

# Profilo® Structura, Current Status and Future Perspectives: A Practical Review

Riccardo Forte, MD  
Giovanni Salti, MD  
Antonello Tateo, MD

Hyaluronic acid (HA)-based injectables continue to grow in popularity and are used worldwide to improve facial changes associated with aging. Profilo® Structura (IBSA Farmaceutici Italia, Lodi, Italy) is a novel HA-based product that uses nano hybrid complex of hyaluronic acid (NAHYCO)® technology to create hybrid cooperative complexes consisting of high and low molecular weight HA. Profilo® Structura's high concentration (45 mg of total HA) and *rheological properties* (ie, *viscosity* [resistance to flow] and *elasticity* [stickiness]) have been specially formulated to restore facial adipose tissue. Because of their early involvement in the facial aging process, the superficial medial and lateral-temporal cheek fat compartments are good candidates for treatment. However, recommendations and guidelines are necessary to ensure that treatment is safe and effective. Three experts were invited to IBSA Farmaceutici Italia Srl to discuss clinical rationale, optimal injection techniques, and clinical outcomes for treating the

superficial medial and lateral-temporal cheek fat compartments with Profilo® Structura. These techniques were developed using patients presenting with either initial hypotrophy of fat compartments within the preauricular area (ie, *sinkers*) or jowl sagging due to hypotrophy within the preauricular and zygomatic areas (ie, *saggers*). Targeting these areas using the optimal injection site can maximize product diffusion and minimize the risk for vascular compromise. Targeting these areas also leads to lateral tightening and lipolifting effects due to adipose tissue restoration. The experts agreed that Profilo® Structura is currently the first and only HA-based injectable treatment that can integrate and restore the adipose tissue in these affected fat compartments.

**Keywords:** Profilo® Structura; Profilo®; hyaluronic acid injection technique

Facial skin aging is a complex physiological process involving multiple layers of the facial anatomy including bone, skin, and soft tissue (Swift et al., 2021). Most antiaging strategies focus on the deterioration and reduction of collagen structure and production, overlooking the important role of reduced facial subcutaneous white adipose tissue (Wollina et al., 2017). Properties of the overlying skin, such as collagen networks and skin fibroblast activity, can be directly influenced by adipose tissue structure and volume (Kruglikov & Scherer, 2017; Wollina et al.,

2017). Adipose tissue is therefore an attractive target for anti-aging approaches (Wollina et al., 2017).

Facial fat compartments can be characterized as either *superficial* (ie, nasolabial fat, superficial middle cheek fat, lateral-temporal cheek fat, and jowl) or *deep* (ie, deep medial cheek fat, buccal fat, and the medial and lateral suborbicularis oculi fat) (Swift et al., 2021). Older adult patients have significantly smaller *adipocytes* (ie, cells contained in adipose tissue) in the deep medial cheek fat relative to superficial nasolabial fat, demonstrating that these compartments are *morphologically* (ie, structurally)

**Riccardo Forte, MD**, is a physician in Private Practice, Como, Italy and Lugano, Switzerland.

**Giovanni Salti, MD**, is a physician in the Aesthetic Medicine Section, Medlight Istituto Medico, Florence, Italy.

**Antonello Tateo, MD**, is a physician in Private Practice, Milan and Pavia, Italy.

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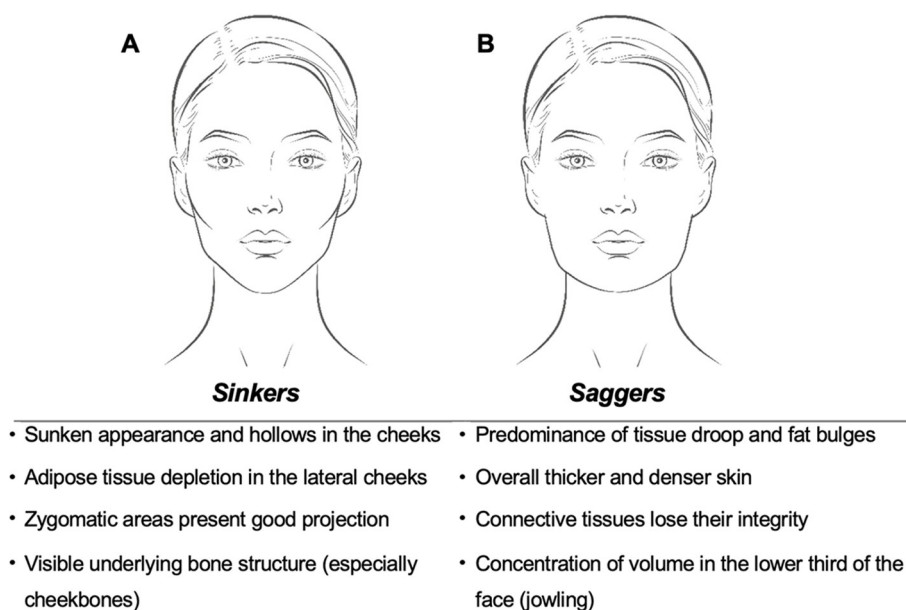
All authors have contributed to conception or design of the study, review of manuscript and final approval of manuscript.

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Address correspondence to Antonello Tateo, MD, Piazza Luigi di Savoia, 220124, Milano, Milan 27100, Italy (e-mail: [tateoantonello@gmail.com](mailto:tateoantonello@gmail.com)).

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**FIGURE 1.** Predominant Aging Profiles Associated with Adipose Tissue Modifications. A = *sinkers* are people characterized by a sunken facial appearance. B = *saggers* are people characterized by a facial appearance with tissue drooping and fat bulges.

diverse (Wan et al., 2014). Depletion and repositioning of adipose tissue are important processes that cause hollowing of the cheeks and loss of fat volume in the middle and lateral-temporal cheek superficial fat compartments, also known as the zygomatic and preauricular areas (Swift et al., 2021). Hollow or sunken cheeks or drooping or bulging tissue with an increase of volume in the lower-third of the face leading to an increase in wrinkle formation may be the predominant appearance of an aging face (Swift et al., 2021) (see Figure 1).

Aesthetic clinicians performing personalized treatments should have a clear understanding of the etiology of the facial aging process (Swift et al., 2021). To minimize procedural risks and achieve the desired natural looking results, practitioners attempting to restore the midface fat compartments must have a comprehensive knowledge of the relevant anatomy that includes an extensive knowledge of blood vessels. Clinicians should employ different techniques and products for injecting the deep or superficial fat compartments (Trévidic et al., 2022).

Hyaluronic acid (HA)-based dermal fillers have gained popularity in aesthetic medicine for reducing the signs of aging (Callan et al., 2013; Fagien & Cassuto, 2012; Fagien et al., 2018; Iranmanesh et al., 2022; Jones & Murphy, 2013). HA-based products have good tolerability and have been shown to safely and effectively improve skin hydration and maintain tissue volume (Jones & Murphy, 2013). Various formulations of HA-based products exist, with differences in HA molecular weight, composition, and concentration (Scrima et al., 2022).

Most HA dermal fillers on the market have several limitations including the use of chemical reagents for crosslinking, fast degradation, and low concentrations (Scrima et al., 2022). By reducing HA degradation and increasing collagen production, researchers have demonstrated improved biological activity with a combination of different molecular weight HAs (Stellavato et al., 2016, 2017). Because each HA filler has unique viscoelastic properties with varying short- and long-term effects, the differences in composition between HA-based dermal fillers also affect injection technique and targeted fat compartments (Trévidic et al., 2022). Hybrid cooperative complexes have been shown to promote and sustain adipose stem cells and adipocytes viability in vitro, leading to longer maintenance of facial fat compartments (Cassuto et al., 2023, 2020; Scrima et al., 2022).

Profilo® Structura is an HA-based injectable product created with hybrid cooperative complexes of high molecular weight HA (H-HA;  $1400 \pm 200$  kDa) and low molecular weight HA (L-HA;  $100 \pm 20$  kDa) obtained by a patented nano hybrid complex of hyaluronic acid® (NAHYCO) technology (Cassuto et al., 2020; Scrima et al., 2022). The formulation technology for Profilo® Structura is similar to Profilo®, which has been on the market since 2015. In addition to having different rheological parameters, Profilo® Structura contains a higher concentration of HA (ie, 45 mg of H-HA plus 45 mg of L-HA in a 2 mL injection volume), while Profilo® contains 32 mg of H-HA plus 32 mg of L-HA in a 2 mL injection volume (Cassuto et al., 2020; Scrima et al., 2022). The

rheological parameters of Profhilo® Structura ( $G' = 95$ ;  $\tan\delta = 1.1$ ) are designed for adipose tissue integration (Cassuto et al., 2023); therefore, Profhilo® Structura should be used for injection of the superficial fat compartments. The rheological parameters of Profhilo® ( $G' = 39$ ;  $\tan\delta = 1.36$ ) are designed for superficial injection; therefore, Profhilo® should be used for intradermal injections (Cassuto et al., 2020).

This review describes the main findings of an Advisory Board composed of key opinion leaders. The aims of the Board were to define the clinical rationale, the most effective protocol, and the optimal injection technique for treating the preauricular and zygomatic areas with Profhilo® Structura; discuss the known aesthetic outcomes following treatment with Profhilo® Structura, and the best treatment options across different categories of facial aging; and compare Profhilo® Structura with other treatment options.

## METHODS

In September 2023, IBSA Farmaceutici Italia Srl invited a group of experts in the field of aesthetic and reconstructive plastic surgery to form a scientific Advisory Board on Profhilo® Structura with special focus on clinical rationale, protocols, injection techniques, clinical outcomes, and alternative treatment options. This panel included 2 plastic surgeons and 1 aesthetic physician. Using their collective judgment and the best available scientific evidence, the Advisory Board addressed the following five questions:

- What is the clinical rationale for treating the middle-lower third of the face with Profhilo® Structura?
- What is the most suitable injection technique for treating the preauricular and zygomatic areas with Profhilo® Structura?
- What are the anticipated aesthetic outcomes after targeting the anatomical region defined by the protocol?
- Which patients should be treated with Profhilo® Structura? What is the link between the type of facial aging and the protocol suggested to maximize aesthetic outcome?
- What are the benefits of Profhilo® Structura compared with other treatment options?

The Board performed comprehensive literature searches of the PubMed and Scopus electronic databases using the keywords *Profhilo® Structura*, *hyaluronic acid*, *fat compartments*, *midface*, *adipose tissue restoration*, *cannula injection*, *tightening effect*, *volume restoration*, *lipolifting effect*, and *anti-aging*. The searches were limited to articles in English published between July 1, 2003 and July 30, 2023.

## RESULTS

### ***What is the Clinical Rationale for Treating the Middle-Lower Third of the Face With Profhilo® Structura?***

Facial aging affects different anatomical layers of the face, including adipose tissue (Swift et al., 2021). The aging of adipose tissue is one of the main drivers of facial aging. Fat compartments can be divided into superficial and deep compartments. Superficial fat compartments contained within the middle-third of the face are delimited by septa into the lateral-temporal, middle, and medial cheek compartments (Rohrich & Pessa, 2008). The superficial fat compartments can be further classified as Ghassemi type 1 and Ghassemi type 2 by their differing histological compositions (Ghassemi et al., 2003). *Ghassemi type 1* facial compartments are found in the posterior part of the face and are composed of a meshwork that envelopes lobules of fat cells with viscoelastic properties. They are also characterized by their weak adhesion to the skin layer (Kruglikov et al., 2016; Wollina et al., 2017). *Ghassemi type 2* compartments are located medial to the nasolabial fold and consist of a dense collagen-muscle fiber meshwork (Ghassemi et al., 2003).

The aging process is a complex mechanism that affects the superficial fat compartments primarily by two mechanisms: ptosis or downward migration with additional hypertrophy of the middle cheek compartment and hypotrophy of the lateral cheek compartment (Gosain et al., 2005). Because the rheological parameters of Profhilo® Structura are designed for adipose tissue integration (Cassuto et al., 2023) and the superficial medial and lateral-temporal cheek fat compartments are the first involved in the visible aging process, they make good candidates for treatment with Profhilo® Structura.

### ***What is the Most Suitable Injection Technique for Treating the Preauricular and Zygomatic Areas With Profhilo® Structura?***

The best option to maximize product efficacy and minimize adverse events due to the presence of facial arteries in the preauricular and zygomatic areas is injecting with a cannula and implementing a gentle retrograde injection of the product (Trévidic et al., 2022). In particular, when treating the preauricular area, aesthetic practitioners should avoid the superficial temporal artery, transverse facial artery, and the parotid gland. Cannula injections are preferred because they are less often associated with vascular compromise or occlusion events (Alam et al., 2021; Trévidic et al., 2022). In a retrospective cohort study that included a random sample of 370 board-certified dermatologists reporting on 1.7 million injections, the researchers found that injections using cannulas had 77.1% lower odds of occlusion compared with injections using needles (Alam et al., 2021).

Clinicians should pay crucial attention when selecting the most appropriate cannula size for treating the preauricular and zygomatic areas. Two protocols recommended by the members of the Advisory Board include injection of the preauricular area with 1 mL of Profhilo® Structura or injection of both the preauricular and zygomatic areas with 0.5 mL of Profhilo® Structura in the preauricular area and 0.5 mL in the zygomatic area (see Figure 2).

When injecting the preauricular area with 1 mL of Profhilo® Structura, the entry point should be 2 cm from the tragus using a 22 G × 50 mm cannula to maximize product diffusion and minimize the risk for vascular compromise. Moreover, the 50 mm cannula length will promote optimal distribution of the 1 mL product volume in the preauricular area. When injecting 0.5 mL in the preauricular area and 0.5 mL in the zygomatic area, a single-entry point should be 3 cm from the tragus using a 25 G × 38 mm cannula to maximize product diffusion and minimize the risk for vascular compromise. When using this injection technique, the shorter 38 mm cannula length allows for easier treatment of both the preauricular and zygomatic areas compared with the 50 mm cannula length.

Clinical evaluations have demonstrated that the clinical improvement following treatment with Profhilo® Structura is maintained up to 4 months after the first injection (Cassuto et al., 2023; Sparavigna et al., 2024); therefore, for both protocols, clinicians should administer 2 injections within 30 days, with a follow-up visit recommended at 4 months after the first treatment.

**What are the Anticipated Aesthetic Outcomes After Targeting the Anatomical Region Defined by the Protocol?**

There are several clinical improvements the clinician can anticipate when targeting the preauricular and zygomatic

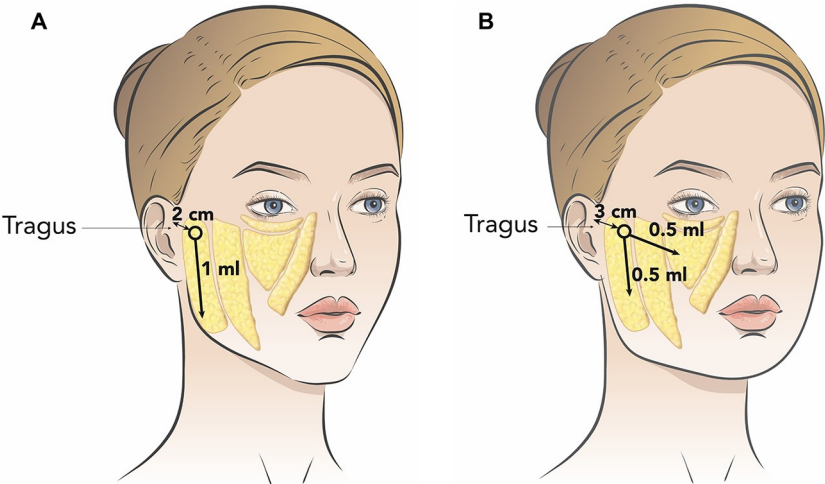
areas with Profhilo® Structura. These include an improvement of structure and support of the interstitial space, generating an increase of tonicity and a lateral tightening effect.

After injection with Profhilo® Structura, the structure and homeostasis of the fat compartment is restored and there is an increase in tissue thickness. This process is identified as *adipose tissue restoration*, a process that improves the age dependent atrophy of fat compartments by giving the interstitial space more structure and support. As a result of this process, the viability and function of the adipocytes is enhanced. The adipose tissue present in the aging preauricular area has specific characteristics that promote a volume deficit. Using Profhilo® Structura makes it possible to restore facial structure, obtain a tightening effect, and achieve a solid structure of the face. The tightening effect is due to the action of Profhilo® Structura on the superficial middle and lateral-temporal cheek fat compartments, which are the first affected by aging.

**Which Patients Should Be Treated with Profhilo® Structura? What is the Link between the Type of Facial Aging and the Protocol Suggested to Maximize Aesthetic Outcome?**

The optimal patient age range for treatment with Profhilo® Structura is 35–55 years. As shown in Figure 1, these patients are either *sinkers* (presenting with initial hypotrophy of lateral-temporal fat compartments within the preauricular area) or *saggers* (presenting with jowl sagging derived from fat repositioning from the middle cheek compartment to the lower third of the face, which also contributes to the loss of zygomatic projections).

Sinkers are the optimal patients for the preauricular injection technique using the *sinkers technique* (ie, injecting 1 mL of Profhilo® Structura using a 22 G × 50 mm



**FIGURE 2.** Injection Sites for Treating Facial Depletion of Adipose Tissue with Profhilo® Structura. A = Preauricular area only (*sinkers technique*). B = Preauricular and zygomatic areas (*saggers technique*). Profhilo® Structura (IBSA Farmaceutici Italia, Lodi, Italy).

cannula to restore the loss of the lateral cheek fat compartment). Saggars are the optimal patients for the *saggers technique* (ie, injecting 0.5 mL preauricular and 0.5 mL zygomatic using a 25 G × 38 mm cannula to obtain a lifting effect that can restore the fat shift within the middle cheek fat compartments). To summarize, patients with fat compartments atrophy, with volume depletion and hollows in the cheek compartments, with tissue ptosis and with laxity of the connective and/or ligamentous structures are the best candidates for treatment with Profilo® Structura.

### **What are the Benefits of Profilo® Structura Compared With Other Treatment Options?**

Various types of injectable treatments are available for treating the preauricular and zygomatic areas including polycaprolactone, poly-L-lactic acid, calcium hydroxyapatite, and calcium hydroxyapatite with HA. These techniques have mechanisms of action that focus on collagen restoration in the dermis, activating fibrotic pathways (Bauer & Graivier, 2011; Christen & Vercesi, 2020; Loghem et al., 2015; Scrima et al., 2022; Yag-Howard & DeNigris, 2021) and are indicated for intradermal injections. Profilo® Structura is the only injectable treatment on the market with the specific indication for adipose tissue restoration.

*Lipofilling* (ie, harvesting and injecting the patient's own fat as a permanent filler) is another technique that can be used for restoring adipose tissue, but it can be time-consuming for both the clinician and the patient. There are also concerns regarding the handling of tissue samples and the general safety of the technique (Huang et al., 2016).

Profilo® Structura is the first and only HA-based injectable product currently available for treating these affected fat compartments that is able to integrate into the adipose tissue and promote adipose tissue restoration.

## **DISCUSSION**

This review documents the insights and clinical findings of the members of the Advisory Board who are key opinion leaders in the field of aesthetic medicine regarding the use of Profilo® Structura to improve age-related changes of the middle face.

Adipose tissue is a major component of facial aging. The aging of facial fat compartments is implicated in the physiological changes that occur across all layers of the facial anatomy (Kruglikov & Scherer, 2017; Wollina et al., 2017). Facial fat is highly compartmentalized; however, changes in the deep fat compartments do not occur simultaneously with changes in the superficial fat compartments (Swift et al., 2021). The deep fat compartments are firmly attached to the underlying bone, providing support (Kahn & Shaw, 2010; Swift et al., 2021; Wan et al., 2013). The superficial fat compartments are more

mobile, and may reposition over time because of changes in the underlying bone structure and weakened ligaments due to the effects of gravity, also causing displacement of the overlying skin envelope (Swift et al., 2021).

The medial and lateral-temporal cheek fat compartments are often the first to be implicated in facial age-related changes, resulting in 1 of 2 predominant appearances: hollow or sunken cheeks (ie, sinkers), or drooping and bulging tissue (ie, saggars) (Swift et al., 2021).

Profilo® Structura is a new medical product that uses the patented NAHYCO™ technology to create hybrid cooperative complexes consisting of 45 mg of H-HA and 45 mg of L-HA. Profilo® Structura is the first and only HA-based injectable treatment currently available that can integrate into the adipose tissue of these superficial fat compartments, and lead to adipose tissue restoration (Cassuto et al., 2023; Stellavato et al., 2016).

Aesthetic clinicians using Profilo® Structura should possess a comprehensive anatomical knowledge of the face and should understand the optimal protocol and injection technique, as well as the composition and concentration of HA-based products (Galadari & Weinkle, 2022; Trévidic et al., 2022). Compared with cross-linked HA formulations, Profilo® Structura has a lower viscosity, but a similar durability profile (Cassuto et al., 2023; Scrima et al., 2022).

In this paper, the authors recommend two separate protocols for treating preauricular and zygomatic areas. Clinicians should inject patients described as sinkers with 1 mL of Profilo® Structura in the preauricular area and patients described as saggars with 0.5 mL of Profilo® Structura in the preauricular area and 0.5 mL in the zygomatic area. Based on previous algorithms to minimize vascular injury, the entry point for the preauricular area should be 2 cm from the tragus using a 22 G × 50 mm cannula. The single-entry point for the preauricular and zygomatic areas should be 3 cm from the tragus using a 25 G × 38 mm cannula (Trévidic et al., 2022).

Researchers with recent clinical experience treating the midfacial fat compartments with Profilo® Structura have reported good efficacy and safety profiles (Cassuto et al., 2023, 2020; Sparavigna et al., 2024). In a recent retrospective case series, Cassuto et al. (2023) found that 6 months after injection with Profilo® Structura, the participants had a persistent improvement in the middle and lower-third of the face, with the large majority of patients reporting an improvement 3 months after the initial treatment. Instrumental evaluations also recorded a significant increase in the tissue thickness (+ 23%) and fat hyperchoic areas, and importantly, there were no adverse events. The observed improvements may be due to the unique composition of Profilo® Structura that includes hybrid cooperative complexes, which have been shown

to support adipocyte stem cell viability (Stellavato et al., 2017). Cross-linked versions of HA dermal fillers have a lower in vitro biological activity; therefore, their effects on facial bioremodelling are questionable (Cassuto et al., 2023; Stellavato et al., 2017; Sundaram & Cassuto, 2013). Other types of injectable treatments follow different biological pathways, such as restoring collagen in the dermis or activating fibrotic pathways (Bauer & Graivier, 2011; Christen & Vercesi, 2020; Loghem et al., 2015; Scrima et al., 2022; Yag-Howard & DeNigris, 2021).

Lipotransfer techniques can be improved by the addition of adipose stem cells, which have been shown to improve fat cell survival (Huang et al., 2016; Shen et al., 2023). However, there are limited studies on the efficacy and safety of facial lipotransfer, the majority of which are small observational studies (Shen et al., 2023).

Future research should focus on larger clinical trials assessing the efficacy, safety, and biological activity of Profill® Structura to treat the middle and lateral-temporal cheek fat compartments. A larger group of key opinion leaders and experts in the field should also be interviewed to disclose their experiences using Profill® Structura in clinical practice after following these recommendations.

In conclusion, this review has outlined the specific injection sites that will provide the most benefit for treating aging adipose tissue in the preauricular and zygomatic areas with Profill® Structura. Due to their early involvement in facial aging, these areas should be a target in facial skin rejuvenation.

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