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Date of prep: November 2021 | UK/OTHR/NP/21/0043

Received: 28 March 2022 | Revised: 7 June 2022 | Accepted: 23 June 2022

DOI: 10.1111/jocd.15200

JCD Journal of Cosmetic Dermatology WILEY

ORIGINAL ARTICLE

Comparative clinical study for the efficacy and safety of two different hyaluronic acid-based fillers with Tri-Hyal versus Vycross technology: A long-term prospective randomized clinical trial

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Abstract

Background: Hyaluronic acid-based fillers have an immediate volumizing effect for the treatment of dermal contour deformities and to smooth dermal depressions formed by the loss of volume. A previous study on 2016–2018 has shown the efficacy and safety of the HA-based filler ART FILLER® Volume on the midface only, but not in a comparative manner.

Methods: In this context, an 18 months prospective randomized single-blind study of the non-inferiority of ART FILLER® Volume versus the reference product Juvéderm Voluma® was performed on the midface, temple, and jawline, and non-comparative study on the chin. The efficacy and the longevity were evaluated for the selected face areas via dedicated clinical scoring systems after a single filler injection without any re-touch or re-injection. The short- and long-term adverse effects were also recorded.

Results: The observations confirmed the non-inferiority of ART FILLER® Volume versus the reference product on the different injected areas. For both fillers, the beneficial effects on volumes restoration were maintained 18 months post-injection; however, these effects were diminished among the time. Furthermore, injections of Art Filler® Volume were well tolerated by the subjects and showed less acute side effects compared with the reference product that may be explained by a lower induction of inflammation.

KEYWORDS
anti-aging, facial injections, fillers, hyaluronic acid, skin rejuvenation

1 | INTRODUCTION

In the face region, aging is characterized by a loss of skin volume, particularly due to a decrease and a redistribution of fat, as well as a dermal atrophy due to a reduction in collagen production by fibroblasts. Thus, preventing the loss of subcutaneous fat or the decrease in dermal thickness represent interesting strategies to counter the apparent aging of the face. The use of skin fillers is one

of the most frequently used techniques to seek face rejuvenation. It allows the augmentation of soft tissues, the filling of wrinkles, and the treatment of superficial defects.[1]

Hyaluronic acid (hyaluronan or HA) is present in the extracellular matrix of the skin dermis and is a commonly used injectable dermal filler showing an excellent efficiency to maintain tissue augmentation for about 6–9 months.[2] Once injected in the skin, HA forms a viscous matrix thanks to its chemical properties based on its coiled structure in aqueous solution. These characteristics allow HA to trap about 1000-fold of its weight in water, making HA an important player in tissue structure and volume.[3] In addition to improve skin moisturizing and its antioxidant potential, Chunlin Ke et al. proved in 2011 that HA promotes skin cell regeneration and stimulates the production of collagen by dermis fibroblasts.[4]

Due to its short half-life in natural form (about 24–48 h),[5,6] HA is chemically stabilized by a crosslinking process; the most used crosslinking agent is BDDE (1,4-butanediol diglycidyl ether). Depending on the molecular weight of the HA, the process and the degree of crosslinking, the modified HA molecules convert into highly viscous and insoluble gel that can be used for skin filling. These rheological characteristics of the HA gel determine its clinical effects and its longevity within the skin.

Hyaluronic acid is a natural linear polysaccharide presenting the advantage to not induce immune responses. Therefore, adverse effects due to HA-based dermal fillers are in most cases minor and occurs principally in the few hours or days post-injection. Apart from these immediate reactions at the injection sites that rapidly resolve, the tolerance to HA-based fillers is very good and more serious events are exceptional.[7]

The ART FILLER® Volume (Laboratoires FILLMED) is an injectable HA-based filler indicated for the restoration of the volumes of the face, by subcutaneous injection, supra-periosteal, or in deep dermis. This filler is characterized by the Tri-Hyal Technology combining 3 different structures of HA (free HA, long, and very long chains). It contains also 0.3% of lidocaine hydrochloride for its anesthetic properties. This concentration is used by many fillers on the market for several years and has no impact on tolerance and effectiveness with a significant benefit in terms of reducing the pain sensation during injections.[8,9] However, based on the European Medical Devices Regulation, such a product needs a longitudinal performance, safety, and clinical benefits evaluation. Thus, to evaluate these parameters for ART FILLER® Volume, a randomized prospective and comparative study was conducted to evaluate the aesthetic performance of this product on the most frequent treated areas on the face, as well as their immediate and long-term tolerance. This study aims to document the filling capacity of ART FILLER® Volume, in comparison with a product presenting similar characteristics and considered as a reference, Juvéderm® Voluma (Allergan).[10,11] The main objective of this study was to measure the restoration of midface, temple, and jawline from baseline to 21 days post-injection and compared with the reference product. The restoration of chin volume was also evaluated without comparison to the reference. The secondary objectives were to evaluate the long-term efficacy of the volume correction on the different face zones over 540 days (18 months), as well as to compare the safety and tolerance of ART FILLER® Volume and Juvéderm Voluma®.

2 | MATERIALS AND METHODS

2.1 | Test items and injection procedure

ART FILLER® Volume is a crosslinked HA of non-animal origin containing 0.3% of lidocaine hydrochloride for anesthetic properties and phosphate buffer at pH = 7.2. The gel is pre-filled in a 1.2 ml graduated disposable syringe. The reference product Juvéderm® Voluma presented the same characteristics for the HA gel and used in pre-filled 1 ml graduated syringe.

The same amount for each product was injected to the subjects via one single supra-periosteal bolus injection with a 27G1/2 (13 mm) TSK® needle or a 25G/55 mm cannula (SoftFil®). Each side of the face received either one or the other product according to the randomization, except for the chin where only ART FILLER® Volume was injected. The injection sites were determined randomly. The amount of product injected varied according to the deficit to be corrected, but maximum 1.2 ml was authorized to be injected for the midface, 1.2 ml for the temples, 1.2 ml for the jawline, and 1.0 ml for the chin (Figure 1B).

2.2 | Population

The pre-selection of the subjects (D-120 to D-7) was carried out by the SYRES company or the investigators according to the inclusion/non-inclusion criteria. Briefly, they were male or female aged 19 years or more, a Fitzpatrick Phototype I to IV, having a score of ≥2 in Global Aesthetic Scale scoring on at least one area of interest. The eligible subjects received the general information on the study scheme (Figure 1A). The subjects who were interested were then invited to proceed to the inclusion/randomization visit (D-7 to D0). During this visit, the baseline evaluation was performed by the investigators in the 5 selected centers. For some subjects, the high-frequency ultrasound imaging was performed at GREDECO for this baseline visit. In total, 98 subjects were enrolled in this study. For each follow-up visit (D21, D90, D180, D270, D360, D450, and D540), the per-protocol population (PP) was defined by all the subjects seen at this visit and having an evaluation from the global aesthetical score. The study design is shown in Figure 1. Safety population includes all subjects enrolled and for whom at least one injection of one of the studied products has been performed.

2.3 | Evaluation criteria

The Global Aesthetic Clinical Score (GACS)[12] was used for the main criteria of the study and was assessed at each visit for each injected area by the clinician in front of the subjects. This score system contains 7 grades scale, from 0 to 3 points with 0.5 point interval (1 grade). The score 0 represented no sagging or no volume loss and

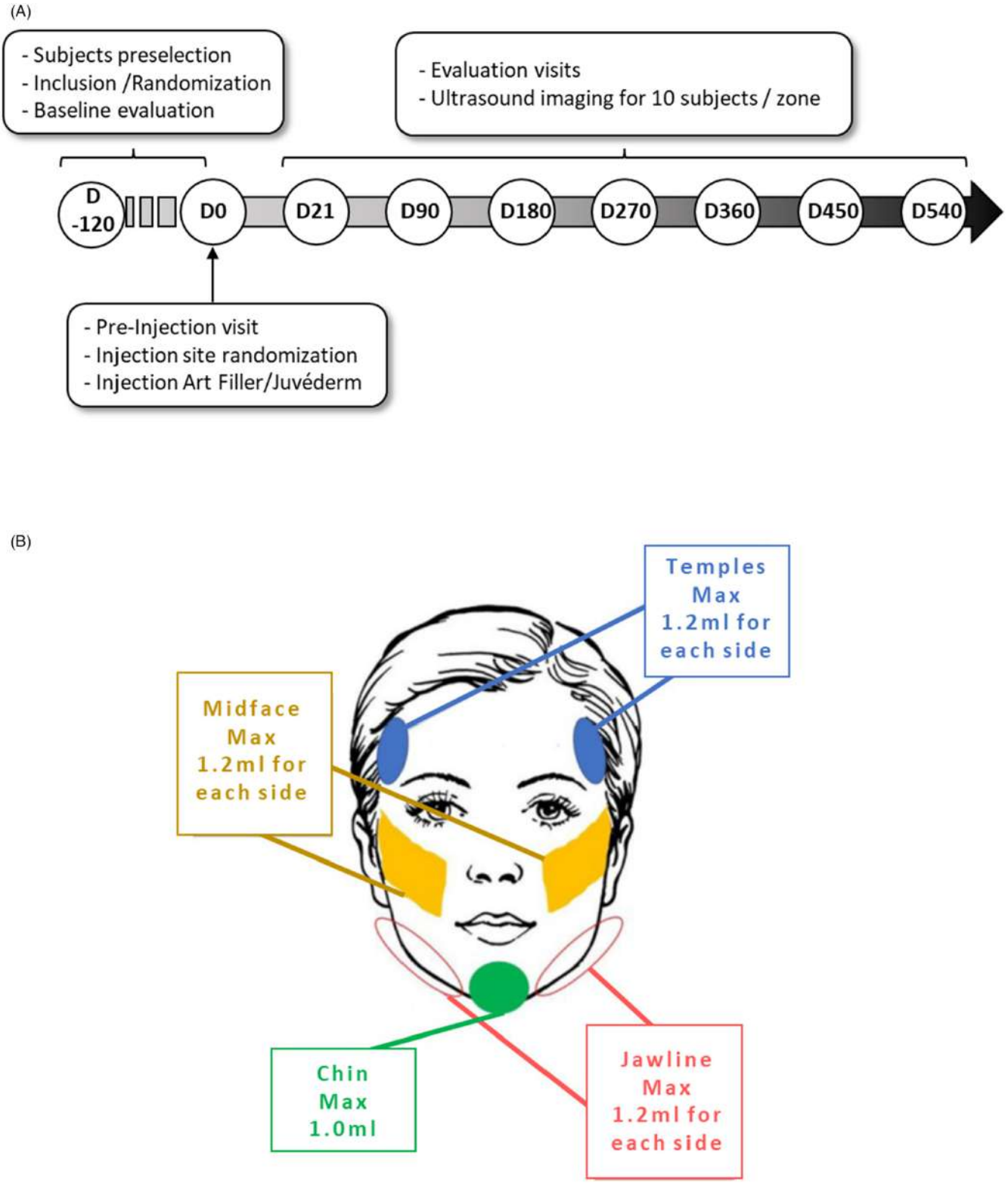

FIGURE 1 (A) Study flow chart over the 18 months period. After a first preselection visit between D-120 and D0, the selected subjects were injected at D0. The follow-up includes seven evaluation visits carried out by the physician who performed the injection and by a dedicated center for subjects enrolled for the ultrasound imaging. (B) Anatomical zones of injection by the fillers. Except for the chin, each zone received randomly one filler type by side

score 3 represented extreme sagging or extreme volume loss. In addition, the Medicis Midface Volume Scale (MMVS), Allergan Chin Retrusion scale, Allergan Temple hollowing scale, and Narins Jawline Scale were used in order to double the check for the evaluation of the secondary criteria. These different scales have been previously validated and published.[13–16]

2.4 | Ex vivo procedure

The skin explants were from donors (women between 32 and 49 years old) undergoing abdominoplasty surgery. A sterile microprobe (CMA/20) with a semi-permeable membrane (threshold 20 kDa) was inserted in the dermis of the skin explants to analyze the dermic interstitial fluid. The probe was continuously perfused (3 µl/min) with a sterile physiological buffer allowing a concentration gradient between the extracellular fluid and the inner part of the probe. After 1 h of stabilization (basal levels), the fillers were injected, and the perfusion liquid was collected each hour during 24 h. The concentrations of IL-8, TNF-α, and histamine in the harvested perfusates were evaluated by standard ELISA technics using specific commercial kits.

2.5 | Safety evaluation

Emerging local and general incidents during and after injections were reported by the subjects on a diary completed over the study and by the physicians who performed the injections on the entire follow-up period of the subjects. Evaluation of the appearance and the adverse events of the treated areas were collected at each visit though interrogation and clinical examination. The adverse events were classified as mild, moderate, and severe according to their intensity reported by the subjects. The causality of an AE in relation to the Investigational Product(s) as a whole was categorized by the clinicians as certain, likely, possible, and excluded.

2.6 | Ethics statement

FILLMED Laboratories submitted this protocol to the Ile de France V CPP (Ethics Committee) (St Antoine hospital, 284 rue du Faubourg Saint Antoine, 75012 Paris). This study was set up in the investigation centers only after obtaining the favorable opinion of this committee.

2.7 | Data analysis

The basal values and the values of the follow-up were calculated for each of the 4 treated zones and for each treatment. A satisfactory correction was defined by a decrease of at least one grade (0.5 point) on the GACS scale. The success percentage was

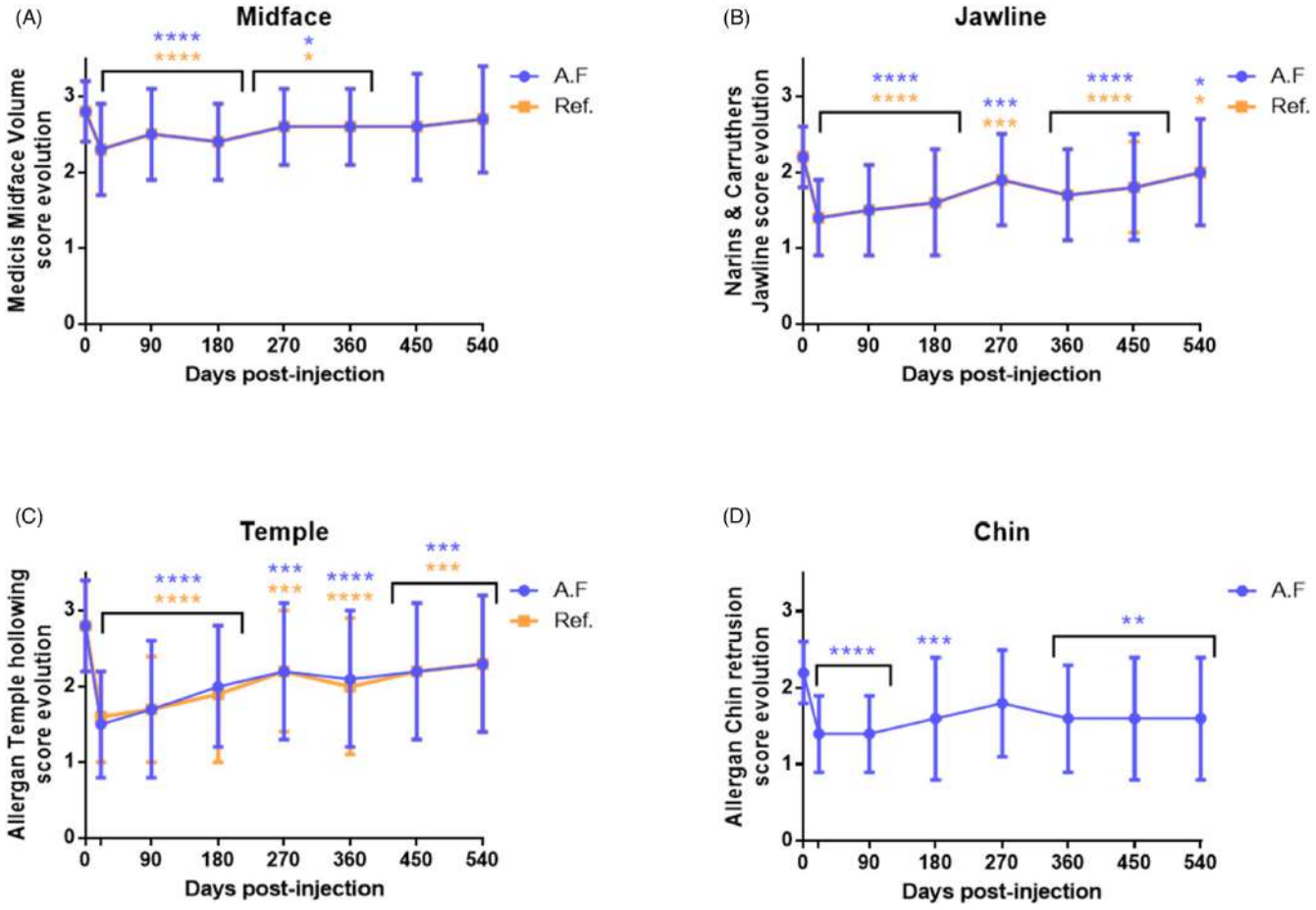

FIGURE 2 Remanence of the global aesthetic clinical scoring (GACS) between D0 and D540 on per protocol population for the midface (A), jawline (B), temple (C), and chin (D). Mean ± SD, ****$p < 0.0001$, ***$p < 0.001$ compared with D0 for each filler

calculated by the ratio of satisfactory responses on each treated area to all PP population. The non-inferiority comparisons were performed on paired data: a Wald confidence interval (CI) was constructed to compare the responder rate between treatments. The non-inferiority of ART FILLER® Volume for one area was concluded if the lower confidence limit was > −15% the lower confidence limit of Juvéderm® Voluma. The mean and the standard deviation changes in scores between D0 and the following days were calculated. The statistical significance of the evolution of the scores was calculated by a Wilcoxon test.

3 | RESULTS

3.1 | Population and subject disposition

In total, 98 subjects were enrolled in this study, 6 males and 92 females were included with an average age of 54.7 years old. Within this intention-to-treat population, 69% had no history of aesthetic treatment, and 20% had been previously submitted to an HA injection. The subject's weight was recorded before injection and during the study to follow their body mass index (BMI). They were injected in the different face area by aesthetic surgeons at five different centers (Figure 1B). Among them, 56 subjects were injected on midface, 72 for jawline, 33 for temple, and 25 for the chin. There was the possibility to inject maximum two zones per subject according to her/his need. During the study, seven subjects stopped voluntary the study before the last evaluation visit.

3.2 | Evolution of the Global Aesthetic Clinical Score (GACS) and the success rate

The main objective of the study was to quantitatively measure the restoration of the chin, midface, jawline, and temple volumes after a single injection of ART FILLER® Volume versus the reference product Juvéderm® Voluma (except for chin where only ART FILLER® Volume was injected). For each area, the volume restoration was assessed according to a Global Aesthetic Clinical Score (GACS), that determine the severity of the volume loss. As shown on Figure 2, the ART FILLER® Volume injection induced a significant reduction of the score for all areas after 21 days. Each injected area started from grade 2 at the

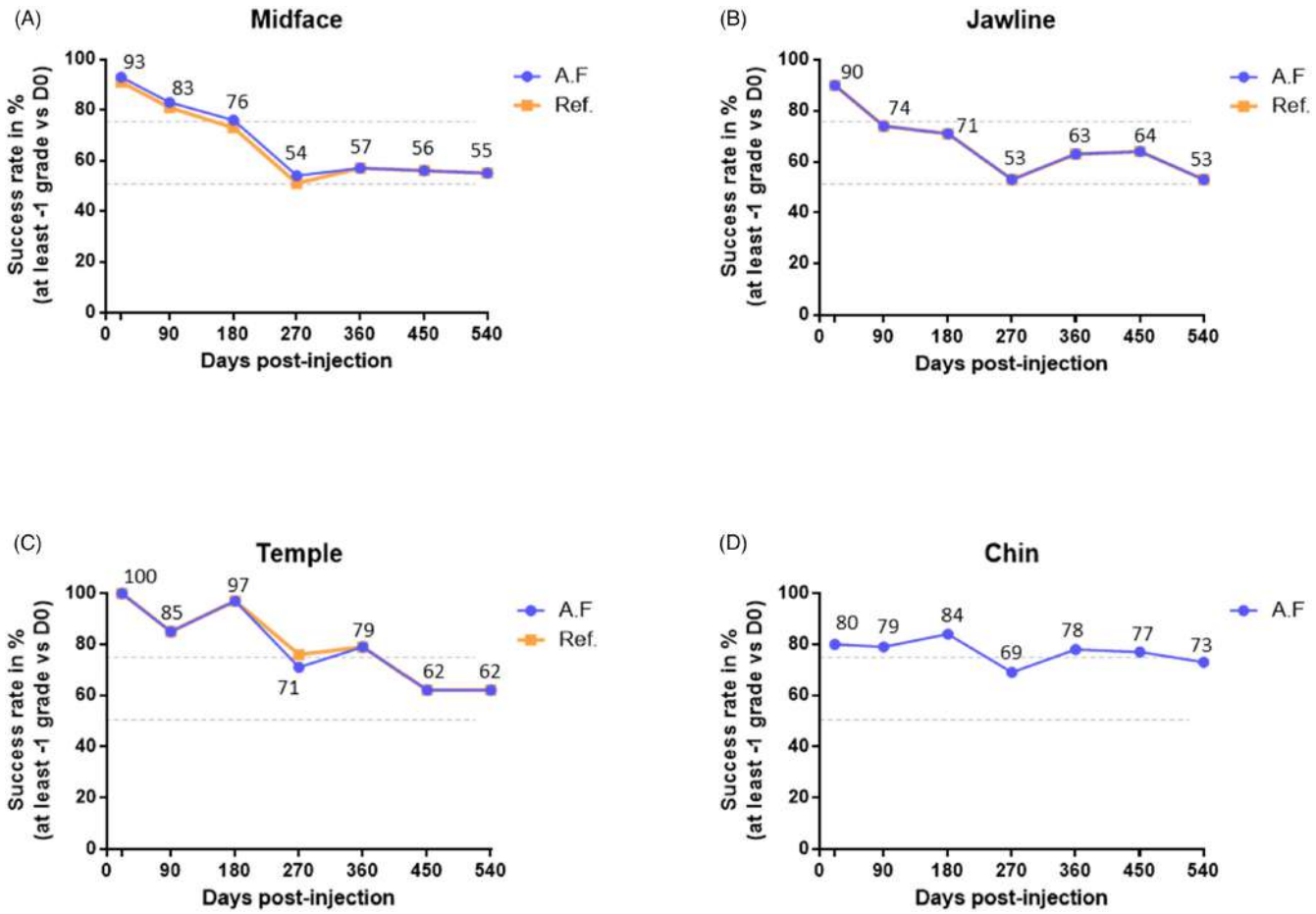

FIGURE 3 Evolution of the success rate representing the percentage of subjects for whom the initial score was reduced from one grade. (A) midface, (B) jawline, (C) temple, and (D) chin. Percentages are calculated from the number of GACS values available for each visit. The upper and the lower dash lines represent 75% and 50% success, respectively

baseline and was averagely reduced to 1.2 for the midface, 1.3 for the jawline, 0.9 for the temple, and 1.4 for the chin. These significant reductions were maintained along all the investigation period until Day 540 (Figure 2). Except for the chin, the contralateral areas that received an injection with Juvéderm showed a similar evolution (Figure 2A–C), confirming the non-inferiority of ART FILLER® Volume for each specific area. The mean injection volume for all studied zones was 1.1 ml for both study products (min 0.8 and max 2 ml for temple for both products, min 0.4, and max 1.2 ml for jawline for both products and min 0.6 for ART FILLER® Volume and 0.5 ml for Juvéderm® Voluma and max 1.2 ml for both products). Considering the total syringe volume for each filler (1,2 ml for ART FILLER® Volume and 1,0 ml for Juvéderm® Voluma), this procedure required only 1 syringe for ART FILLER® Volume while 2 syringes were needed for the reference product.

The percentage of success 18 months after injection, represented by the subjects for whom the initial GACS score was reduced from 1 grade (0.5 point) on the GACS scale was of 55% for midface, 53% for jawline, and 62% for temple with both treatments (Figure 3A–C). The best success was observed on chin with 73% of subjects for whom a decrease of one grade was still present at Day 540 (Figure 3D).

3.3 | Evaluation of the remanence of the fillers with area's specific scales

To further quantify the restoration longevity of the of face volumes by the fillers, each injected area was evaluated according to its specific scale. The Medicis Midface Volume score (MMVS) was significantly reduced by 18% at Day 21, and this reduction was kept significant until day 360 (−7%) (Figure 4A). The Narins and Carruthers Jawline score was significantly reduced after the injection, from −36% at day 21 to −9% at Day 540 (Figure 4B). Similarly, the Allergan Temple Hollowing score was reduced by −46% at Day 21 and was kept significantly reduced until Day 540 by at least −18% (Figure 4C). Of note, all these scores evolved in a similar way for the contralateral side that was injected by the reference product Juvéderm® Voluma (Figure 4A–C). Finally, the Allergan Chin Retrusion score was also significantly reduced after the ART FILLER® Volume injection (from − 36% at Day 21 to −27% at Day 540) except for one time point at Day 270 (Figure 4D). The longevity of fillers efficacy is illustrated by the follow-up pictures on Figure 5, showing a visible reduction of the volume loss that was maintained until 18 months.

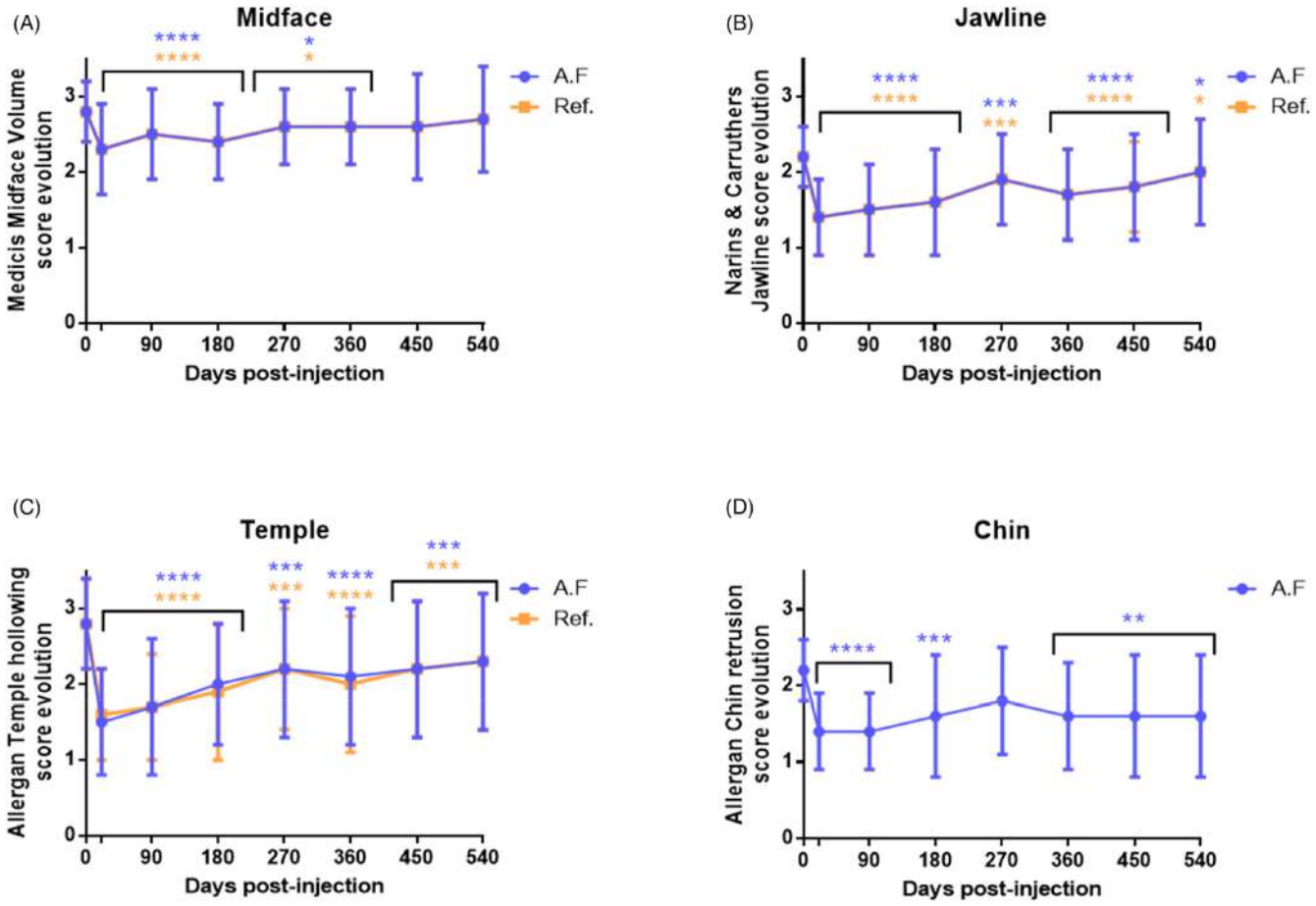

FIGURE 4 Evolution of clinical scoring (from photographical scales) between D0 and D540 on the per protocol population. Evolution of the Medicis Midface Volume score (A), the Narins and Carruthers Jawline score (B), the Allergan Temple Hollowing score (C), the Allergan Chin Retrusion score (D). Mean ± sd, ****$p < 0.0001$, *** $p < 0.001$, *$p < 0.05$ compared with D0 for each filler

3.4 | Remanence and aesthetic benefits confirmed by the Global Aesthetic Improvement Scale (GAIS)

The investigator and subject satisfaction rates were assessed by the seven levels Global Aesthetic Improvement Scale (GAIS) score (from +3 for very much improved to −3 for very much worse). The overall impression of the expert investigators (iGAIS) was correlated to the score from the subjects themselves (sGAIS) for each treated area and at each timepoint. As shown on Figure 6, the evolution curves for ART FILLER® Volume and Juvéderm® Voluma overlaid confirming the similar efficacy of the fillers on volume restoration. Furthermore, the GAIS assessment performed by the investigators (Figure 6 left panels) was conformed to the score recorded by the subjects (Figure 6 right panels). Interestingly, although no difference was observed between the 2 fillers for midface, jawline, and temple; the proportion of subjects feeling an aesthetic improvement at D540 was higher than the proportion of investigators (Table 1). This data support that the investigators opinion on GAIS was reliable.

3.5 | Assessment of skin characteristics by high-frequency ultrasound

To further characterize the long-term morphological effects of filler injections, the dermal density and thickness were assessed at each visit for a selected number of subjects per zone (Figure 7). For the midface area (Figure 8A), the available data showed no significant effect on skin thickness for both fillers. However, a significant increase of skin density was observed only with ART FILLER® volume at D90 and D180. For the jawline (Figure 8B), no significant effect on skin thickness for both fillers was measured, but both products induced a significant increase of skin density that was observed until D540. Interestingly, this increase in skin density was more relevant with ART FILLER® Volume than with the reference product. For the temple area (Figure 8C), only a tendency to increase in skin density was observed for both fillers. Similarly, a tendency to increase of the chin skin density was measured for each time points and was significant for D90 only (Figure 8D).

3.6 | Analysis of the side effects induced by the fillers

Most of reported reactions were slight pain during injection, erythema just after injection or irregularities at palpation (Table 2). All detected events were expected and routinely seen with HA-based fillers. Most of these events disappeared at D21 and no serious adverse events have been reported during the study for both fillers. However, there is an important but not statistically significant difference in the tolerability of two products in the favor of ART FILLER® Volume. As shown on Table 2, the total number of adverse events tended to be higher by 30% for the reference product compared with ART FILLER® Volume.

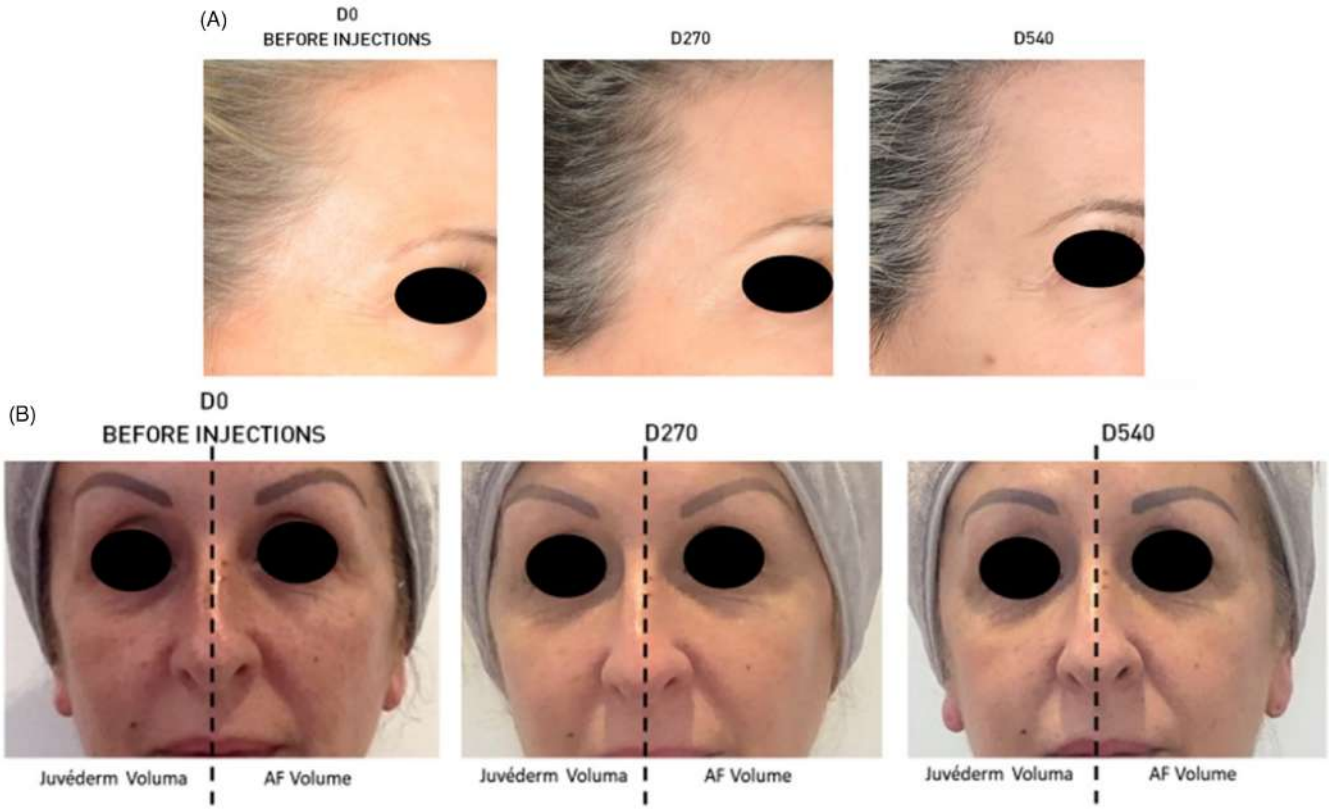

FIGURE 5 Representative photos of the remanence of clinical results on the temple at D0, D270, and D540 after a single injection of ART FILLER® Volume on temple (A) or the midface (B)

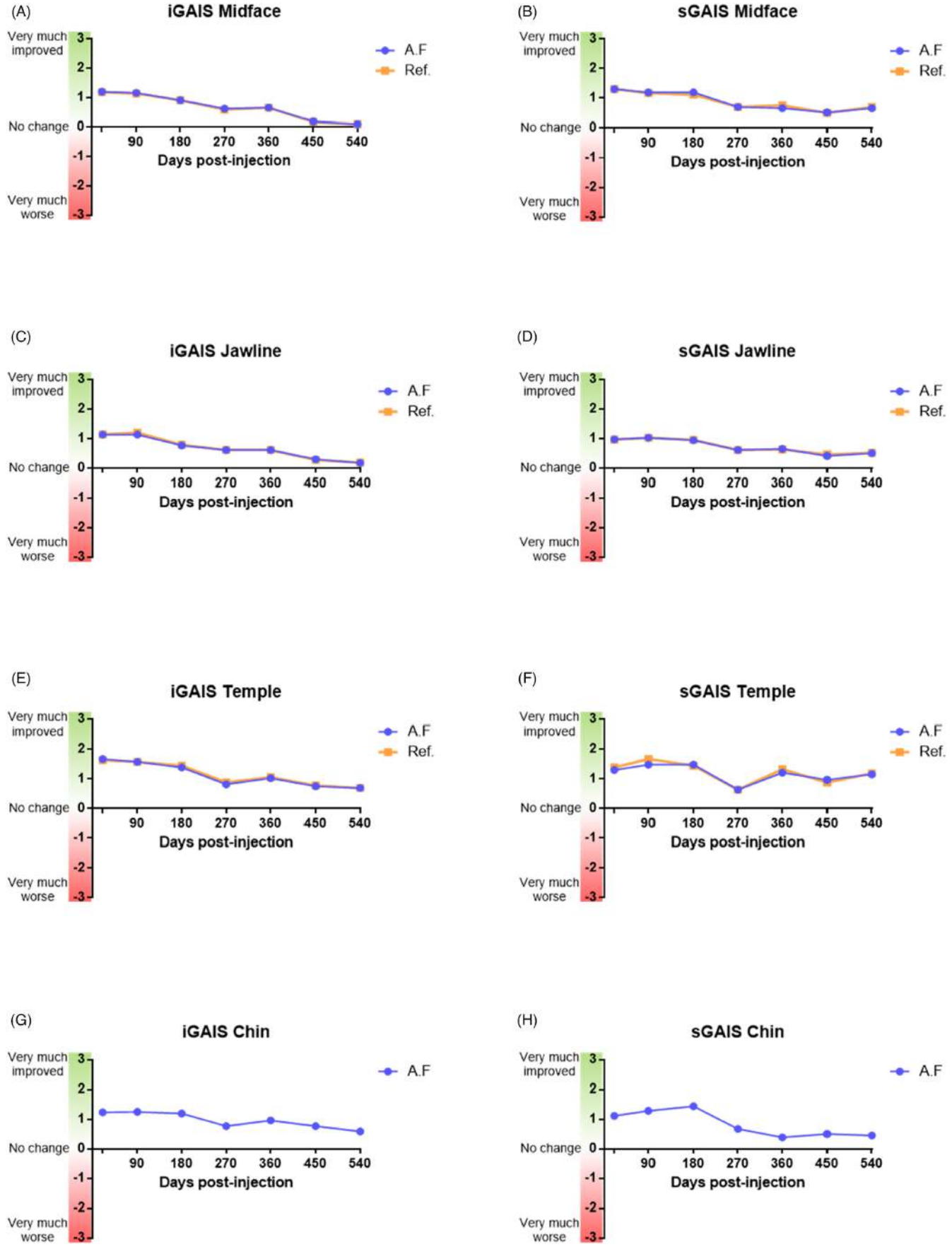

FIGURE 6 Global Aesthetic Improvement Scale assessed by the investigators (iGIAS) or the subjects (sGIAS) from D21 to D540 on the per protocol population for the midface (A and B), jawline (C and D), temple (E and F), and chin (G and H). Data are mean calculated from the number of values available for each visit

3.7 | Ex vivo characterization of fillers-induced skin inflammation

To understand the differences regarding the slight and moderate side effects observed during the clinical phase, we analyzed the potential inflammation induced by the fillers on human skin explants. Using the skin micro-dialysis technic, we measured the levels of Interleukin 8 (IL-8), tumor necrosis factor alpha (TNF-α) and histamine after the injection of saline solution, ART FILLER® Volume or the reference product. Injection of fillers, such as hyaluronic acid, has been shown to induce local mechanical stress induced by the needle but also by the tissue deformation due to volumes augmentation.[17] This mechanical stress is translated by biochemical, metabolic, and secretory profile modifications of the surrounding cells.[17] Here, we found that injection by the reference item induced a rapid release of IL-8 that remained significant until 12 h post-injection and disappeared after 24 h (Figure 9A,B). This increase of IL-8 secretion was not observed neither in control nor for ART FILLER® Volume. Similarly, histamine secretion was rapidly increased by injection of both products (Figure 9E,F). However, this secretion was significantly higher with the reference item at 1 and 6 h post-injection comparing with ART FILLER® Volume. Finally, none of the tested fillers induced an effect on TNF-α release (Figure 9C,D).

TABLE 1 Proportions of subjects with improvement in Global Aesthetic Improvement Scale in treated area assessed by investigators or subjects

	Art Filler		Reference	
	D21	D540	D21	D540
Midface				
Investigators	100%	23%	98%	23%
Subjects	85%	48%	87%	50%
Jawline				
Investigators	97%	22%	97%	23%
Subjects	74%	38%	71%	39%
Temple				
Investigators	97%	50%	97%	50%
Subjects	91%	75%	91%	75%
Chin				
Investigators	92%	36%	n.d	n.d
Subjects	84%	36%	n.d	n.d

Note: The percentages are given at D21 and 18 months post-injection (D540). % are calculated from the number of values available for each visit.

4 | DISCUSSION

This study brought evidence for the non-inferiority of ART FILLER® Volume versus the reference Juvéderm® Voluma regarding volume restoration for midface, jawline, and temple. Moreover, a satisfactory result was observed for all the studied area (including the chin) injected with ART FILLER® Volume. Three weeks post-injection, a significant improvement of the chin was observed for 80% of the subjects, 90% for the jawline, 93% for midface, and 100% for the temple. The positive evolution was still observed 18 months post-injection (55% for midface, 53% for jawline, 62% for temple, and 73% for chin), and no significant difference between products was observed. Interestingly, these results were obtained without any touch-up injection during the whole study.

The success rates after injection observed in this study were similar to those reported previously.[18,19] However, we noticed a faster decrease of the success rate for the midface when compared with previous studies using the same reference product Juvéderm Voluma (76% of success rate at 6 months versus 86% in Baumann, L. et al. and Jones, D. et al.[18,20] studies and 96% in Jung, J.M. et al.[19] study, then 55% after 18 months versus 72% in Baumann, L. et al.[18]). Similarly, the satisfaction of the subjects was slightly higher on other published article, (71% of subjects that rated themselves as improved on the GAIS scale after 6 months versus 97% published by Baumann, L. et al. and Jones, D. et al.[18,20] studies, and 50% after 18 months versus 71% published by Baumann, L. et al.[18]). These differences in the long-term efficacy may be related to the injected volume of filler

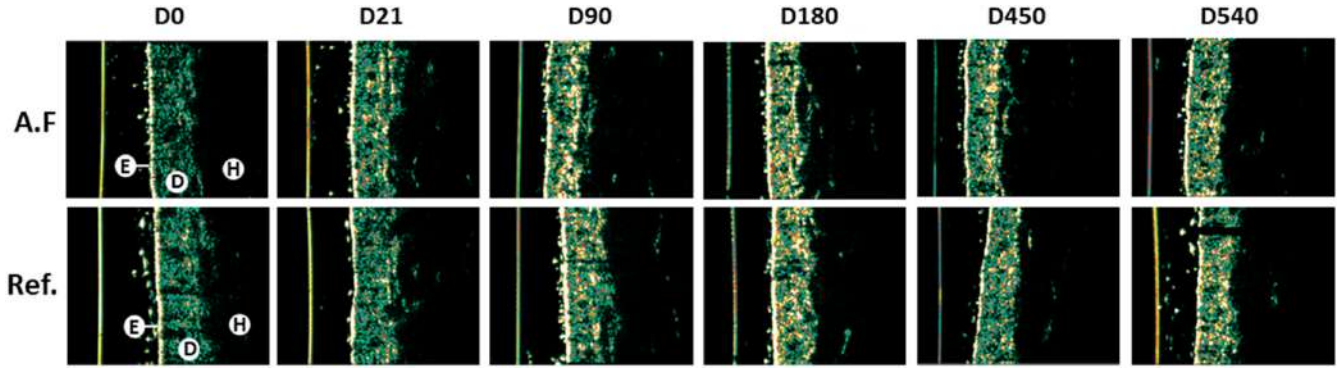

FIGURE 7 Representative images of skin thickness and density follow-up of the jawline area by high-frequency ultrasound analysis at different time points. The skin density resulting from collagen accumulation is revealed in yellow intensity. E, Epidermis, D, Dermis, and H, Hypodermis

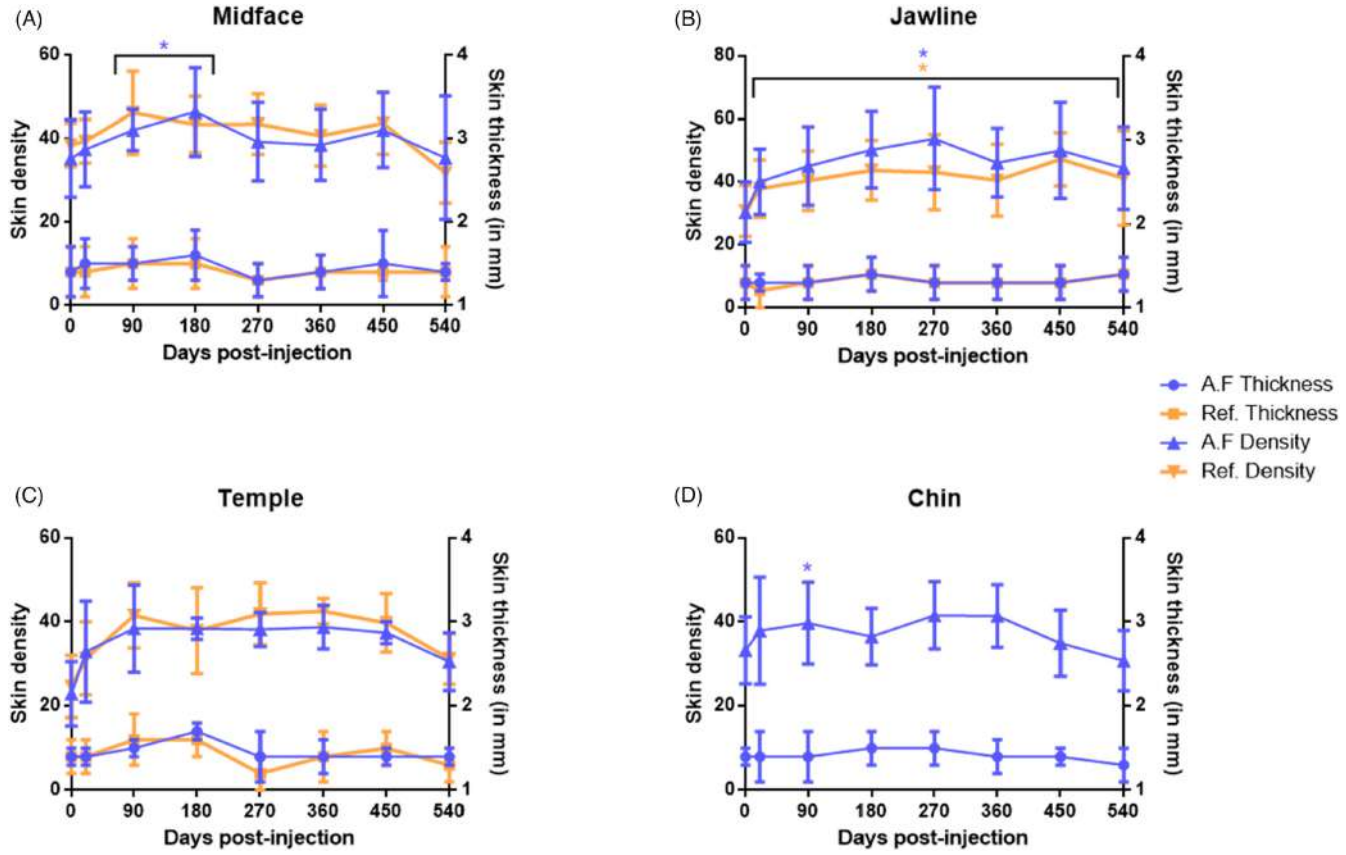

FIGURE 8 Evolution of the skin thickness (in mm) and density assessed by ultrasound imaging for (A) the midface, (B) the jawline, (C) the temple, and (D) the chin during the investigation period. Data are means ± SD, $^*p < 0.05$ compared with D0 for each filler

	Slight		Moderate		Severe	
	A.F	Ref.	A.F	Ref.	A.F	Ref.
Erythema	11	13	0	0	0	0
Ecchymosis	2	2	0	0	0	0
Hematoma	2	2	1	5	0	0
Oedema	0	1	0	0	0	0
Dyschromia	0	1	0	0	0	0
Irregularity at palpation	1	1	0	0	0	0
Necrosis	0	1	0	0	0	0
Tyndall effect	0	1	0	0	0	0
Over-correction	0	0	0	0	0	0
Spontaneous pain	17	13	4	9	1	1
Pain at palpation	1	2	0	0	0	0
Total Events	34	37	5	14	1	1

TABLE 2 Summary of the adverse events related to injections in the midface, jawline, and temple areas at D0 after injections

Note: The events were divided in 3 categories slight, moderate, and sever.

and the possibility of touch-up injections during the studies. Here, 1.2 ml maximum was injected in the midface whereas an average of 6.6 ml was injected in Baumann, L. et al.[18] 6.65 ml in Jones, D. et al.[20] and 6.68 ml in Few, J., et al.[21] studies.

It has been demonstrated that an increase of the dermis density and/or thickness is associated to an improvement of skin quality and smoothing of dermal depressions.[22,23] The ability of the skin to reflect ultrasound echogenic signals comes principally from the dermis network of collagen and elastin fibers. Assessment of these parameters by high-frequency ultrasound revealed that the observed volume restoration was mainly due to an increase in dermis density. Interestingly, the dermis thickness has not been increased in any of

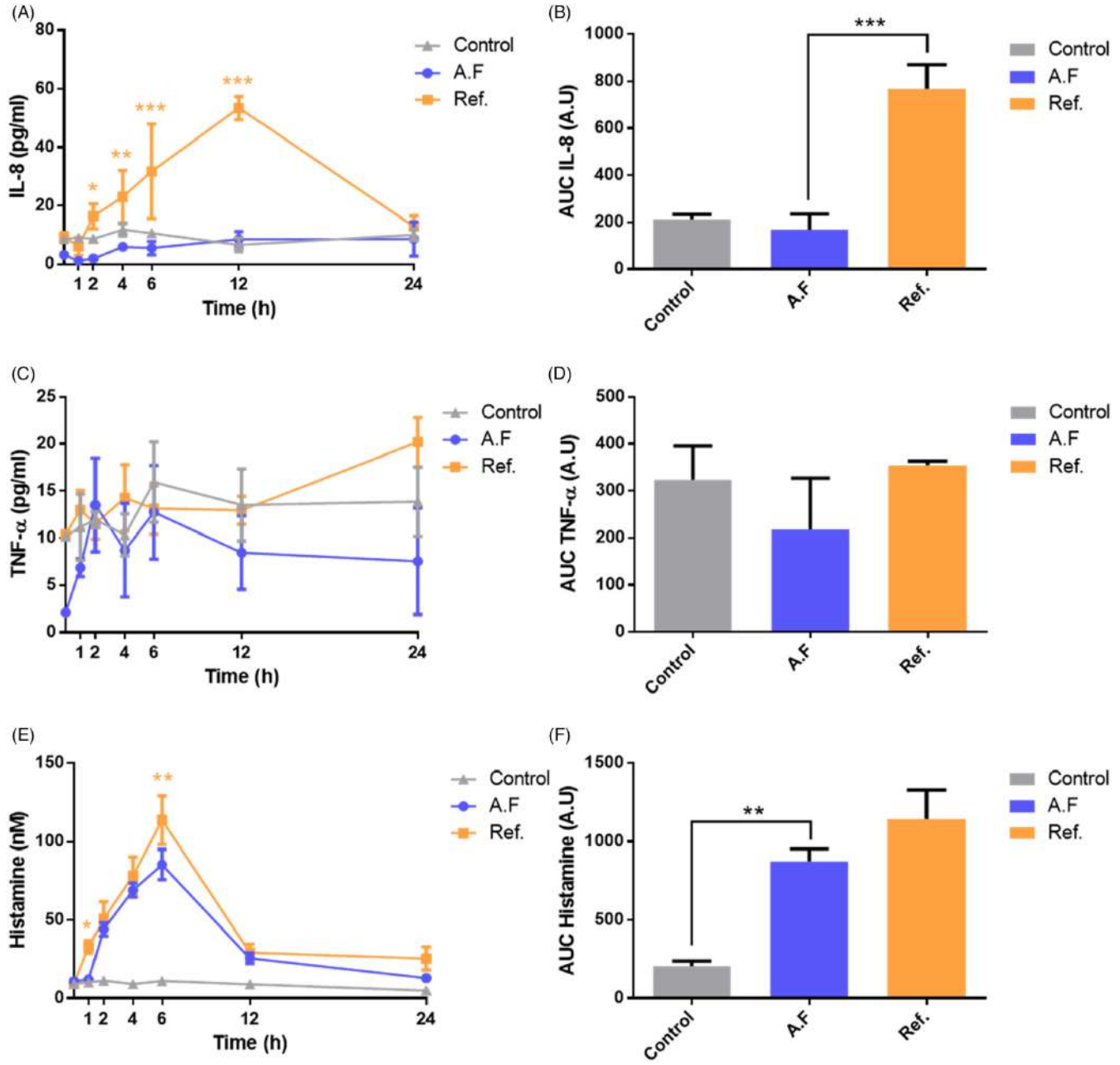

FIGURE 9 Quantity of IL-8 (A), TNF-α (C), and Histamine (E) in the micro-dialysates after fillers injection. $^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$ Ref. versus A.F. The areas under the curves were calculated for IL-8 (B), TNF-α (D), and Histamine (F). $^{**}p<0.01$ and $^{***}p<0.001$

the assessed areas despite a significant restoration of volume. We hypothesize that absence of modification in skin thickness was due to the deep injections of the fillers. Indeed, these injections were far from the dermis layer and thus, the observed volume restorations could result from the interactions of the fillers with the hypodermis fat layer. Recently, a published article by Nadra et al.[24] supports this hypothesis that the human adipocyte life cycle is influenced by highly cross-linked HA. The authors have demonstrated that in addition to their filler property, HA-based fillers are excellent carriers of adipocyte cells to reconstruct and maintain the dimensions of volume loss.[24] However, given that the echogenicity of the hypodermis is very low, our selected method of investigation did not allow us to measure these effects on the subcutaneous fat layer. Furthermore, the assessments remained exploratory and were performed on a small panel of subjects only. Still, the observations suggested that injection of ART FILLER® Volume or the reference product tended to increase the density of the skin (whatever the studied area) and that this effect persists over time. The possible reason for the higher effect of the ART FILLER® Volume may be due to Tri-Hyal Technology, which provides a good viscosity to the ART FILLER® Volume thanks to free HA within the composition.

Hyaluronic acid is the most used soft-tissue filler for facial revolumizing treatment due to its favorable outcomes and safety profile. In this study, the injections were well tolerated, causing a

few numbers of expected side effects such as erythema, hematoma, or spontaneous pain. The intensity of these reactions varied from light to moderate, beginning soon after application and promptly disappeared within few days. The reported side effects were those typically expected following HA filler injection.[25,26] As previously hypothesized by Micheels P, some rare inflammatory episodes due to allergic responses could explain such acute reactions.[27] In addition, mechanical stress has been also described as the increase in pressure occasioned by the injection causes the filler to flow naturally toward areas that deforms easily such as the hypodermis, leading to a local modification of the biochemical, metabolic, and secretory profile of the surrounding cells. In this study, we observed a slight difference in the safety level of the two products in the favor of ART FILLER® Volume (31% more events with the reference product). This hypothesis was explored using ex vivo human skin explants. A higher potential of the reference product, Juvéderm® Voluma to promote the secretion of IL-8 (a cytokine secreted by epithelial cells), and histamine (a factor secreted by macrophages) was observed. These data suggested a better tolerability and safety of ART FILLER® Volume regarding the acute inflammation induction compared with the Juvéderm® Voluma which could explain the safety clinical results. However, many variables can influence inflammation, including the filler properties, the application technique, the site of the injection, and the individual sensibility. Even if the 2 fillers were compared by contralateral injections and with similar treatment procedures, further exploration are needed to conclude about the superiority of ART FILLER® Volume on Juvéderm® Voluma on the acute inflammation. More recently, a direct effect of the COVID vaccination or infection has been demonstrated on the inflammatory reactions post-injection by HA-fillers.[28]

5 | CONCLUSION

In conclusion, this study validated the efficacy and safety of the injectable hyaluronic acid-based filler, based on Tri-Hyal technology versus Vycross technology with a sustained efficacy for at least 18 months for the midface, temple, jawline, and chin. The evaluation methods used in this study confirmed its non-inferiority to the CE-marked comparator for all injected areas, except for the chin where the evaluations were non-comparative. Taken together, the methodology and observations brought a reliable approach for the long-term assessment of HA fillers.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the acquisition of data, drafting and revising the manuscript for important intellectual content, approved the final version, and have agreed to be accountable for all aspects of the work. Further, FF and KN conducted the study design, management, and data analysis. FB, PG, HD, FL, LB, and PK were all study investigators. FB, FF, PG, HD, FL, LB, KN, and PK made substantial contribution to the interpretation of the data.

ACKNOWLEDGEMENT

A special thanks to Hanane Issa and Shannel Curic for their remarkable help for monitoring and data recovery. The authors deeply thank Sophie Mac, Jean-Marie Sainthillier, Marie-José Moschetti, Ana De Lemos, Luc Sentier, Elizabetta Izzo, and Berengere Boucly for their dynamic supports from concept to execution of the study.

CONFLICT OF INTEREST

FF and KN are employees of FILLMED Laboratories. There is no conflict of interest for any other authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Braccini F, Fanian F, Garcia P, et al. Comparative clinical study for the efficacy and safety of two different hyaluronic acid-based fillers with Tri-Hyal versus Vycross technology: A long-term prospective randomized clinical trial. *J Cosmet Dermatol*. 2022;00:1-13. doi: 10.1111/jocd.15200