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Smart Dual System - A novel approach for redensification and volumization of face with PEGDE cross-linked hyaluronic acid fillers

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Abstract

Since the late 1990s, hyaluronic acid-based soft tissue fillers have become the preferred choice for tissue augmentation due to their favorable safety profile and minimally invasive nature. Their popularity has surged over the past two decades, accompanied by a broader range of available fillers and an expanding array of aesthetic procedures they support. This growth reflects increasing accessibility and patient awareness, making HA filler treatments among the most common cosmetic procedures globally. The evolution of these fillers has focused on enhancing both safety and effectiveness. A significant advancement is the introduction of hyaluronic acid cross-linked with Poly (Ethylene Glycol) Diglycidyl Ether (PEGDE), which promises improved performance and safety for facial volumization and redefinition.

The article presents the Smart Dual System (SDS), an innovative approach to aesthetic medicine built around this advanced PEGDE-cross-linked HA filler. It outlines a structured methodology for using these products effectively and safely. The SDS is based on comprehensive anatomical and technological knowledge related to the products used, as well as a tailored approach to each patient's needs. We provide a detailed overview of this innovative system, including its principles, results, effectiveness, safety, and the advantages of this approach. This System aims to offer a guideline for maximizing both effectiveness and safety, reflecting a patient-oriented approach.

Introduction

Skin sagging is one of the most noticeable indicators of aging, typically beginning to appear on the face in the third decade of life [1]. Nowadays, minimally invasive non-surgical procedures to prevent or treat such conditions are highly sought after due to their better acceptance and tolerance. These treatments effectively reduce facial wrinkles and enhance facial volume and contours. Specifically, the injection of dermal fillers into or beneath the skin results in immediate rejuvenation and aesthetic improvements. When properly administered, dermal fillers provide excellent clinical outcomes with little to no downtime [2,3]. Changes in the volume of soft tissues and bones play a significant role in altering facial appearance as we age. The reduction in bone density and soft tissue thickness, along with the redistribution of fat and the loss of skin elasticity, leads to the formation of wrinkles and folds characteristic of aging. In the mid-face, this results in flattening and furrowing of the central mid-cheek area, causing a pronounced deepening of the nasolabial folds [4].

Today, there are more treatment options available due to the development of soft tissue fillers and advancements in injection techniques. Initially, dermal fillers were used to enhance skin tone, firmness, and texture by managing surface lines and wrinkles. Later, they were also employed to address volume deficits

through subcutaneous and deep injections, using a wide array of specifically designed products [5,6]. Furthermore, as patients have reported enhanced psychosocial well-being as a result of these treatments, many techniques have been refined in recent years to restore facial volume and improve the appearance of the skin, even scars [7-11].

Such procedures include dermal fillers, autologous fat grafts, lasers, and dermabrasion. Hyaluronic Acid (HA) fillers, among the newest types of dermal fillers, are currently regarded as the "gold standard" due to their ideal properties. HA is a naturally occurring biopolymer found in the extracellular matrix of soft connective tissues, the skin dermis, the vitreous body of the eye, hyaline cartilage, synovial joint fluid, the nucleus of intervertebral discs, and the umbilical cord. During cross-linking, HA interacts with a cross-linking agent, forming covalent bonds between HA chains. This chemical cross-linking is crucial for extending HA's longevity in the dermis [12].

HA is available commercially in various pharmaceutical forms, including nanoparticles, nanocomplexes, matrices, and hydrogels [13]. The chemical and biochemical characterization of hydrogels has been conducted for several purposes, such as safety assessment, quality assurance, and understanding hydrogel properties like rheology, degradation, and suitability for specific applications [14,15]. The cross-linking parameters are particularly important as they significantly influence the rheological and swelling properties of hydrogels, which are critical for their clinical use [16].

Hyaluronic acid soft tissue fillers

Hyaluronic Acid (HA) fillers are the most commonly used worldwide due to their effective results, high biocompatibility, and excellent safety profile [17,18]. The first HA-based filler was introduced in Europe in 1996, and it received FDA approval in the United States in 2003. Nowadays, treatments in aesthetic medicine utilizing both cross-linked and non-cross-linked hyaluronic acid are among the most popular procedures. Soft tissue fillers are the primary materials employed in aesthetic medicine to counteract soft tissue atrophy in the face and other body areas. HA is available in gel form, with products varying widely in density, rheological properties, and concentration. This diversity allows for optimal product selection based on the specific application, the anatomical area being treated, the application depth, the technique used by the physician, and the individual patient's needs.

The effect of hyaluronic acid can be extended through the cross-linking process. Cross-linking HA fillers involves forming covalent bonds between HA chains and a cross-linking agent, creating a three-dimensional structure. This process improves the physicochemical properties of HA while maintaining the biocompatibility and biological activity of the resulting soft tissue filler [19]. HA fillers are distinguished by HA chains linked together by a cross-linker agent. The most common cross-linking agents used in producing soft tissue fillers include Butanediol Diglycidyl Ether (BDDE), 1,8-Diepoxyoctane (DEO), Divinyl Sulfone (DVS), and Polyethylene Glycol Diglycidyl Ether (PEGDE). The cross-linking technologies vary by manufacturer, differing in the degree of cross-linking, the amount of cross-linking agent used, and the concentration of HA. These modifications significantly affect the rheological properties of the resulting gels, influencing the aesthetic outcome [20]. The latest innovation in HA production and cross-linking is the use of Polyethylene Glycol (PEG) polymer. PEG offers significant benefits in terms of safety and performance. Both PEG and HA are polymers, and their cross-linking forms matrices with a scaffolding structure similar to a three-dimensional network, ensuring better filler integration with the tissue [21-23]. Cross-linking with PEG results in a soft tissue filler with excellent rheological properties, such as cohesivity, viscoelasticity, and plasticity, optimizing adaptation and integration with anatomical structures [15,16,24].

Within all the pegylated filler options for use in soft tissues, there is a wide range of indications and treatments that are performed in the clinical practice of aesthetic medicine, however, to date, there is no systematic methodology described for its application.

Here, we reported the effectiveness, safety and patient satisfaction, with the use of a novel application system developed by the author, working with PEGylated hyaluronic acid fillers and rejuvenation protocols.

Material and methods

The concept of the Smart Dual System is an innovative approach to addressing the aging process of the face. It is a holistic method for facial harmonization and rejuvenation. This offers the possibility of enhancing aesthetic outcomes for virtually every patient, regardless of gender or age. It enables counteracting the first signs of aging as well as mitigating more advanced symptoms. When performing the procedures, we take an individualized approach to each patient, focusing on restoring age-related volume loss, deeply hydrating skin, and redensification, which means restoring the density of the skin in each of its layers. Our goal is to reach a synergistic approach to the patient, tailoring techniques and products to the overall appearance, needs, and expectations of the patient, as well as considering anatomical limitations. We strive for maximum personalization of the procedure, in line with the patient's understanding and perception of beauty. We use minimal amounts of hyaluronic acid-based products to maintain a natural, non-exaggerated facial appearance and improving the safety of the procedure and reducing the risk of adverse events. This approach to aesthetic medicine procedures, combining standardized techniques, treatment plans, and understanding of the technology, ensures repeatable results while maintaining a high safety profile. The presented proprietary Smart Dual System is a method of comprehensively addressing all layers of facial tissues, from deep to superficial (Table 1).

Table 1: 5 stages of smart dual system.

1	2	3	4	5
Structure	Redensification	Focal Regions	Skin Regeneration	Synergy
Focus on bone structures	Restoring age-related volume loss	Areas that are critical for each patient	Restoring the homeostasis of all skin layers	Combined protocols

Regardless of the patient, we must always pay attention to:

1. The bone structure of the face and its changes related to the aging process.
2. Restoring age-related volume loss and improving the density and tension of soft tissues, by a redensification effect.
3. Areas that are critical for each patient, which require a special approach, such as the nose, lips, and periorbital area.
4. Restoring the homeostasis of all the skin layers through appropriate hydration, renewal, and regeneration.
5. Applying combined protocols that can integrate different technologies, such as HA with Infra-Red (IR), Radio Frequency (RF), or lasers.

Following stages 1-5, in the prescribed order, standardizes and simplifies facial treatments while maintaining an individualized approach to the patient. Each of the stages is composed of an specific number of steps, which correspond to a sequence of key anatomical areas, focal regions or layer of the skin, that will be a guideline to perform the application of the fillers and will help to potentiate and improve the results. These steps can be performed or skipped depending on the requirements of each patient, the injector must individually plan the treatment areas, identify anatomical structures, and select appropriate products based on their physicochemical properties and the final effect (e.g., PEGDE-crosslinked hyaluronic acid). It is important to adjust the treatment technique and consider possible scenarios related to potential complications. Standardization and a holistic approach significantly impact for a better aesthetic outcome, beside the possibility of using a smaller number of products and less volume of injections. At the end of the process, on stage five, we are going to be able to assess the results and, in consultation with the patient, decide on the use of combined therapies, such as combining hyaluronic acid with IR, laser, or RF. This approach ensures a synergistic treatment and can enhance the therapeutic effects [25,26].

Hyaluronic acid filler used in Smart Dual System

The product we used contains HA crosslinked with PEGDE, with glycine and L-proline (Matex Lab S.A., Geneva, Switzerland):

- Neauvia Intense 28 mg/ml
- Neauvia Intense LV 26 mg/ml
- Neauvia Intense Flux 26 mg/ml
- Neauvia Intense Rheology 22 mg/ml
- Neauvia Intense Lips 24 mg/ml
- Neauvia Stimulate 26 mg/ml + 1% CaHA
- Neauvia Stimulate Man 28 mg/ml + 1% CaHA
- Neauvia Hydro Deluxe 18 mg/ml + 0,01% CaHA (not crosslinked product)

PEGDE- HA seems to offer considerable advantages in the field of fillers for aesthetic use, both in terms of safety and efficacy, patient and doctor satisfaction. This filler was also described in the literature in aesthetic procedures, where it demonstrated effectiveness and a high safety profile [14,15,24,26]. A very important and particularly useful feature of PEGDE-HA for us was the increased resistance of the filler to thermal and mechanical stress. This allows us to safely combine such crosslinked fillers with heat-emitting devices, even in the same treatment session, working synergistically to enhance the achieved effect [26].

Rheological characterization of hyaluronic acid hydrogels

Rheological characterization of HA hydrogels shows that their viscoelastic behaviour significantly impacts their performance in skin treatments. The following key parameters were evaluated for HA hydrogels:

- **Storage modulus (G')**: Represents the stiffness of the gel, contributing to its ability to resist deformation from skin tension and facial movements.
- **Loss modulus (G'')**: Measures the viscous behaviour of the gel.
- **Tangent phase angle (tan δ)**: This ratio describes the balance between the elastic and viscous properties of the gel.
- **Complex modulus (G*)**: Reflects the overall viscoelasticity of the gel.
- **Complex viscosity (η)**: Indicates the gel's capacity to flow from the needle, with the parameter decreasing as shear strain increases beyond the Linear Viscoelastic Region (LVER).

These seven HA hydrogels demonstrated varying abilities to return to their original shape ("spring back") and resist deformation, which is crucial in maintaining natural contours, particularly in areas prone to facial movements like the jowls or nasolabial folds [16].

Below is a table showing the rheological properties of different HA hydrogels obtained at a fixed shear strain (1%) and temperature (25°C) in their Linear Viscoelastic Region (LVER):

Table 2: Rheological properties of pegylated fillers.

Product	G´ (Pa)	G´´ (Pa)	G* (Pa)	tan δ	η* (Pa s)
HA hydrogel 22 mg/mL	84.05±2.12	27.13±1.14	88.32±2.15	0.32±0.01	14.05±0.34
HA hydrogel 24 mg/mL	82.34±3.72	31.92±1.49	88.32±3.8	0.39±0.02	14.05±0.06
HA hydrogel 26 mg/mL LR	38.90±8.66	27.96±3.90	47.13±9.74	0.73±0.06	7.62±1.48
HA hydrogel 26 mg/mL LV	91.42±4.84	38.86±2.57	99.34±5.44	0.42±0.01	15.81±0.87
HA hydrogel 26 mg/mL with CaHA	164.67±2.94	55.84±5.07	173.93±4.37	0.34±0.03	27.67±0.70
HA hydrogel 28 mg/mL	172.83±3.02	62.63±5.97	183.83±4.72	0.36±0.03	29.26±0.75
HA non cross-linked hydrogel 18 mg/mL	3.80±0.57	13.09±0.54	13.64±0.60	3.50±0.52	2.17±0.09

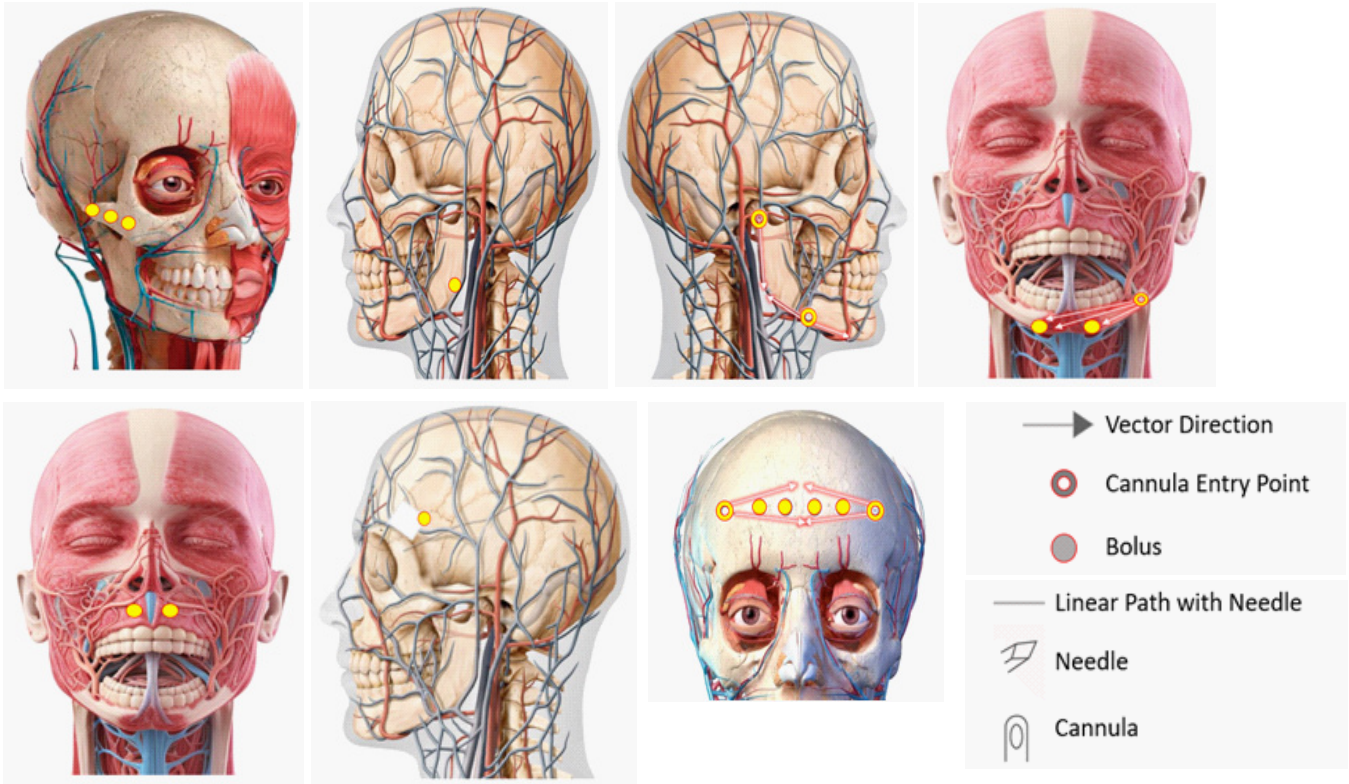


Figure 1: Stage 1–Technique visualization - The areas assessed include: zygomatic arch, Lower Maxilla (mandibular angle, mandibular ramus and chin), canine fossa, temporal fossa, frontal bone. The following are marked on the photos: entry points, bolus, vectors, linear paths with needle.

Table 3: Summary of Stage 1 steps.

Stage 1 steps:		Injection Plane	Injection Device	Product	Injection Technique	Volume	Important Anatomical Structure	Risk
1 . Zygomatic arch		Supraperiosteal	Needle 27G or 25G Cannula 22G	Neauvia Intense Neauvia Intense LV	3-5 boluses	0.05-0.06 ml	Zygomaticofacial artery	Moderate
	Mandibular Angle	Supraperiosteal or SCT (Subcutaneous Cellular Tissue)	Needle 27G or 25G Cannula 22G	Neauvia Intense Neauvia Intense LV Neauvia Stimulate Man	1-2 boluses	0.1-0.3 ml	Courses of Facial Artery	High
2. Lower Maxilla	Mandibular Ramus	Supraperiosteal or Deep Dermis	Cannula 22G	Neauvia Intense Neauvia Intense LV Neauvia Stimulate Neauvia Stimulate Man	Vectors	0.1-0.5 ml	Courses of Facial Artery	High
	Chin	Supraperiosteal or Deep Dermis	Needle 27G or 25G Cannula 22G	Neauvia Intense Neauvia Intense LV Neauvia Stimulate Neauvia Stimulate Man	Boluses or Vectors	0.1-0.5 ml	Mental Artery	High
3. Canine Fossa		Supraperiosteal	Needle 27G or 25G Cannula 22G	Neauvia Intense Neauvia Intense LV	1 bolus	0.1-0.3 ml	Facial and Angular Artery	Very high
4. Temporal Fossa		Supraperiosteal (When we treat structure)	Needle 27G or 25G Cannula 22G	Neauvia Intense Neauvia Intense LV	1 boluses	0.1-0.3 ml	Temporal Arteries	Very high
5. Frontal Bone		Supraperiosteal	Needle 27G or 25G Cannula 22G	Neauvia Intense Flux	4-5 boluses or vectors	0.1-0.06 ml	Supraorbital and Supratrochlear Arteries	Very high

SMART DUAL SYSTEM - STAGE 1 – STRUCTURE

The first stage of the Smart Dual System focuses on assessing the impact of bone resorption and poor projection of key cranial structures that affect the support of soft tissues. The areas assessed include: Zygomatic arch, mandibular angle, mandibular ramus, chin, canine fossa, temporal fossa, frontal bone (Table 3, Figure 1).

The treatment of bone structures will depend on whether a deficiency is observed during the clinical evaluation. It is important to emphasize that the bone structures addressed in this sequence have the greatest impact on facial restructuring due to the anatomical support they provide to soft tissues. Although treating the temporal fossa initially can be effective and is supported by clinical evidence [27], it often requires a larger injection volume. Therefore, it is recommended to use this as a fourth step, aiming to achieve excellent results with minimal syringe use. The choice between using a cannula or needle will vary based on the injector's technique and the anatomical structures at risk.

Ideal products for this stage

Neauvia stimulate man and neauvia intense: These products are ideal due to their high hyaluronic acid concentrations

(28 mg/ml), excellent cohesiveness, and balanced viscoelastic properties, which allow for effective projection.

Neauvia stimulate: Preferred for its combination of hyaluronic acid and spherical calcium hydroxyapatite microspheres, supporting tissue homeostasis and versatile application.

Neauvia intense LV and intense flux: Suitable alternatives, especially for patients with thin superficial tissues or severe photodamage, where over-projection is not desired.

Treatment steps

1. Zygomatic arch: Treat the zygomatic arch, composed of the temporal and zygomatic bones. Apply product from lateral to medial, pulling the tissue as the product is injected to support facial ligamentous structures. Adjust the number of application points or boluses based on the patient's needs. If noticeable superficial volume occurs, press the product against the bone to shape it.

2. Lower maxilla: Begin treatment at the mandibular angle. Evaluate the area due to varying definition and projection among patients. Avoid supraperiosteal application if shear forces from the platysma muscle are evident. This is important because the product will not be able to provide adequate projection in these patients and much larger volumes would be required, instead, use subdermal application through a cannula for a more visible and prolonged result. Avoid injecting in areas like the jowl to prevent increased weight and consider the mandibular notch as a reference point for the facial artery. For the chin, use small volumes at various injection points, always evaluating the response of the tissue to minimize risk, particularly due to the mental vascular-nervous bundle.

3. Piriform fossa: Address the piriformis fossa to improve its anterior projection, which directly affects the nasolabial fold. Apply product medial to the sulcus to reduce the risk of facial artery location and avoid large volumes at a single point.

4. Temporal fossa: Ensure correct plane of application. Palpate the superficial temporal artery, particularly its frontal branch. For deeper applications, ensure product placement is supraperiosteal and avoid caudal boluses that might migrate through the buccal fat pad. For superficial or interfacial application, use small volumes and avoid altering the contour.

5. Frontal bone: Aim to restore the convex shape of the frontal bone, which flattens with aging. Due to the high vascular risk, avoid direct needle application at the supraperiosteal level; instead, try to perform a very conservative treatment in this area or skip it altogether. If using a cannula, inject perpendicular to arterial structures. Neauvia Intense Flux is ideal for this area due to its high hyaluronic acid concentration, fluid consistency, and high cohesiveness, which prevents migration and ensures even distribution.

It is possible to combine the techniques with ultrasound support if the injector considers necessary.

SMART DUAL SYSTEM- STAGE 2- REDENSIFICATION

The second stage of the Smart Dual System focuses on restoring age-related volume loss and improving the density and tension of soft tissues (Table 4) (Figures 2 & 3).

The areas addressed include: temporal fossa, malar region, nasolabial fold, marionette lines.

Figure 2: Stage 2-Technique visualisation.

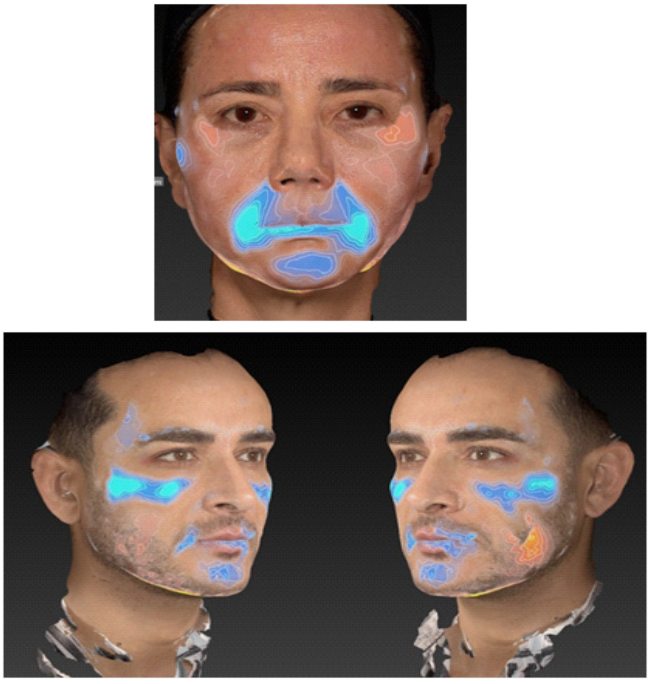


Figure 3: Stage 2-technique visualisation, outcomes.

The ideal products for this stage of tissue redensification are Neauvia Stimulate, Intense LV, and Intense Flux. Neauvia Stimulate is preferred for all stages due to its combination of hyaluronic acid and spherical microspheres of calcium hydroxyapatite in small concentrations. This combination facilitates tissue homeostasis and allows for versatile application in vectors, boluses, or microboluses across multiple facial areas, ensuring safe integration into the tissue. Neauvia Intense LV, with its appropriate rheology, can also be used in these areas to mimic superficial or deep fat pads. Neauvia Intense Flux is a good option if a more subtle volumization of the treatment areas is desired.

Table 4: Summary of stage 2 steps.

Stage 2 steps	Injection plane	Injection device	Product	Injection Technique	Volume	Important anatomical structure	Risk
1. Temporal fossa	Supraperiosteal Intrafascial	Cannula 22G	Neauvia Intense LV Neauvia Intense Flux Neauvia Stimulate	micro boluses vectors	0,02-0,04 mlx vector	Temporal arteries	Medium
2. Malar region	Subcutaneous Supraperiosteal	Cannula 22G	Neauvia Intense LV Neauvia Intense Flux Neauvia Stimulate	micro boluses vectors	0,02-0,04 ml x e tor	Infraorbital artery	Medium
3. Nasolabial fold	Deep Dermis Subdermal	Cannula 22G	Neauvia Intense LV Neauvia Intense Flux Neauvia Stimulate	micro boluses vectors	0.02-0.04 ml) vector	Angular facial artery	High
4. Marionette lines	Deep Dermis Subdermal	Cannula 22G	Neauvia Intense LV Neauvia Intense Flux Neauvia Stimulate	micro boluses vectors	0.02-0.04 ml) vector	Facial artery Mental artery	Medium

Treatment steps

Temporal fossa: Tempo lateral cheekfat and retro orbicularis oculi fat

The temporal fossa should be addressed first when aiming to redensify the tissue. If, after conducting a structuring evaluation in the previous stage, loss of volume is evident in structures such as the Lateral Temporal Cheek Fat and the Retro Orbicularis Oculi Fat (ROOF), Neauvia Stimulate, Intense LV, or Intense Flux can be used to replenish these areas and achieve the desired aesthetic effect. Neauvia Stimulate is ideal due to its hyaluronic acid and calcium hydroxyapatite microspheres, which support tissue homeostasis and versatile application. Intense LV may also be used for mimicking fat pads, and Intense Flux is suitable for subtle volumization.

Malar region

The next step is to address the malar region, focusing on both superficial and deep tissues. Given the impact of fatty pads and face ligaments on the aging process, it is crucial to recognize the high-risk nature of this area due to the proximity of the infraorbital artery and the ocular retaining ligament, above which no application should be made. If the intention is to simulate deep or superficial fat pads, Neauvia Stimulate or Neauvia Intense LV would be the ideal options, but, to reduce the transition between the lower eyelid and the malar region, Neauvia Intense Flux in small quantities is a good option due to its moulding capability and low hygroscopicity, which minimizes subsequent edema, which is one of the most frequent complications in this area and where detailed knowledge of the rheology of the products is essential [28].

Nasolabial folds

For the nasolabial folds, treatment can be performed at different planes, with the possibility of slight subcision using a cannula to reduce depth and enhance redensification. Neauvia Stimulate, Intense LV, or Intense Flux are good options, but the choice will depend on the tissue quality and the volume that needs to be replaced.

Marionette lines

Finally, for marionette lines, a lateral approach with a cannula is recommended. This technique helps release important adhesions between the skin and the depressor anguli oris muscle, allowing for long-term myomodulation. As this area tends to have more skin damage due to chronic tissue movement, Neauvia Stimulate would be the best option.

SMART DUAL SYSTEM- STAGE 3- CRITICAL FOCUS AREAS

The third stage focuses on areas that are critical for each patient and require a special approach, such as the nose, lips, and periorbital area (Table 3), (Figure 5).

Figure 4: Stage 3-Technique visualisation.

Table 5: Summary of stage 3 steps.

Stage 3 steps	Injection plane	Injection device	Product	Injection Technique	Volume	Important anatomical structure	Risk
1. Tear trough	Supraperiosteal	Cannula 22-25G	Neauvia Intense Flux Neauvia Intense Rheology	micro boluses and or vectors	0,1-0,3 ml bolus	Infraorbital artery	Medium Infraorbital artery
2. Nose	Supraperiosteal	Cannula 22G	Neauvia Intense Neauvia Intense LV	micro boluses vectors	0,1-0,5 ml	Nasal dorsal artery and columella artery	Very high
3. Lips	Supeficial	Needle 27G cannula 25G	Neauvia Intense Lips Neauvia Intense Flux Neauvia Intense Rheology	micro boluses vectors, lines	0.1-1ml	Superior and inferior labial artery	High

Tear trough: Treatment will be approached only if the desired aesthetic result has not been achieved with previous stages. This is typically due to significant resorption of the orbital rim or congenital factors. In such cases, using a controlled concentration of hyaluronic acid, such as Neauvia Intense Rheology or Neauvia Intense Flux, is a good option, preferably applied in deep planes (supraperiosteum). It is important to assess that patients who tend to retain fluids are not ideal for this type of treatment. Additionally, a thorough understanding of the area's anatomy is essential to avoid adverse effects.

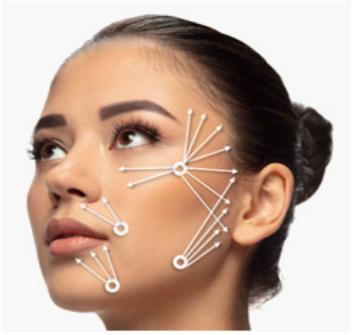
Nose: Various aesthetic enhancements can be achieved with hyaluronic acid, such as lifting the tip, projecting it, supporting the nasal wings, refining the dorsum, and even supporting the columella. However, this is a very high-risk area, which is why many practitioners prefer not to treat it. If treatment is desired, it is recommended to use ultrasound to assess vascular structures and determine precise application areas. A cannula is preferred for slow injection of small volumes. Ideal products for this region include Neauvia Intense and Neauvia Intense LV, due to their support, projection, and cohesiveness, ensuring a natural and long-lasting result without migration or edema.

Lips: This is one of the most popular procedures worldwide, but it is also high-risk. Anatomical studies indicate that the major vascular pathways (upper and lower labial artery) are usually within 2 mm of the skin surface. Thus, techniques involving superficial pillars and the use of a cannula have replaced deep injections or large boluses. The ideal product for this region is Neauvia Intense Lips, designed for superficial application with high performance, making low-volume application effective. Neauvia Intense Flux can also be used for hydration or Neauvia Intense Rheology for profiling.

SMART DUAL SYSTEM- STAGE 4- SKIN REGENERATION AND HOMEOSTASIS

The task of the fourth stage of the Smart Dual System is restoring the homeostasis of the skin layers (both deep and superficial) through appropriate hydration, renewal, and regeneration (Table 6), (Figures 5,6).

In this stage, our focus will be on enhancing and maintaining skin homeostasis.



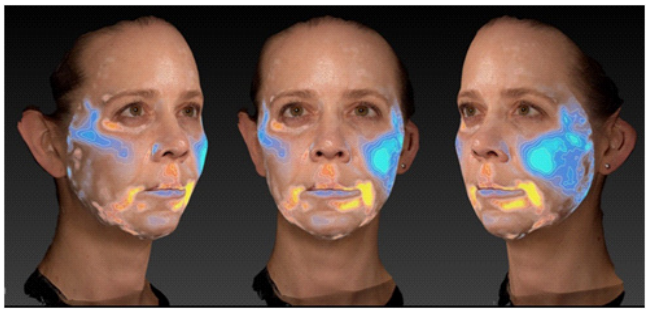
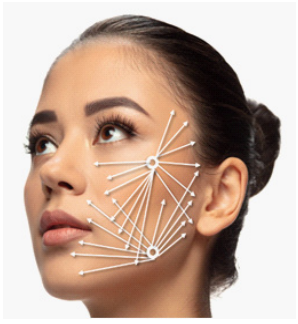


Figure 5: Deep Skin Layers – Techniquevisualisation, outcomes.



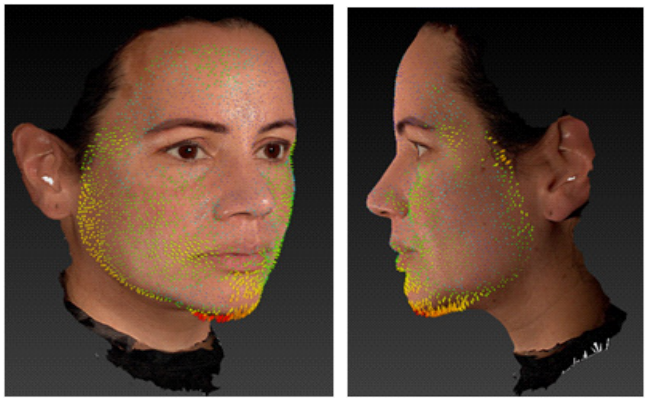


Figure 6: Superfitial skin layers – Techniquevisualisation, outcomes.

Table 6: Summary of stage 4 steps.

Stage 4 steps	Injection plane	Injection device	Product	Injection Technique	Volume	Risk
1. Skin deep layers	Deep dermis Subdermal	Cannula 22G	Neauvia Stimulate Neauvia Stimulate Man	vectors	0.02-0.06 mlx vector	Medium
2. Skin superficial layers	Dermis-epidermis junction Superficial dermis	Needle 30G cannula 25G	Neauvia Hydro Deluxe	papules vectors and papules	0,02-0,06 mlx vector	Medium

Deep skin layers: small quantities of Neauvia Stimulate or Neauvia Stimulate Man, distributed over a significant area using a vector technique, are recommended This method will provide a subtle volume replacement and lifting effect in the treated regions. Over the following months, this will restore tissue homeostasis and rejuvenate skin characteristics lost due to photoaging. Care should be taken when applying the product to heavier facial areas such as the jowls or nasolabial folds, as these regions might become accentuated due to the product's rheological properties. It is recommended to be careful with the volumes injected into the vectors, in order to ensure that the paths do not become visible.

Superficial skin layers: This step focuses on deep hydration in addition to homeostasis. will use needle mesotherapy to treat the entire face with 2.5 ml of a non-cross-linked hyaluronic acid solution (Neauvia Hydro Deluxe). This solution contains 18 mg/ml of hyaluronic acid, 0.01% Calcium Hydroxyapatite (CaHA) microspheres, glycine, and L-proline. The procedure involves multiple intradermal or subcutaneous injections, administering a total of 2.5 ml of the non-cross-linked HA using a 30G needle (or a 25G cannula) and an ampoule-syringe

SMART DUAL SYSTEM- STAGE 5- SYNERGY

Synergy, combination of different technology at the same time or session, without causing damage to the tissue, is a new approach to the aesthetic medicine. Instead of treating fillers, devices and cosmeceuticals as separate, independent factors, combination between PEGylated HA and IR or bipolar RF has been scientifically proven their ability to interact with one another on the basis of a holistic concept, identifying combinations that may act more effectively than a single treatment [25,26]. It has been proven that patients treated with combination therapy obtain better results than those treated with the stand-alone approach (Table 7).

This result translates into greater satisfaction for both the patient and the physician. It also supports the relationship between the patient and the doctor, in which the doctor is always perceived as a true "beauty partner" whom patients can turn to for ongoing consultation regarding self-care.

Table 7: Summary of stage 5 steps.

Stage 5 steps:	Technologies
1. Smart combination therapy	Near infrared technology bipolar radiofrecuency, Laser non ablative 1470 nm

Discussion & conclusion

Beauty, attractiveness, body perception, and the management of aging effects are multifaceted and influenced by various perspectives, including gender and ethnicity [29]. In this study, we introduced a pioneering approach using hyaluronic acid cross-linked with PEGDE, which involves two polymers to create a 3D molecular scaffold. It enhances tissue integration and provides a durable filling effect. The cross-linking with PEGDE offers improved resistance to thermal and mechanical stresses [26,30]. Published data indicate that the HA-PEGDE fillers are safe, showing no signs of immune system activation or adverse effects. The PEG properties, including hydrophilicity, non-toxicity, and non-immunogenicity, are transferred to the filler through PEGylation, offering added protection against unwanted immune reactions [26,31]. The filler integrates smoothly with anatomical structures and displays excellent rheological properties such as cohesion, viscoelasticity, and plasticity. It maintains its shape over time, delivering a satisfactory aesthetic outcome. A key advantage of PEGylation is its effect on thermal resistance, enabling the use of PEGDE-cross-linked fillers with heat-emitting devices like IR, RF, or lasers. Combining these therapies in a single session not only enhances the visual effect through synergistic action but also reduces treatment time and the number of sessions required [25,26]. The synergy between infrared energy-based treatments and PEGDE-cross-linked hyaluronic acid has shown beneficial skin changes, supported by histological, immunological, and biomechanical evaluations. This combined therapy significantly improves skin elasticity and hydration in both short and long term. After 150 days, skin elasticity increased by 72% and hydration by 49% (with interim increases of 60% in elasticity and 45% in hydration after 21 days). These improvements are highly desirable for both patients and practitioners [26]. The expanding market for aesthetic medicine and increasing demand for appearance-enhancing treatments necessitate new protocols and techniques.

Our discussion highlights the Smart Dual System, which represents a novel approach for PEGylated products. Unlike previous systems, which primarily utilized BDDE-based products and lacked synergistic effects due to their inherent properties, this system offers a new guideline for safely injecting PEGylated products. It serves as a valuable resource for both new and experienced practitioners in the Neauvia portfolio, outlining how to inject safely, the appropriate products for specific areas, recommended volumes, and particular considerations for these technologies. This is made possible by the unique characteristics of Neauvia injectable products and energy-based devices, supported by clinical evidence demonstrating their safety, effectiveness, thermostability, and compatibility with other therapies. The Smart Dual System and PEGDE-cross-linked product have proven effective and safe, yielding high patient satisfaction with significant improvements in facial proportions. The results were achieved using less product compared to other market options, delivering a natural effect that met both patient and physician expectations.

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