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Safety and Performance of RHA4 in the Midface Using the Multilayering Technique: Preclinical and Clinical Evidence

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Background: Resilient hyaluronic acid (RHA) fillers are used to treat dynamic wrinkles or provide tissue lifting in facial aesthetics. This study explored the biological, biomechanical, and clinical safety and performance of RHA4, a volumizing hyaluronic acid filler tailored for tissue support in dynamic facial areas, upon interaction with human subcutaneous adipose tissue (AT).

Methods: RHA4 underwent cytocompatibility testing with human fibroblasts and adipose stem cells. A 1-year rat in vivo implantation study tracked tissue integration, local effects, and filler degradation. Biomechanical tests assessed RHA4's impact on subcutaneous AT mechanics. Clinical outcomes, safety, injection volumes, and techniques were evaluated in 35 patients, treated in midface deep and superficial fat compartments via a multilayering methodology. Dynamic outcomes and 2-year follow-up of RHA4 in the midface using multilayer treatments were described.

Results: RHA4 demonstrated excellent biocompatibility and tissue integration both in vitro and in vivo, exhibiting minimal local inflammation and rapid collagen bundle formation within the filler. It integrated gradually over time and was well tolerated, allowing for increased extracellular matrix presence, neovascularization, denser collagen deposition, and AT growth. Ex vivo, RHA4 did not impede fat motion biomechanics but visibly lifted the tissue. Clinically, RHA4 proved safe and effective for lifting both deep and superficial fat compartments in the midface without affecting facial expressiveness.

Conclusions: Preclinical and clinical evidence confirmed that RHA4 is a versatile filler capable of lifting tissue efficiently, whether deep or superficial, particularly through the multilayering treatment approach. Importantly, RHA4 preserves AT biomechanics, adapts to the dynamism of the face, and ensures natural-looking outcomes.
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INTRODUCTION

Minimally invasive techniques for addressing age-related facial imperfections have become commonplace, with hyaluronic acid (HA)–based soft-tissue fillers used for nonsurgical aesthetic procedures now accounting for approximately 80% of all fillers used for rejuvenation and volume replenishment.[1] In recent years, the usability of these products has significantly progressed due to a better comprehension of facial anatomy and the development of a broad portfolio of products with a wide range of rheological properties.[2,3] HA fillers boast low complication rates, commendable durability, cost-effectiveness, and the capability for reversibility through hyaluronidase injection.[4–6] Resilient hyaluronic acid (RHA) 4 (Teoxane SA, Geneva, Switzerland) manufactured using preserved network technology (PNT)[3,4,7] is a 23 mg/mL cross-linked HA-based filler containing 0.3% (wt/wt) lidocaine or mepivacaine.

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It is provided in a 1.2-mL short syringe format designed to provide precision and ease of handling for practitioners. PNT represents an innovation in the cross-linking of high molecular weight (Mw) HA, using gentle mixing and no heating reaction conditions to maintain high Mw HA integrity and prevent the formation of low Mw HA fragments.[3] RHA fillers also contain a small amount of very high Mw noncross-linked HA to improve tissue integration[8,9] and drastically reduce and smooth extrusion forces. Such conditions lead to a low degree of modification and a more natural and durable collection of dynamic fillers.[3,4,10–14] RHA4 is suited to restore facial tissue volume loss due to the natural aging process, filling deep wrinkles, restoring facial contours, and creating dynamic projection. A continuous evaluation of the safety and performance of all the above-mentioned evidence is a regulatory requirement.[10,11,15] This study aimed to bridge preclinical assays on the physicochemical and biological properties of RHA4 with real-life clinical performance and safety data. This was achieved by performing cytotoxicity studies with human adipose stem cells (ASCs) and fibroblasts (FBs)—which are key cells from the skin and fat tissue—evaluating biocompatibility and local tissue response in an animal model, and studying its mechanical behavior once injected into human adipose tissue (AT) samples. These results are contextualized by examining the clinical advantages of using RHA4 for midface tissue projection, utilizing the multilayering technique (MLT) methodology to effectively attain the desired natural-looking aesthetic results.[16,17]

PATIENTS AND METHODS

Preclinical Biocompatibility Study

Preclinical biocompatibility studies were performed by NAMSA (France) under the OECD Good Laboratory Practice, the US Food and Drug Administration Good Laboratory Practice regulations and following the ISO 10993-6 standard. (**See appendix, Supplemental Digital Content 1**, which displays the supplementary information, **http://links.lww.com/PRSGO/D878**.)

Stress Relaxation on Human AT

Discs of 4-cm diameter AT obtained from the abdominal region of a 37-year-old woman undergoing abdominoplasty were subjected to mechanical testing under a constant axial force of 2 N, following a previously published procedure.[18] Human abdominal skin was collected immediately after surgery from the Department of Plastic, Aesthetic and Reconstructive Surgery (Geneva University Hospital, Geneva, Switzerland). The study was approved by the Central Committee for Ethics in Research (CER: 08-150 [NAC08-051]), and the authorization was renewed by the Cantonal Commission on Research Ethics (Project-ID: 2021-01578). These tests were conducted with and without the presence of 1 mL of RHA4, administered uniformly through multiple 0.1-mL boluses. The tests were performed in triplicate.

Takeaways

Question: How effective and safe is the soft-tissue filler resilient hyaluronic acid (RHA) 4 for lifting and supporting tissue in dynamic facial areas?

Findings: In preclinical conditions, RHA4 integrated well within the skin tissue, promoting rapid tissue ingrowth with minimal local effects and successfully lifting tissue without affecting fat motion. Clinically, RHA4 proved to be safe, providing natural-looking results in dynamic facial areas. Tools were finally provided to healthcare practitioners for efficient midface treatments with RHA4.

Meaning: RHA4 is a safe and effective hyaluronic acid filler for lifting and supporting tissue in dynamic facial areas, providing natural-looking results.

Illustration of the MLT Concept

The MLT concept was illustrated after the injection of 2 boluses of 0.1 mL of RHA4 into the upper and lower layers of an artificial skin (Practi-SimSkin, Wallcur, San Diego) and further compared with a single 0.2-mL bolus injection in the lower layer of the same skin sample.

Treatments

Data from patients of both sexes receiving a session of aesthetic treatment with RHA4 to correct volume deficiency in the midface during clinical practice were collected from educational activities in 2023 at the Teoxane Academy and from a long-term case study selected from a private clinic (courtesy of Dr. Tseng). At the Teoxane Academy, injections were performed by trained international experts after a full face, anatomical, and aesthetic patient assessment considering age, skin type, and ethnicity following the ATP approach (anatomy, technique of injection, and selection of the appropriate product).[16] Each patient was requested to sign an informed consent before the treatment including the image rights for publication purposes. The choice of treatment was left to the clinician's judgment and practice, with respect to each product's instructions for use, and after the patient's assessment, to achieve a natural aesthetic improvement.[16] When injecting the midface, the clinician could also implement the MLT, injecting both the deep and superficial fat pads during the same session. Data from 35 patients injected in the midface area were extracted from the full patient database and analyzed.

In addition to demographics, data related to injections were recorded (eg, site and depth of injection, volume, the device [needle or cannula], and technique) for all the treatments of the mid-cheek/cheekbone area, which is described as the anteromedial and lateral malar region. Aesthetic improvement was assessed by the clinicians and patients by using specific scales and/or the Global Aesthetic Improvement Scale. Safety data were recorded as adverse events (AEs). In the live injections, before and after pictures were also taken by a QuantifiCare LifeViz Mini. (**See Video [online]**, which displays before and after 3-dimensional images of a 35-year-old woman following treatment with MLT in the cheekbone area using QuantifiCare LifeViz Mini. RHA4 boluses of 0.6 mL per

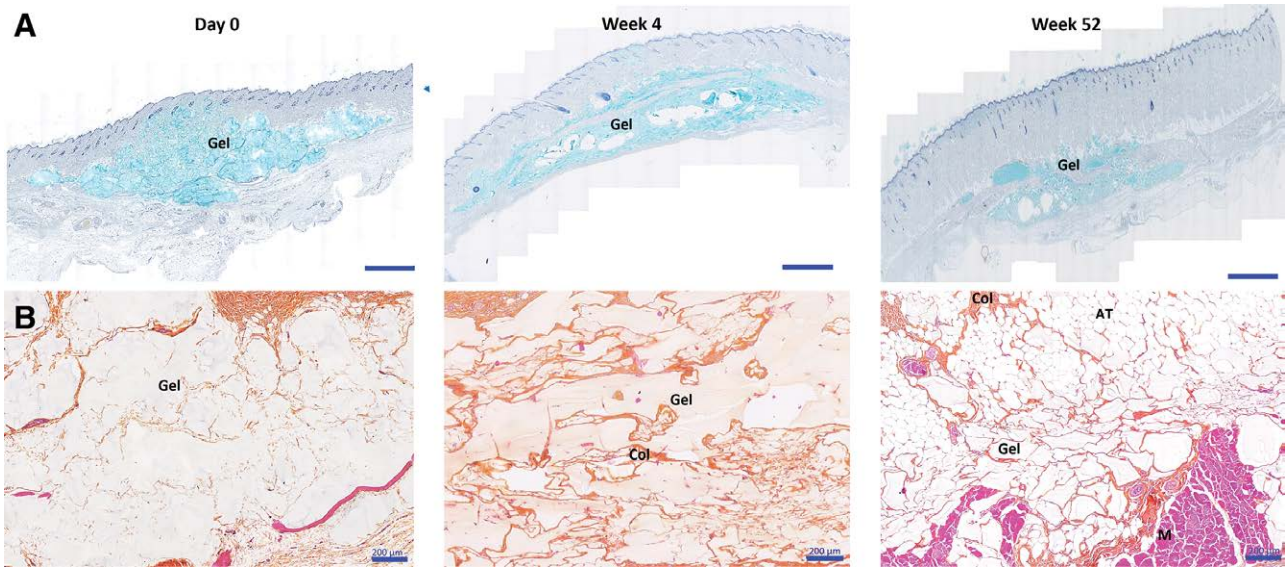

Fig. 1. In vivo biocompatibility testing of RHA4. At the study endpoint of 0, 4, and 52 weeks, histological assessment of rat skin structure and gel integration was performed. A, Alcian blue–stained skin sections, with deep blue highlighting acidic polysaccharides (RHA4 filler). Scale bars = 2 mm. B, Safranin–hematoxylin–eosin–stained skin sections. "AT," adipose tissue; "M," muscular tissue; "Col," collagen bundles. RHA4 appears slightly pale. Scale bars = 200 µm.

side were injected with a needle [TSK 27G/13 mm] on a deep plane onto the supraperiosteal layer to support the medial and lateral sub–orbicularis oculi fat [SOOF] zones and deep medial cheek fat [MCF]. An additional 0.6 mL per side was injected superficially in the MCF using a cannula [TSK 25G/50 mm] with a linear retrograding fanning technique from the zygomatic arch.)

Statistical Analyses

Patients' demographics were reported using minimum–maximum and mean ± SD for age, and injected volumes were reported using minimum–maximum per side (mL) and mean ± SD.

RESULTS

Safety Profiles

In Vitro Cytocompatibility and In Vivo Biocompatibility Studies

Evaluating the preclinical safety of dermal fillers intended for injection in facial tissues is paramount to evaluating their safety profiles in clinical practice. The cytocompatibility of infant polydactyly or adult FBs and ASCs in contact with RHA4 was first evaluated and found to exceed 70% of the nontreated control. (**See figure, Supplemental Digital Content 2**, which displays in vitro and in vivo biocompatibility testing of RHA4. A, In vitro evaluation of polydactyly FBs and ASC cytocompatibility on 3 different donors in contact with RHA4. B, Cytocompatibility determination of ASCs and FBs in adult and infant donors in contact with RHA4. Results are presented as mean ± SD. C, [i] Dorsal view of a rat injected with RHA4 and implantation sites, [ii] after injection, and [iii] 4 weeks after injection, **http://links.lww.com/PRSGO/D879**.) Hence, cell types from the dermis (FBs) and fat (ASCs) layers remained viable in contact with RHA4.

Biocompatibility testing was next performed for 52 weeks on RHA4 samples following the ISO10993-6 standard (**Supplemental Digital Content 1**, **http://links.lww.com/PRSGO/D878**). At day 0, gels remained cohesive in the implantation site (Fig. 1). At week 4, cell infiltration inside the densely packed gel was observed with the progressive deposition of newly synthetized collagen fibers. At weeks 26 and 52, minimal tissue reaction and progressive gel absorption could be observed with noticeable tissue integration and ingrowth, and an absence of fibroplasia, indicative of a good biocompatibility profile and a progressive remodeling of the gel into a new tissue.

Safety Profile of RHA4 in Clinical Practice

In clinical practice in 2023, the overall rate of AEs reported by HCPs injecting RHA4 was 3.7 cases per 10,000 syringes, independent of the indication, the technique of injection, or the volume used. This was in line with the mean rate of AEs over the past 4 years (2020–2023) of 3.6 cases per 10,000 syringes worldwide.

AEs collected from 2020 to 2023 were considered mild and transient and are summarized in Table 1. Considering all reported cases, the main AEs were injection site mass (17.4% of total reported, corresponding to a rate of 1.41) followed by skin swelling (10.8%, rate of 0.88), induration (10.7%, rate of 0.87), and skin edema (10.2%, rate of 0.82). Pain, injection site inflammation, and erythema represented 8.4%, 6.7%, and 5.5% of the total reported cases (with rates of 0.68, 0.54, and 0.44 per 10,000 syringes), respectively; the remaining cases (27% of total reported) consisted of an aggregate of all AEs with less than 3.0% occurrence. All AEs reported for RHA4 are consistent with the literature,[19] or the investigations led to the conclusion that the causality with the product cannot be confirmed.

Table 1. Common AEs With Their Percentage of Total Reported Cases and Rate

Type of Reported AEs	Percentage of Total Reported Cases	Rate (n per 10,000 Syringes)
Injection site mass	17.4	1.41
Skin swelling	10.8	0.88
Skin induration	10.7	0.87
Skin edema	10.2	0.82
Pain	8.4	0.68
Injection site inflammation	6.7	0.54
Erythema	5.5	0.44
Vascular skin disorder	3.0	0.25

Performance and Clinical Evidence

Preclinical Performance

As a dynamic volumizer, RHA4 is intended to lift and volumize the fat pads of the face. RHA4 should, therefore, be injected with ease and without altering its rheological properties. As seen in Supplemental Digital Content 3, the extrusion of RHA4 through a 27G needle only required moderate force (average force = 9.2 N), without significant peaks (maximum force = 11 N) even during needle priming, ensuring precise control over the injection. (**See figure, Supplemental Digital Content 3**, which displays usability analyses of RHA4. A, Injection profile of RHA4 during filler extrusion at a constant speed of 12.5 mm/min through a 27G 0.5-in needle. B, Comparison of the storage modulus [*G′*] and linear viscoelastic region of RHA4 samples, connected or not to a 27G 0.5-in needle [TSK], **http://links.lww.com/PRSGO/D880**.) To evaluate if the injection process through the provided needle alters the gel's performance, rheology studies were performed on RHA4 samples connected, or not, to a 27G needle. No statistical differences between the elastic modulus, *G′*, and the linear viscoelastic region, and thus, the strength score,[3] were observed for RHA4, proving that the hydrogel retains its properties after extrusion.

To investigate the physical effect of RHA4 on the subcutaneous fat pads, 1 mL of RHA4 was injected into human AT samples obtained from an abdominoplasty and submitted to stress-relaxation tests. This test was developed to evaluate if a filler would alter tissue mobility. Although the injection of 1-mL RHA4 increased the overall height of the sample by approximately 1.5 mm (Fig. 2A), it did not alter the ability of the AT to relax under a constant deformation (Fig. 2B). Normalized plots of relaxation curves for a noninjected control and for RHA4 injected controls were superimposed (Fig. 2C), indicating that acute implantation of RHA4 does not change the mechanical properties of AT, suggesting a high degree of mechanical compatibility with a commonly injected tissue plane. The lifting capacity of RHA4 was evaluated by comparing the injection of 0.2 mL of RHA4 in 1 single bolus in the deep layer versus an MLT with successive injections of 0.1-mL RHA4 in the superficial and deep layers of an artificial skin as clinically reported by Trévidic et al.[16,17] As seen in Figure 2D, the MLT was able to achieve a better projection of the skin while also limiting the spreading of the gel, thus confirming previous clinical findings.

Clinical Performance

Records of 35 patients treated with RHA4 in the midface (with MLT) during 2023 were selected from the Teoxane Academy database (Table 2). Among these, 5 female patients, 48 ± 8 years of age, were treated both superficially and deeply with only RHA4. For deep injections, 27G 13-mm needles were used with a mean volume of 0.6 mL per side using a regular bolus technique, generally divided into 3 boluses of approximately 0.2 mL each in the medial SOOF, the lateral SOOF, and the deep MCF[16,20]—the volumes should be adjusted to the patient facial morphology during the assessment. For superficial injections, a mean volume of 0.7 mL per side of RHA4 was injected using a 25G/50 mm cannula and a fanning technique in the medial and the middle cheek fat pads. If more support was required (thicker skin or severe volume loss), patients (n = 30) were treated deep with Teosyal PureSense Ultra Deep, a high-strength, low-stretch volumizing filler, and superficially with RHA4 via the MLT approach as indicated by Trévidic et al.[16,17] For US applications, a highly projecting filler designed for supraperiosteum injection and compatible with the MLT is under clinical investigation (NCT05973877). In the supraperiosteal layer, a mean volume of 0.6 mL per side of Ultra Deep was injected mostly using a regular bolus with a 27G/13 mm needle or sometimes with a linear threading for patients with thin skin to avoid visibility or palpability using 22G/50 mm or 25G/38 or 50 mm cannulas. In the superficial fat pads, RHA4 was injected using a mean volume of 0.6 mL per side and a 25G/50 mm cannula with a fanning technique. When asked for their opinion on the aesthetic outcome 2 weeks following treatment, patients who responded to surveys considered themselves aesthetically improved (n = 13, 65%) or much improved (n = 7, 35%) according to the Global Aesthetic Improvement Scale. To illustrate the short-term performance of MLT using RHA4, a case study is presented in the video (**see Video [online]**). Projection gains up to 3.3 mm were observed, including postinjection slight swelling (**see Video [online]**, before [left] and right after [right] treatment). The patient did not experience any common treatment reactions and did not report any safety complaints and AEs during the 2-week follow-up. No delayed reactions to the treatment were reported.

Two-year Performance Case Study

In this case study, a 64-year-old woman with volume loss and sagging was treated in her midface using the multilayering technique with RHA4, accompanied by improvement in her eye bags/lid–cheek junction and visual effect of the lifting of malar soft tissue over a 2-year period to showcase the persistence of the treatment (Fig. 3). The treatment plan included an improvement in her nasolabial folds with RHA4 deep in the pyriform fossa and RHA2 or 3 superficially along the nasolabial folds. Improved definition of her jawline and reduced jowls with RHA4 in her prejowl sulcus and RHA2 in her marionette lines were concomitantly achieved. The patient was followed up for 2 years without any additional touch-ups. The results were maintained with no apparent filler migration, leading to long-lasting improvement in

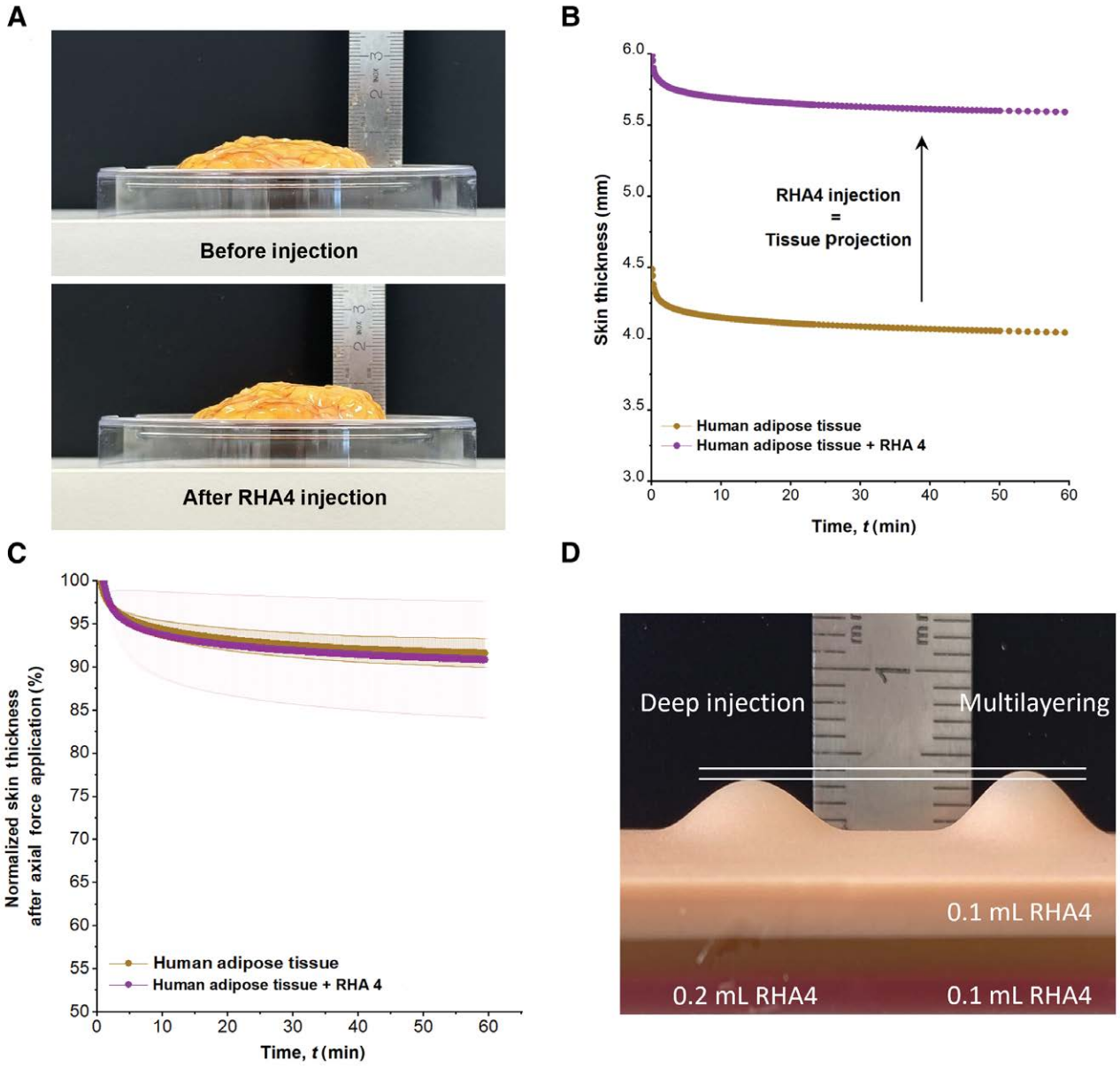

Fig. 2. Biomechanical analyses of RHA4. A, Illustration depicting the projection of human AT following injection of 1-mL RHA4. B, Relaxation test (compression over time) of 4-cm AT discs with and without 1-mL RHA4 under a constant axial force of 2 N. C, Normalized stress-relaxation curves of human AT samples injected or not with RHA4. D, Visualization of the MLT performed with 0.2 mL of RHA4 injected into an artificial skin. All experiments were performed in triplicates and are presented as mean ± SD.

her midface sagging, lid–cheek junction, nasolabial folds, and jowls (Fig. 3A). This long-lasting improvement and the maintenance of the expressiveness of the face (Fig. 3B) was the result of a durable projection with the RHA range. (**See figure, Supplemental Digital Content 4**, which displays the before treatment and after 2 years of treatment comparison of the patient's rejuvenation, **http://links.lww.com/PRSGO/D881**.) The patient was a good example of how RHA4 with both high strength and relatively high stretch can withstand the pressure from muscle movement and skin layers while maintaining the desired contour correction and facial expressiveness.

DISCUSSION

In this article, the safety and performance of the soft-tissue filler RHA4 have been investigated at the preclinical and clinical levels. As RHA4 is used in multiple layers of the skin, we thought to investigate the behavior of FBs (dermis) and ASCs (AT), which are key cell types in the midface region.[21] FBs and ASCs in contact with RHA4 did not show any cytotoxic effects, in line with recently published data.[22] Consistent with these initial findings, minimal inflammation was observed following long-term RHA4 implantation in rats. Although inflammation is required for tissue healing,[23] chronic inflammation may

Table 2. Summary of the Treatments and Techniques of Injections Using the MLT for the Midface

Treatment	Patient Total (Minimum–Maximum Age, y; Mean ± SD)	Depth of Injection*	Volume of Injection (Minimum–Maximum Per Side, mL; Mean ± SD)	Device	Technique of Injection
Multilayering RHA4	5 (35–55; 48 ± 8)	SP RHA4	0.2–1.2; 0.6 ± 0.3	Needle 27G/13 mm	Regular bolus
		SF RHA4	0.3–1.2; 0.7 ± 0.3	Cannula 25G/50 mm	Fanning technique
Multilayering RHA4/ Ultra Deep	30 (23–63; 42 ± 8)	SP Ultra Deep	0.1–1.2; 0.6 ± 0.3	Needle 27G/13 mm	Regular bolus
				Cannula 22–25G/38–50 mm	Retrograde threading (for thinner skin)
		SF RHA4	0.1–1.2; 0.6 ± 0.3	Cannula 25G/50 mm	Fanning technique

*SF, superficial; SP, supraperiosteal.

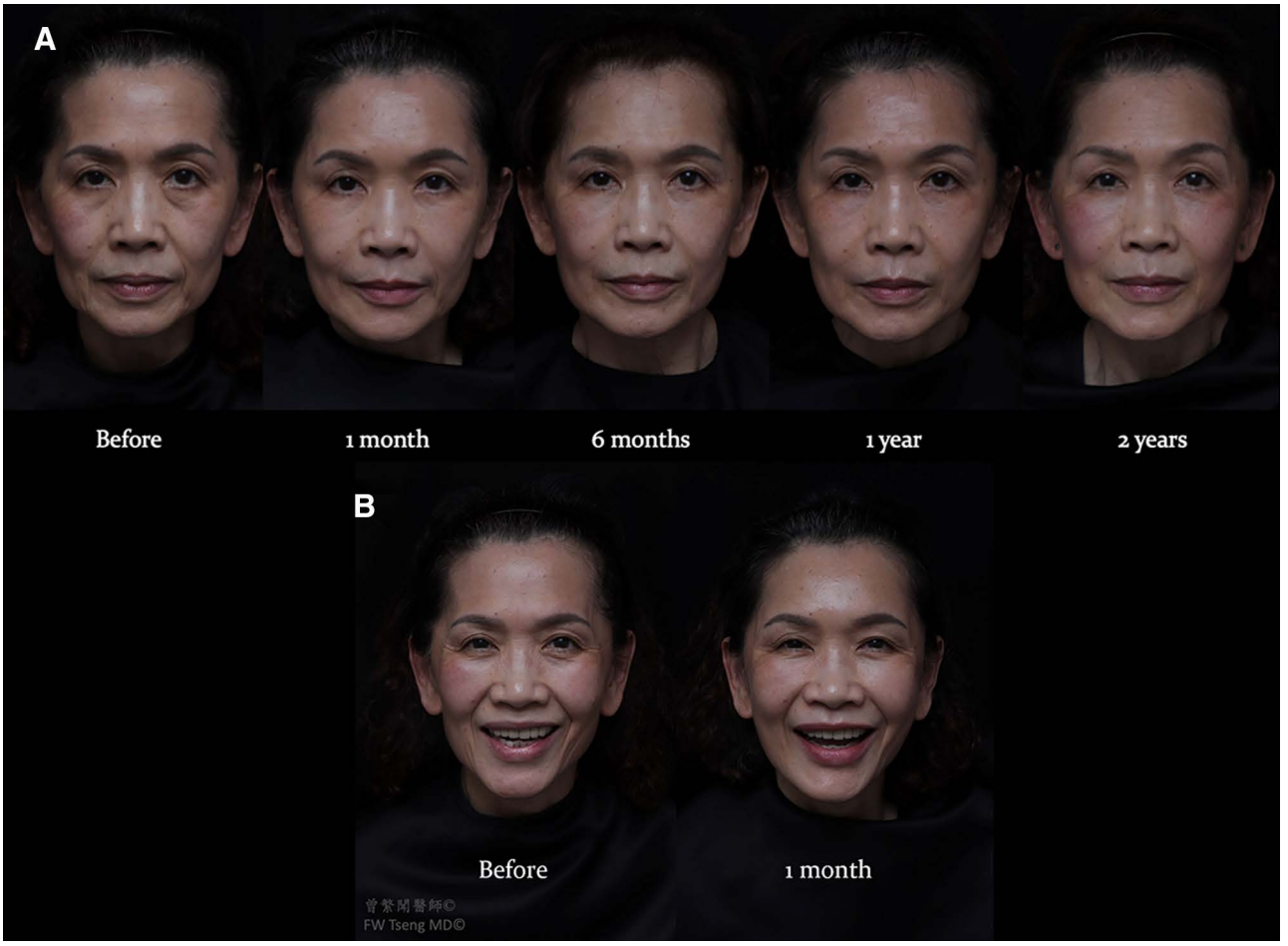

Fig. 3. Example of the potential of RHA fillers, including RHA4 using the MLT in the midface for durable improvement (2 years follow-up) of aesthetic outcomes without any prevention of facial expressiveness. A, Follow-up over a 2-year period after treatment, without any additional touch-up. Right side, 0.2 mL deep (supraperiosteum) + 0.2 mL superficial (subcutaneous fat); (left side) 0.4 mL deep (supraperiosteum) + 0.15 mL superficial (subcutaneous fat). The treatment plan also included improvement in her nasolabial folds with RHA4 deep in the pyriform fossa and RHA2 or 3 superficially along the nasolabial folds. Improved definition of her jawline and reduced jowls with RHA4 in her prejowl sulcus and RHA2 in her marionette lines. B, Before treatment and after 1 month of treatment comparison of the patient's expressiveness. Courtesy of Dr. Fang-Wen Tseng.

degenerate into foreign body reactions,[24] leading to AEs for the patient.[25] Because HA is generally regarded as a safe biomaterial, chronic inflammation may originate from bacterial contamination,[24] the presence of very low Mw cross-linked fragments generated during cross-linking,[3,24] or other impurities.[26] Locally, a collagenous matrix was deposited within the implanted HA, concomitant with progressive gel absorption. Mechanical stretching of the cell following tissue filling,[27] direct contact with key cell receptors (ie, CD44),[28] and local inflammation following injection have been reported to directly influence collagen secretion. When used in accordance with the instructions for use, RHA4 produced only a few mild and transient AEs, in line with those commonly reported for dermal fillers and mostly related to the injection itself.[19,29,30]

In clinical practice, the injectability of a filler is central. RHA4 injection through a 27G needle showed a regular and smooth profile,[31] leading to a low but controllable injection force.[32] Such characteristic is noticeable because RHA fillers use short syringes, which generate about twice the extrusion force (larger diameter) of the longer syringes (extra-long format) that equip most soft-tissue fillers on the market. RHA4 formulation was optimized to reduce the injection force while maximizing its volumizing properties via the addition of a small proportion of free very high Mw HA. Besides, injecting through the provided needle did not alter the rheological properties of RHA4.[3] However, using thinner needles than those recommended may impart the rheology of dermal fillers and potentially impact clinical performance.[16,17] As a volumizing filler, RHA4 is mostly injected into the subcutaneous or deep AT to provide contour and projection or restore lost volume.[14,16] The AT strongly contributes to the overall biomechanics of the face, and any changes in its nature may impact physical appearance, as seen during facial aging.[33,34] Although the viscoelastic behavior of the AT has been well described,[35–39] little is known about the influence of a filler on its biomechanics. Recently, Vassallo et al[40] showed that AT was weakened by an HA solution. Here, stress-relaxation tests performed on RHA4-injected AT samples revealed tissue projection without interfering with the ability of the AT to move under stress. Although these experiments were performed in an unconfined environment, RHA4 appeared to neither soften nor stiffen the tissue, which could have a negative impact on AT motion and clinical outcomes. RHA4 being a versatile volumizer with both high projection capacity (strength) and good ability to spread (stretch),[18] it can be used in an MLT for both deep and superficial fat pad injections.[16,17] This approach achieves similar tissue projection with more efficient volumes of injection, mitigating the risk of overfilling, especially of the deep compartment.[17] The MLT with RHA4 was used during Teoxane Academy live injections with different volumes, needles and cannulas, and techniques of injection, offering a handy tool for the practitioner for the midface treatment. To complete this approach, a practical roadmap of assessment and injection guidelines has been recently published.[20] Aesthetic global improvement is highlighted by the immediate and long-term effects of the MLT with RHA4 with preservation of the facial structure at rest and tissue dynamics in motion as demonstrated in the biomechanical observations. This study evaluated for the first time the mechanical integration of a soft-tissue volumizer into human subcutaneous tissue and highlighted the use of RHA4 as a dynamic volumizing filler suitable for the MLT. A limitation of this study is the use of a single stress-relaxation test that cannot fully capture the complexity of facial dynamics. Ongoing investigations are seeking new mechanical test development to better appreciate the behavior of fillers once injected into the skin layers.

CONCLUSIONS

We reported a multipronged approach for the in-depth characterization of the safety and performance of a soft-tissue filler. The candidate filler was RHA4, manufactured using the PNT and presenting the unique mechanical features of both tissue projection and accommodation of dynamic conditions. Overall, RHA4 was confirmed as a well-tolerated and versatile injectable product for midface augmentation, allowing multiple injection strategies including the MLT approach targeting both the superficial and deep fat pads.

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DISCLOSURES

Dr. Flégeau, Dr. Ballarini, Dr. Brusini, Vantou, Bourdon, and Dr. Faivre are employees of Teoxane SA, Geneva, Switzerland. Drs. Hirt-Burri and Liao have received financial support for the project provided by Teoxane SA. Dr. Tseng is a consultant and trainer for Teoxane SA.

PATIENT CONSENT

The patient provided written consent for the use of her image.

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