compliance and high doctor- and patient satisfaction.[23]

## Materials and methods

The purpose of the present monocentric retrospective observational study is to prove the clinical efficacy of Profhilo® injections in improving the appearance, hydration and biomechanical properties of facial skin in patients

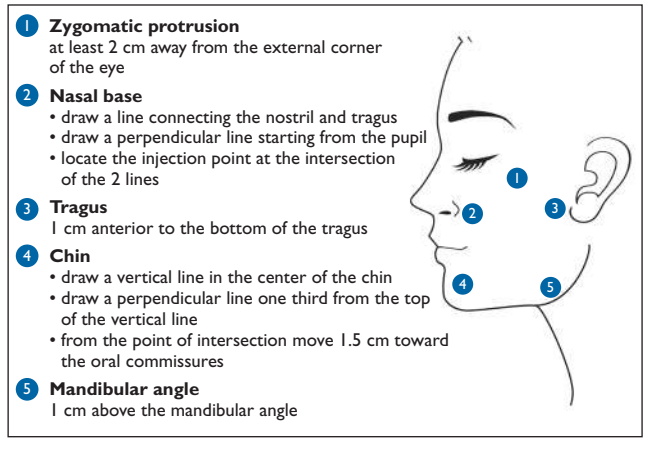


**Figure 1.**—The BAP (Bio Aesthetic Point) technique for the treatment of skin laxity of the malar and submalar areas.
[Modified from: Laurino C *et al.*].[19]

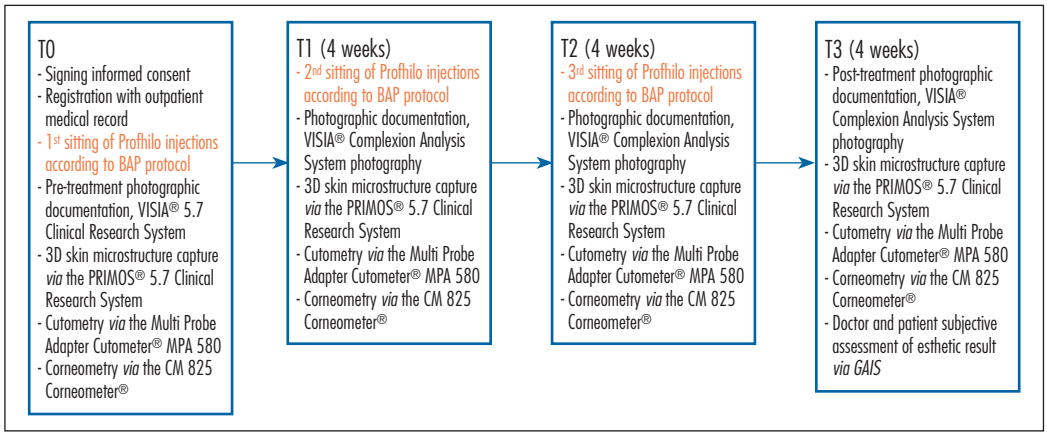


**Figure 2.**—Study timeline.

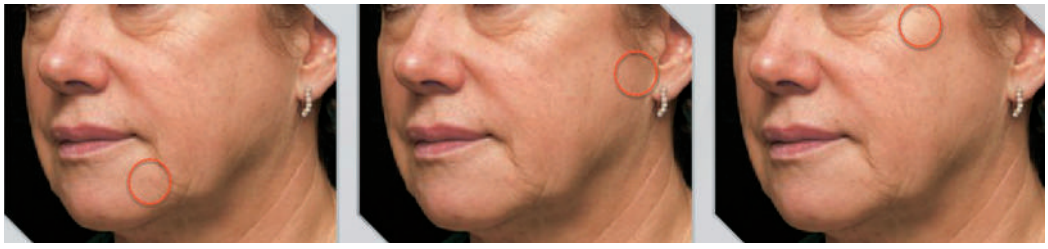

**Figure 3.**—Facial areas studied for corneometry, cutometry and 3D skin measurements: lateral-zygomatic, labio-mental and near-tragus areas.

aged more than 40 years with signs of aging (Glougau grade 2-3).

A total of 10 subjects were included in the present study: the subjects were all females aged 42 to 62 (mean=51 years) treated at the NEO-Clinic in Tyumen, Russia.

The inclusion criteria were the following:

• the presence of signs of involutional skin changes in the face: dehydration, reduced tone and elasticity of the skin, moderate depression of facial soft tissues, presence of static wrinkles, signs of cutaneous photodamage, moderate photoaging, early brown spots visible, visible capillaries (telangiectasias);

• voluntary informed consent for the participation in the clinical study.

The exclusion criteria were the following:

• pregnancy or lactation;

• aesthetic procedures in the 6 months prior to the start of the study: injection of fillers, plastic surgery of the face, botulinum toxin injections, laser exposure, ultherapy, chemical peeling;

• the presence of permanent fillers;

• a history of hypersensitivity to the studied product or to its components;

• dermatological diseases of facial skin;

• serious common diseases such as decompensated diabetes mellitus, renal failure, hepatic failure, heart failure, lung diseases, oncologic diseases, neurological or psychological diseases, acute respiratory diseases at the time of the procedure, inflammatory/immunodeficiency diseases;

• the use of anti-inflammatory or antihistamine drugs, external and systemic corticosteroids, narcotic drugs, antidepressants, immunosuppressants, and any other drug which might affect the study result according to the researchers.

The study design consisted of 4 specialist evaluations at 4-week intervals. In the first visit (T0), patients signed informed consent and were registered with an outpatient medical record. At T0, T1 and T2 patients underwent Profhilo® injections following the BAP (Bio Aesthetic Points) protocol. Pre-, during and post-treatment data collection was performed, with the following analysis performed at all 4 timepoints (T0-T3):

1. photographic documentation via the VISIA® Complexion Analysis System photography by Canfield.

2. 3D skin microstructure capture via the PRIMOS® 5.7 Clinical Research System by Canfield.

3. cutometry via the Multi Probe Adapter Cutometer® MPA 580 by Courage + Khazaka.

4. corneometry measuring hydration levels of the epidermis's stratum corneum via the CM 825 Corneometer® by Courage + Khazaka.

The study timeline is illustrated in Figure 2.

Cutometry, corneometry and 3D skin structure measurements were performed in 3 areas of interest, namely the lateral-zygometic, labo-mental and near-tragus areas (Figure 3).

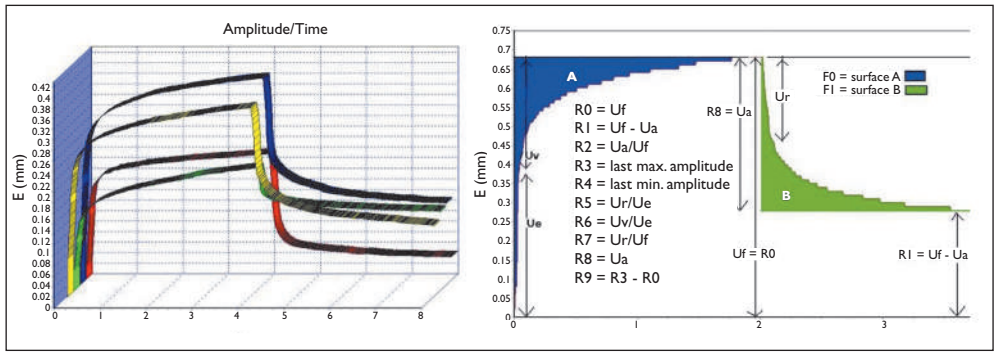


**Figure 4.**—Sample MPA 580 Cutometer® plot and parameters. Figures adapted from MPA 580 Cutometer® by Courage + Khazaka information leaflet.

The VISIA® Complexion Analysis System allows for the capture of high quality standardized facial images to document progress over time of surface and subsurface skin conditions. In this study, VISIA's IntelliFlash®, cross-polarized and UV light were employed to record and measure changes in wrinkles and skin texture.[24]

The PRIMOS® 5.7 Clinical Research System is a 3D measurement and analysis system used for the investigation of skin microstructure. Via 3D mapping visuals and quantitative height and volume measurements, it evaluates and tracks changes in the skin's roughness, texture, wrinkles and fine lines.[25]

Cutometry measures skin viscoelasticity. The MPA 580 Cutometer® utilizes the suction method, in which negative pressure deforms the skin mechanically; the skin's resistance to suction (firmness) and its ability to return to its original position (elasticity) are plotted as curves in real time (Figure 4).[26] In this study, the two parameters measured were R0 and F0. R0 (Uf) is the maximum suction depth, hence an index of the firmness/compliance of the skin: the higher the R0, the more stretchable the skin. F0 is an area parameter, represented by the above the curve in the (Uf x suction time) rectangle. The smaller F0, the more elastic the skin; completely elastic material will have F0=0.

Corneometry is a method for the measurement of hydration level of the skin surface. The CM 825 Corneometer® uses the capacitance measurement of a dielectric medium, here the stratum corneum, whose dielectric constant varies based on the hydration levels of the medium.[27]

Lastly, post-treatment, both patients and doctors were asked to subjectively assess the aesthetic result of the treatment via the Global Aesthetic Improvement Scale (GAIS).

Statistical analysis of quantitative results was performed using one sample Student t-test; P values<0.05 were considered significant.

## Results

Visual pre- and post-treatment comparisons via the VISIA® Complexion Analysis System showed a clear decrease in wrinkle depth and smoothing of skin microrelief (Figure 5, 6). 3D skin measurements via the PRIMOS® Clinical Research optical system likewise displayed evident visual trends with the amelioration of skin roughness and texture (Figure 7, 8).

Corneometry recorded a statistically significant increase in skin hydration in the lateral-zygomatic (from 62.8±2.8 conventional corneometric units (CCU) at T0 to 77.1±3.2 CCU at T3, P<0.05), labio-mental (from 46.7±4.0 CCU at T0 to 66.0±3.7 CCU at T3, P<0.05) and near-

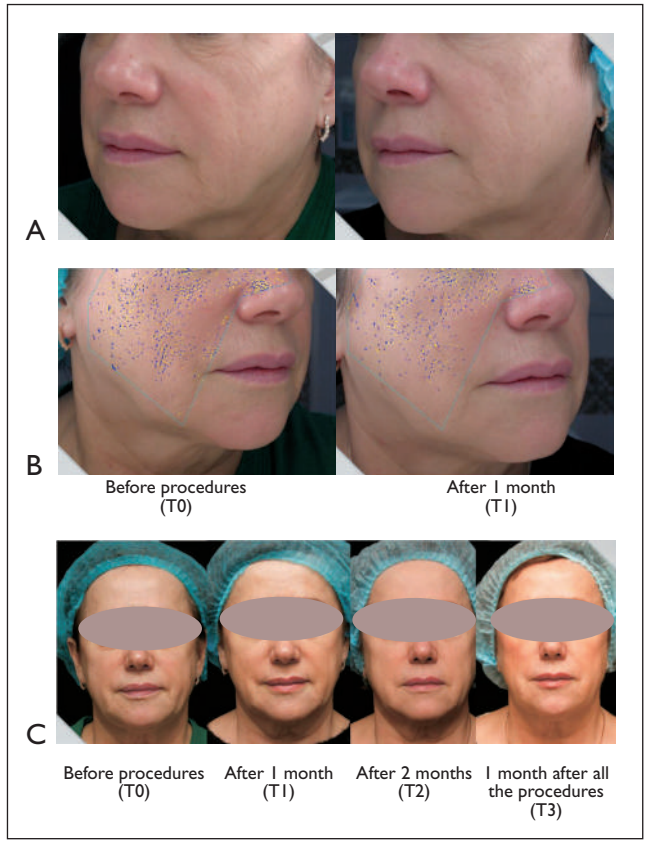


**Figure 5.**—VISIA® Complexion Analysis. Patient L, 62 years. Photographical evidence (A) and skin texture analysis (B) at T0 and T1; pre-, during and post-treatment photographical documentation (C).


**Figure 6.**—Patient M, 58 years. Pre- and post-treatment photographical evidence (A) and wrinkle analysis (B) at T0 and T3.

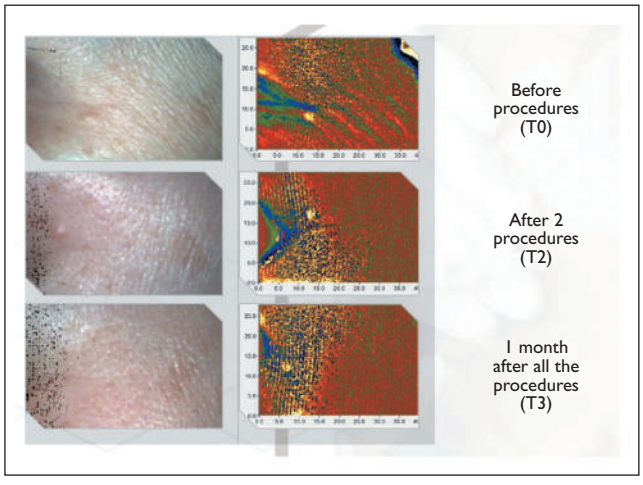


**Figure 7.**—PRIMOS® CR optical system analysis output. Patient N (54 years old), skin microrelief analysis in the lateral zygomatic area pre-, during and post-treatment.

tragus (from 40.3±4.7 CCU at T0 to 59.2±3.4 CCU at T3, P<0.05) areas (Figure 9). In the three face areas combined, corneometry recorded a statistically significant mean 29% increase in skin hydration.

Cutometry also recorded a statistically significant (P<0.05) improvement both in skin compliance (R0) and elasticity (F0) in the lateral-zygomatic, labio-mental and near-tragus zone, with a mean overall decrease between

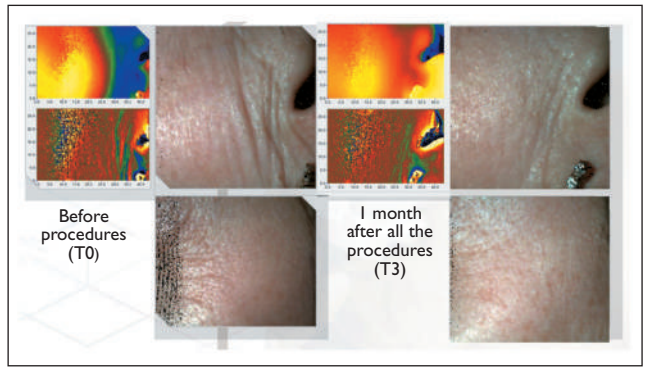


**Figure 8.**—Patient L (62 years old), skin microrelief analysis in the near-tragus and lateral zygomatic areas.

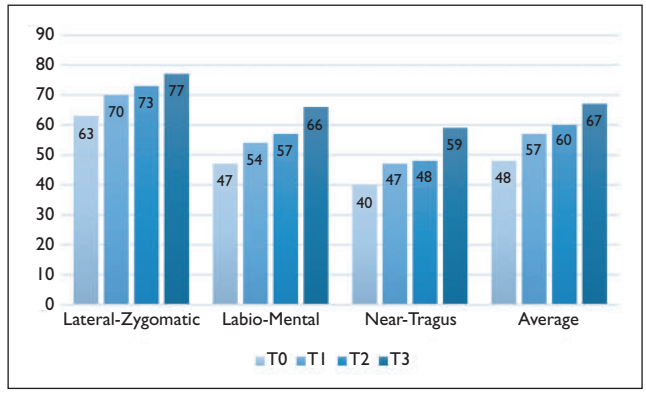


**Figure 9.**—Corneometry assessment output.

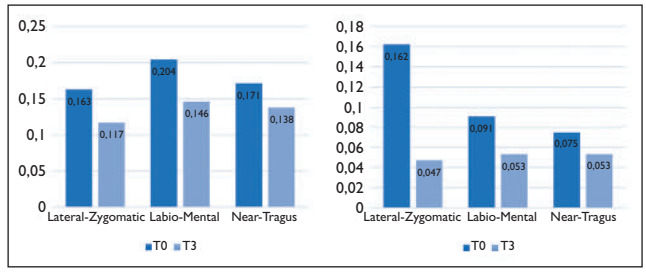


**Figure 10.**—Subjective assessment of aesthetic improvement as measured by GAIS score 0.162.

T0 and T3 of 25,1% for R0 and 47.4% for F0 (Figure 10, Table I).

Both patients' and doctors' subjective assessment of aesthetic improvement as evaluated by GAIS score was positive, with 60% of both doctors and patients noting "Very improved patient" (score=2) and 40% noting "Improved patient" (score=3), no scores below 3, and with an average GAIS score of 2,6 for doctors and 2,8 for patients (Figure 11).

Overall the treatment course was well-tolerated, and no notable side effects or undesirable events were recorded.

**Table I.**—*Cutometry assessment output.*

| Area | Cutometry parameter | T0 | T3 | T3-T0 |
|---|---|---|---|---|
| Lateral-zygomatic | R0 | 0.163±0.012 | 0.117±0.005 | -28.2%* |
| | F0 | 0.162±0.01 | 0.047±0.01 | -71.2%* |
| Labio-mental | R0 | 0.204±0.01 | 0.146±0.01 | -28.4%* |
| | F0 | 0.091±0.01 | 0.053±0.01 | -41.8%* |
| Near-tragus | R0 | 0.171±0.012 | 0.138±0.01 | -19.3%* |
| | F0 | 0.075±0.01 | 0.053±0.01 | -29.3%* |
| Overall | R0 | | | -25.1%* |
| | F0 | | | -47.4%* |

*When compared to T0, P<0.05. When using parametric methods for assessing the statistical significance of differences between average values (Student's criterion) it was confirmed that differences were statistically significant.

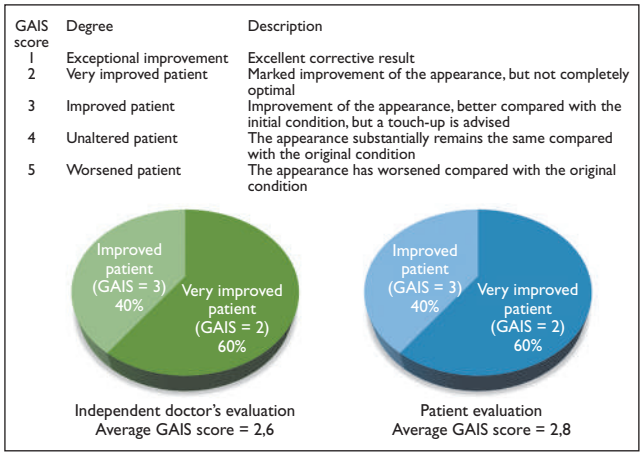


**Figure 11.**—Cutometry assessment output.

## Discussion

Facial aging is due to a decrease in the skin's elastin and collagen content, HA synthesis and hydration levels. The aesthetic consequences of these metabolic and structural alterations are loss of elasticity, facial laxity and tissue ptosis; superficial wrinkling, increased roughness and alterations of skin texture.

The studied product is an exclusive skin bioremodeling treatment for loss of facial volume and elasticity. Differently from all other HA-based injectable products to date, the product's patented thermal production process yields stable, cooperative hybrid HA complexes without the need for BDDE or other chemical agents. *In-vitro* studies have proven the product's effectiveness in promoting tissue repair, extracellular matrix remodeling, neofibrogenesis and adipogenesis. Furthermore, its efficacy and tolerability has been tested on 120 patients in 4 independent published clinical studies, with excellent quantitative results in terms of skin moisture, elasticity and patient- and doctor-satisfaction rates.

The present work is a monocentric retrospective observational study on the clinical use of Profhilo in the facial area according to the Bio-Aesthetic Points (BAP) technique. 10 patients, all females aged 42 to 62, were treated with superficial injections of Profhilo following the BAP protocol in 3 sittings at 4-week intervals (T0, T1, T2). Data was collected at each treatment sitting, plus at one additional time point 1 month after completion of the treatment course (T3).

The results proved the reliable clinical efficacy of Profhilo injections in the facial area according to the BAP technique in terms of improving the appearance, hydration levels and biomechanical properties of facial skin. Specifically, 3D optical measurement and analysis systems showed a clear decrease in wrinkle depth and smoothing of skin texture. Furthermore, corneometry analysis showed a statistically significant 29% increase in skin hydration between T0 and T3. Likewise, cutometry analysis highlighted a clear amelioration in the biomechanical properties of the skin (elasticity and compliance, as indicated by F0 and R0), demonstrating a statistically significant improvement in R0 and F0 by 25.1% and 47.4%, respectively, between T0 and T3.

A good tolerability and the absence of side effects and undesirable events was noted. Lastly, both doctors and patients positively evaluated the treatment's aesthetic result according to the GAIS scale (average GAIS 2.6 and 2.8, respectively), indicating the procedure's excellent subjective assessment in terms of improving the appearance of facial skin.

## Conclusions

These results confirm the excellent efficacy and high satisfaction levels of the studied product and the BAP technique for facial skin rejuvenation even in patients with a severe aging (Glougau grade 3) of the skin, further supporting this unique product as a highly tolerable nonoperative skin bioremodeling treatment.

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**25.** PRIMOS® CR by Canfield Scientific information leaflet.

**26.** Cutometer® MPA 580 by Courage + Khazaka Electronic information leaflet.

**27.** Corneometer® CM 825 by Courage + Khazaka Electronic information leaflet.

*Conflicts of interest.*—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

*Funding.*—The medical writing has been supported by IBSA Farmaceutici Italia Srl.

*Acknowledgments.*—The authors are grateful to Alba Sommerschield for help in writing the manuscript.

Manuscript accepted: November 20, 2019. - Manuscript received: October 4, 2019.