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ORIGINAL ARTICLE

Long-term efficacy and safety of a hyaluronic acid dermal filler based on Tri-Hyal technology on restoration of midface volume

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Abstract

Introduction: Art Filler Volume (AFV) is a hyaluronic acid (HA)-based filler formulated with "Tri-Hyal" technology, a unique combination of three sizes of HA chains. This study assessed AFV efficacy and safety over 18 months when used to restore midface volume.

Methods: During this open-label study, a maximum of 1.8 mL AFV was injected into each cheek area on Day 0 (D0). Subjects were evaluated at D21, when, if necessary, a retouch could be performed (maximum 1.2 mL per cheek). Subjects were evaluated at seven follow-up visits through to D540. The primary assessment was based on the evolution of the Medicis Midface Volume Scale (MMVS) grade on D21. Secondary outcomes were local and general adverse events, investigator- and subject-assessed Global Aesthetic Improvement Scale scores and changes in self-esteem.

Results: Of the 79 healthy Caucasians enrolled (mean age 54.8 years), 25 required a second injection. In the intention-to-treat population, mean overall MMVS scores improved significantly from D0 (3.2 ± 0.4) to D21 (1.8 ± 0.6) and D42 (1.7 ± 0.6) (all $p < 0.0001$). MMVS scores for each cheek also improved significantly, irrespective of retouch on D21: 22% of injections showed a persistent benefit at D540 without retouch. The most common adverse events were pain on palpation (19%), erythema (15%) and edema (13%); most were mild or moderate and resolved within 2 weeks.

Conclusion: AFV produces a sustained objective and subjective midface volume restoration in female and male subjects, often without retouching, and was well tolerated.

KEYWORDS
dermal filler, hyaluronic acid, midface, Tri-Hyal technology, volume restoring

1 | INTRODUCTION

Age-related aesthetic changes to the face, which generally begin in a person's late 30s, may adversely impact other people's perception of the subject as well as undermining the person's self-esteem, body image, and confidence.[1,2] These changes arise from reductions in the thickness of the skin, and in the volume of bone, muscle, and superficial and deep fat pads.[1] Total and dermal collagen, and elastin content also decline.[3] The loss of volume tends to be most marked in the deeper layers, following age-related reductions in subcutaneous fat and bone.[3]

The cumulative effect of these age-related changes can profoundly affect facial appearance.[1,3–5] For instance, the loss of volume can result in: reduced midface projection, such as a diminution in the prominence and width of the malar eminence; lead to a heart-shaped face becoming rectangular or pear-shaped; and deepening of the nasolabial fold.[1,3–5] A crescent-shaped hollow beneath the lower edge of the orbicularis oculi muscle, lowering of the malar fat pad and cheek skin, which results in a visually apparent segmentation of facial compartments, and reduced jaw angle are also common age-related changes.[1,3–5] Subjects may also show age-related dermatological alterations, including loss of skin elasticity, increased skin roughness, and xerosis.[1,3–5]

Injectable hyaluronic acid (HA) fillers restore facial volume, which reduces the appearance of sagging skin and skin folds.[1,5–10] Art Filler® Volume is a high G' HA filler with good cohesivity which can be injected in the hypodermis or supra-periosteal for a volumizing effect. The high viscosity of the gel allows it to be injected easily through a needle or cannula. This filler is indicated to restore facial volume by subcutaneous, supraperiosteal or deep dermis injections. Art Filler Volume (AFV) is formulated with Tri-Hyal technology, a proprietary combination of three types of cross-linked HA designed to optimize smoothing and volumizing results. This open-label study, performed at eight centers in France, assessed AFV's efficacy and tolerability for 18 months follow-up when used to restore cheek volume.

2 | METHODS

2.1 | Treatment

AFV was injected bilaterally into the cheeks. A maximum of 1.8 mL AFV was injected into each cheek (total 3.6 mL) on Day 0 (D0). Subjects were evaluated at D21 when, if deemed necessary by the subject and clinician, a retouch could be performed using a maximum of 1.2 mL AFV per cheek. No further reinjections into the cheeks were permitted during the study. Subjects were evaluated at D42, D90 (3 months), D180 (6 months), D270 (9 months), D360 (12 months), D450 (15 months), and D540 (18 months). Figure 1 summarizes the study design.

2.2 | Assessment

The primary assessment was the change in volume of each treated cheek (right and left) overall on D21 after the first AFV injection based on the Medicis Midface Volume Scale (MMVS) score.[11] Each side was considered as its own control and there was no comparison between the two cheeks, even if there was an asymmetry. The MMVS score rates midfacial appearance using a 4-point scale: (1) fairly full midface, cheek prominence projected beyond the infraorbital rim at 45° view; (2) mild loss of fullness in the midface area, flatness of the midface, cheek prominence at or behind infraorbital rim; (3) moderate loss of fullness with slight hollowing below malar prominence, the presence of the nasojugal groove extending past the mideye; (4) substantial loss of fullness in the midface area, clearly apparent hollowing below the malar promence.[11] "Satisfactory" volume restoration was defined as a reduction of ≥1 point compared with baseline in the MMVS score.[11] If a retouch was deemed necessary by the subject and clinician on D21, the subject was also assessed on D42. The persistence of the correction was evaluated at D90, D180, D270, D360, D450, and D540.

Local and general adverse events were recorded at each study visit. Investigators and subjects assessed outcomes on the Global Aesthetic Improvement Scale (GAIS) at each clinic visit. Subjects also completed a validated self-esteem questionnaire (Echelle Toulousaine de l'Estime de Soi [ETES]), at baseline, at D180, and at D360.

2.3 | Ethical approval

Ethical approval was provided by the committee of "Île-de-France VI Comité de protection des personnes," at Pitié-Salpêtrière Hospital, Paris. Subjects provided informed consent for the study and use of images. The study was conducted in accordance with ISO 14155:2011.

2.4 | Inclusion and noninclusion criteria

The study enrolled males or females aged 19 years or older, with a Fitzpatrick Phototype of I–IV and a MMVS score of 3 or 4, who did not plan to undergo a facial cosmetic procedure during the whole study.

Noninclusion criteria included a lifetime history of facial injections, implants, or treatments that employed nonabsorbable fillers or a skin-retaining device on the face, such as mesh, gold wire, liquid silicone, or other particulate material. The subjects could not have had any corrective facial aesthetic injections (botulinum toxin or HA facial filler) in the cheeks for the last 12 months. Subjects who underwent medical treatment by laser, ultrasound, deep chemical peeling, or facial dermabrasion in the last 3 months or who planned

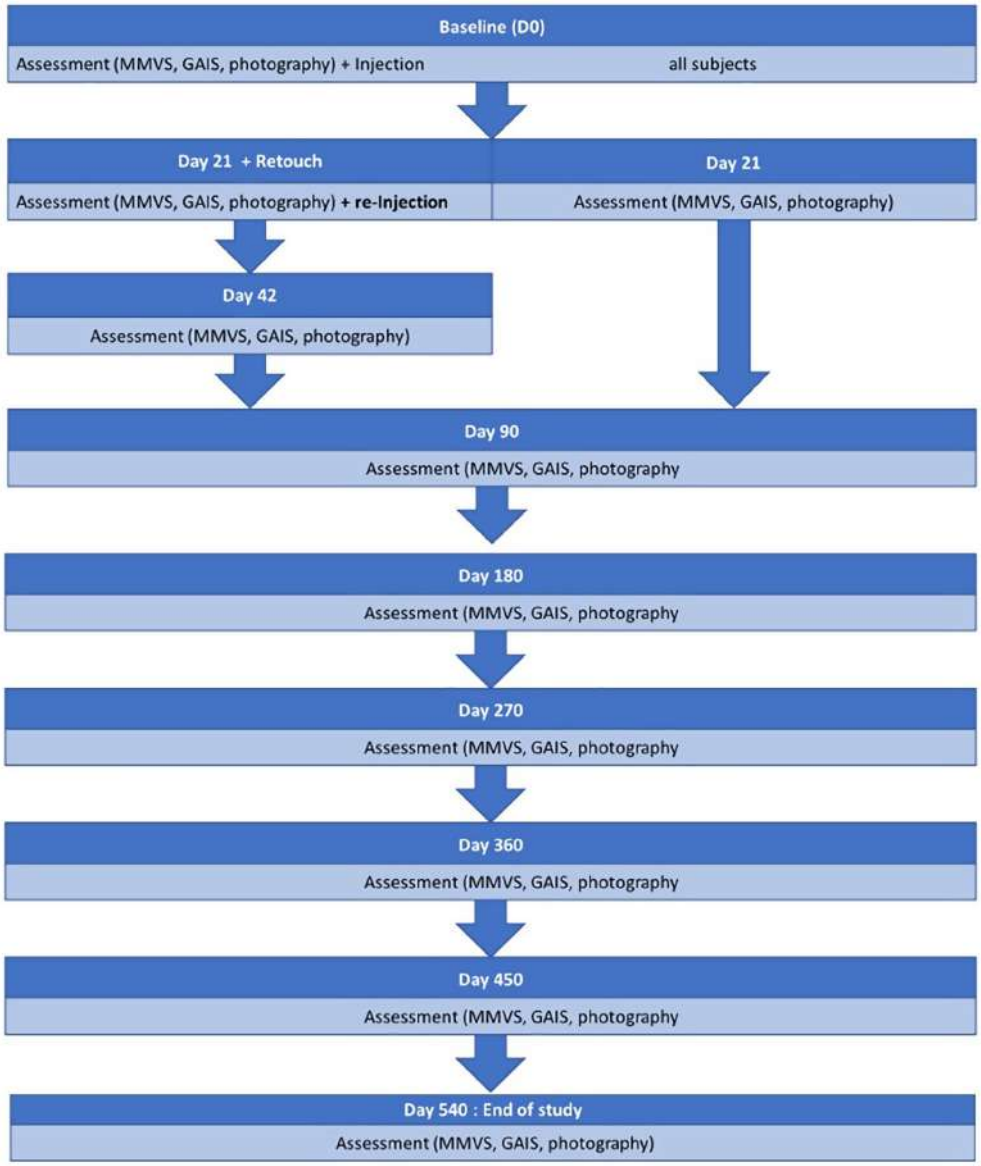

FIGURE 1 Study design.

to undergo such treatment during the study, people with a history of hypertrophic, keloid or dyschromic scarring, multiple severe allergies or anaphylactic shock, or hypersensitivity to any ingredient were not included.

2.5 | Statistical analyses

Satisfactory volume restoration was defined as an improvement of ≥1 point on the MMVS[11] compared with baseline, assessed separately for the right and left cheeks and overall (both cheeks). A satisfactory volume correction rate of 95% was expected at D21 (D42 for subjects who received a second injection). To detect this rate with an accuracy of 5% (95% confidence interval), 73 cheeks would need to be injected. Therefore, the study aimed to assess at least 100 cheeks.

The MMVS score of each injected area, measured at D21 (3 weeks) or D42 (6 weeks, if retouched at 3 weeks) after the first injection, defined the optimal aesthetic score for a given target area. The maintenance of this score for treated areas was calculated at D90, D180, D270, D360, D450, and D540 without any reinjection according to the difference in the MMVS score between these time points and the D21/D42. Success was defined as ≥1 point improvement in MMVS and was considered over time in the intention-to-treat (ITT) population. The persistence rate of the aesthetic correction was defined as the percentage (with its 95% confidence interval) of areas that maintained a ≥1 point improvement in MMVS, with no or negative difference, compared to D21/D42 without further reinjection (number of cases with difference ≤0/total number of areas treated) at subsequent time points. These calculations were performed on the per protocol population (PPP).

The analyses encompassed three populations. The ITT population included all subjects enrolled. The PPP included subjects with results at D21 after the first injection or D42 in those who received a second injection. The safety population included all subjects who received at least one AFV injection.

The MMVS analysis was performed on the ITT population based on the mean changes between baseline and each time point for the right and left cheeks and overall (both cheeks). The statistical significance of the change between baseline and D21 and D42 was assessed using the Wilcoxon test. Analyses were repeated using the PPP.

The GAIS score has 7 levels (from +3 for very strongly improved to −3 for very strongly worsened) and was assessed at each time point for each cheek and overall, on both sides. This analysis was performed in the PPP. Changes in the ETES score at D180 and D360 were calculated using subjects with these values at baseline and the given time point.

3 | RESULTS

3.1 | Demographics

The study enrolled 79 healthy Caucasian subjects, 7 males and 72 females, with a mean age of 54.8 ± 9.7 years. The study ran between September 2016 and July 2018. Table 1 summarizes the baseline demographics and MMVS scores.

TABLE 1 Demographics and baseline MMVS scores (ITT population).

Characteristic	*N*: 79
Gender, *n* (%)	
Male	7 (9)
Female	72 (91)
Age (years)	
Mean (±SD)	54.8 (±9.7)
Median (range)	56 (33–76)
Phototype	
I, *n* (%)	8 (10)
II, *n* (%)	32 (41)
III, *n* (%)	34 (43)
IV, *n* (%)	4 (5)
Missing data	1 (1)
Body mass index (kg/m^2)	
Mean (±SD)	21.3 (±6.2)
Median (range)	20.5 (17.3–31.3)
Hormonal status (females only, *n* = 72)	
Post-menopausal, *n* (%)	51 (71)
Childbearing potential, *n* (%)	21 (29)
MMVS: Left cheek	
Fairly full midface	0
Mild loss of fullness	0
Moderate loss of fullness	67 (85)
Substantial loss of fullness	12 (15)
MMVS: Right cheek	
Fairly full midface	0
Mild loss of fullness	0
Moderate loss of fullness	67 (85)
Substantial loss of fullness	12 (15)
MMVS: Both cheeks	
Fairly full midface	0
Mild loss of fullness	0
Moderate loss of fullness	134 (85)
Substantial loss of fullness	24 (15)

Abbreviations: ITT, intention-to-treat; MMVS, Medicis Midface Volume Scale.

3.2 | Volume injected

The mean volume for the first injection was 1.1 ± 0.4 mL per side (maximum authorized volume was 1.8 mL per side). Twenty-five midface zones required a second injection at D21 (14 injections on the left and 11 injections on the right side), a total of 16% across 158 midface zone injected. The mean total volume injected during the study was 1.1 ± 0.5 mL per side at baseline and 0.7 mL for reinjection at D21. The maximum injected volume was 2.4 per side.

3.3 | Initial efficacy

In the ITT population, mean MMVS scores ± SD for the left cheek improved significantly from 3.2 ± 0.4 at baseline to 1.8 ± 0.7 at D21 and 1.7 ± 0.6 at D42, including those that received a retouch ($p < 0.0001$). For the right cheek, the mean score improved significantly from 3.2 ± 0.4 at baseline to 1.8 ± 0.6 at D21 and 1.7 ± 0.6 at D42 ($p < 0.0001$). The mean overall score improved significantly from 3.2 ± 0.4 to 1.8 ± 0.6 and 1.7 ± 0.6 at D21 and D42, respectively ($p < 0.0001$). At baseline, no subject showed MMVS scores of 1 (fairly full midface) or 2 (mild loss of fullness) according to the inclusion criteria while at D21, 32% of left cheek, 33% of right and 32% of both cheeks showed MMVS scores of 1. This percentage was 41% at D42, for the population who received a retouch at D21. At D21 and D42, 54% and 53% respectively showed MMVS scores of 2 in all three analyses (Figure 2). At D21, 91% of left cheek, 92% of right cheek, and 92% of both cheeks overall showed an improvement of at least one MMVS grade compared with baseline. At baseline, 85% of subjects had Grade 3 and 15% had Grade 4 MMVS scores on both sides of the midface. By D21, none of the subjects were rated as Grade 4, and the number of Grade 3 scores were reduced to 14% on the left and 13% on the right. For the subjects who were reinjected on D21 (14 subjects were reinjected on the left [18%] and 11 on the right side [14%]),

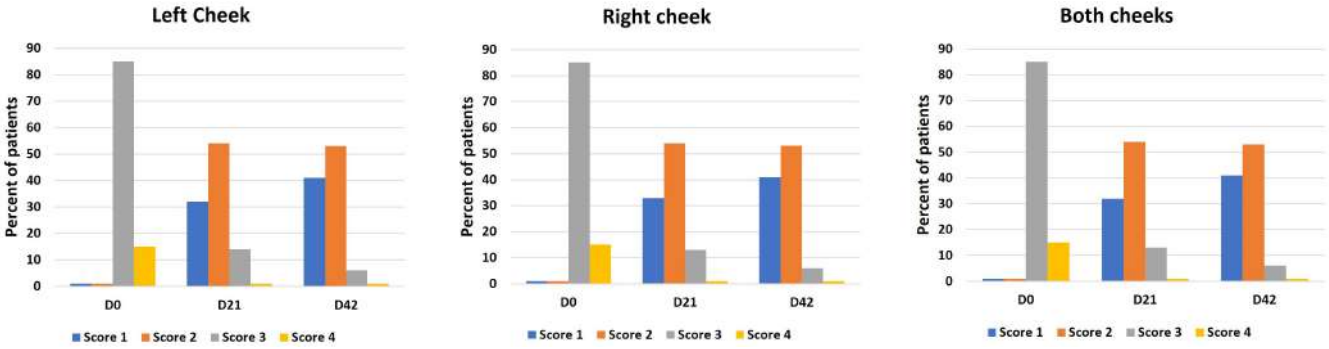

FIGURE 2 Evolution of Medicis Midface Volume Scale score after injection of AF volume on midface. Score 1: fairly full midface; (2) mild loss of fullness; (3) moderate loss of fullness; (4) substantial loss of fullness.

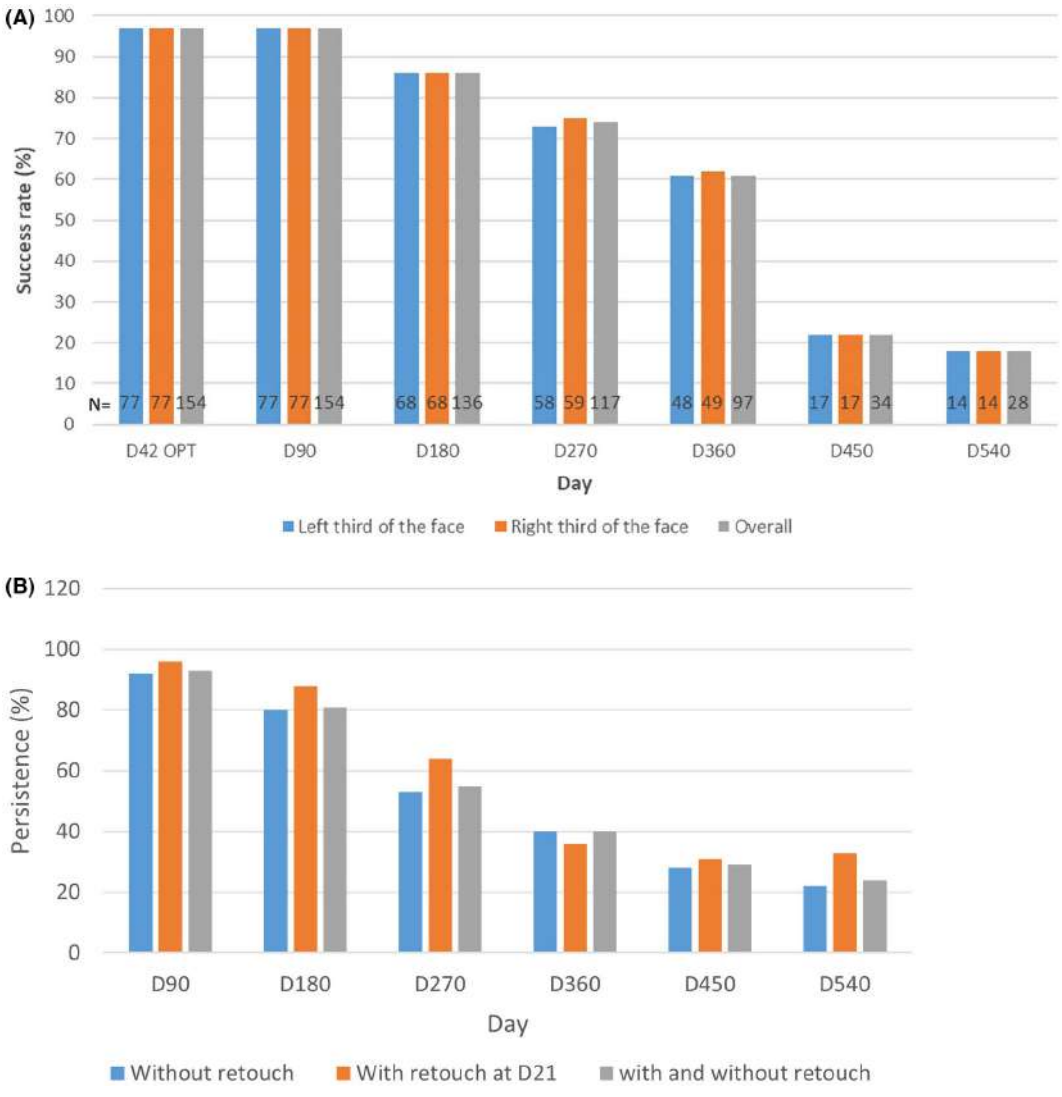

FIGURE 3 (A) Evolution of Medicis Midface Volume Scale (MMVS) scores for left and right cheeks and overall (both cheeks; ITT population). n: number of injections in either/both cheeks; OPT: subjects showing a satisfactory result ± retouching and reassessment after an additional treatment at D21; Success rate: proportion of subjects showing a satisfactory improvement. (B) Persistence of MMVS scores in three groups: with a retouch, without a retouch, or both with and without a retouch (both cheeks; per protocol population).

the success rate at D42 was 97% in all three analyses (left, right, and both sides) (Figure 3). Success rates (≥1 point improvement in MMVS) were considered separately overtime (Figure 3) and the per protocol (data not shown) and ITT analyses showed similar results. Among 79 subjects injected in the midface, 77 (97%) experienced >1 point improvement in MMVS scores at 3 weeks after the injection. This result

was maintained at D90 (3 months after the injection); however, this number decreased to 68 (86%) at 6 months, 59 (75%) at 9 months, 49 (62%) at 1 year, 17 (22%) at 15 months, and 14 (18%) at 18 months in the ITT population (Figure 3).

3.4 | Persistence

The persistence rate was calculated based on the maintenance of success rate at each time point compared to D21/D42. This parameter revealed 11% in all ITT analyses (left, right, and both sides) at 18 months (D540) (data not shown). In addition, we revealed that persistence was almost the same between groups without or with touch up at D21 or the global population (both groups) in the PPP, 22% ($N = 51$), 33% ($N = 15$), and 24% ($N = 66$), respectively (Figure 3B). An example of before and after treatment images is shown in Figure 4.

According to the GAIS evaluated by subjects and investigators, the proportion rating facial fullness as "improved" or "much" or "very much improved" was 90% at D21 (100% at D42 for the retouched group) and 68% at D540 (18 months) (Tables 2 and 3). ETES score at D180 and D360 showed no significant changes compared with baseline.

3.5 | Safety and tolerability

Table 4 summarizes the adverse events. Overall, 47% of subjects developed at least one treatment-emergent adverse event (TEAE), 27% on the left, and 20% on the right cheeks. The most reported TEAEs were pain on palpation (19%), erythema (15%), and edema (13%). No instances of ecchymosis were reported. Most TEAEs were mild or moderate. In 85% of the cases, the duration of the TEAE was 2 weeks or less. One subject discontinued due to adverse events not related to treatment (breast cancer).

FIGURE 4 Before and after treatment images for patients S04-16 and S04-02 who received 1.8 mL and 1.6 mL, respectively, per side on Day 0 without retouch compared with Day 360 and Day 540.

TABLE 2 Evolution of the Global Aesthetic Improvement Scale performed by the physician for both cheeks.

	D21 ($n = 158$)	D42 ($n = 25$)	D90 ($n = 154$)	D180 ($n = 140$)	D270 ($n = 144$)	D360 ($n = 144$)	D450 ($n = 70$)	D540 ($n = 68$)
Very much worse (−3), *n* (%)	0	0	0	0	0	0	0	0
Much worse (−2), *n* (%)	0	0	0	0	0	0	0	0
Worse (−1), *n* (%)	0	0	0	0	1 (1)	5 (3)	0	0
No change (0), *n* (%)	9 (6)	0	8 (5)	6 (4)	23 (16)	36 (25)	18 (26)	11 (32)
Improved (+1), *n* (%)	81 (51)	7 (28)	90 (58)	110 (79)	112 (78)	101 (70)	50 (71)	23 (68)
Much improved (+2), *n* (%)	58 (37)	18 (72)	50 (32)	20 (14)	8 (6)	2 (1)	2(3)	0
Very much improved (+3), *n* (%)	10 (6)	0	6 (4)	4 (3)	0	0	0	0
Average score, mean (median)	1.4 (1)	1.7 (2)	1.4 (1)	1.2 (1)	0.9 (1)	0.7 (1)	0.8 (1)	0.7 (1)

Note: % are calculated from the number of values available for each visit.

TABLE 3 Evolution of the Global Aesthetic Improvement Scale performed by the subject for both cheeks.

	D21 (*n* = 158)	D42 (*n* = 25)	D90 (*n* = 154)	D180 (*n* = 140)	D270 (*n* = 144)	D360 (*n* = 143)	D450 (*n* = 70)	D540 (*n* = 68)
Very much worse (−3), *n* (%)	0	0	0	0	0	0	0	0
Much worse (−2), *n* (%)	0	0	0	0	0	0	0	0
Worse (−1), *n* (%)	4 (3)	0	2 (1)	2 (1)	1 (1)	3 (2)	0	0
No change (0), *n* (%)	13 (8)	0	22 (14)	18 (13)	33 (23)	47 (33)	20 (29)	22 (32)
Improved (+1), *n* (%)	82 (52)	14 (56)	78 (51)	95 (68)	102 (71)	87 (61)	48 (69)	46 (68)
Much improved (+2), *n* (%)	51 (32)	11 (44)	42 (27)	21 (15)	8 (6)	6 (4)	2 (3)	0
Very much improved (+3), *n* (%)	8 (5)	0	10 (6)	4 (3)	0	0	0	0
Average score, mean (median)	1.3 (1)	1.4 (1)	1.2 (1)	1.1 (1)	0.8 (1)	0.7 (1)	0.7 (1)	0.7 (1)

Note: % are calculated from the number of values available for each visit.

TABLE 4 Treatment-emergent adverse events (safety population).

	Left cheek (*n* = 79)	Right cheek (*n* = 79)	Both cheeks (*n* = 79; 158 injections)
≥1 Treatment-emergent adverse event, *n* (%)	28 (27)	21 (20)	49 (47)
Pain on palpation, *n*	8	7	15
Erythema, *n*	6	6	12
Edema, *n*	6	4	10
Nodule, *n*	4	3	7
Spontaneous pain, *n*	1	1	2
Burning sensation, *n*	1	1	2
Pain on cold	1	-	1

4 | DISCUSSION

This study provides evidence that a HA filler based on Tri-Hyal technology is effective and well tolerated when used for facial midface volume restoration. These data are similar to published data.[1,5–10] At D21, more than 90% of those who received AFV showed an improvement of ≥1 MMVS grade compared with baseline for the left and right cheeks, and overall. At D42, which includes those who received a retouch at D21, the success rate was 97% in all three analyses. Only 25 patients (24%) required a retouch suggesting that a single injection suffices for most people presenting for midface volume restoration.

At baseline, no subjects showed MMVS scores of 1 (fairly full midface) or 2 (mild loss of fullness) while at D21, about a third of subjects showed MMVS scores of 1. This score is a little higher (41%) at D42 for the subjects who receive a retouch. In addition, at D21 and D42, half of the subjects had MMVS scores of 2 in all three analyses with no difference between the two sides of the face. These data demonstrate that more than 80% of the subjects had a "fairly full midface" or only "mild loss of fullness" after treatment while they all showed "moderate to severe loss of fullness" before the treatment. A small proportion of patients (6% at D21 or D42 in the retouch group) were still rated as demonstrating "moderate loss of fullness" after treatment. This is due to partial correction of the patients with Grade 4 (substantial loss of fullness) MMVS at baseline; although they had a one grade improvement in MMVS after treatment, these patients were still rated as Grade 3 (moderate loss of fullness). The mean volume of injection was 1.1 mL per side, which is very low compared to other volumizing products,[1,12] suggesting that AFV has a good volumizing capacity.

AFV shows a sustained objective (MMVS) and subjective (investigator and subject GAIS) benefit that persists in some subjects (22% for the group without any touch up and 33% with touch up at D21) for at least 18 months. The results were consistent across multiple assessment methods, suggesting the findings are robust and clinically meaningful. Scores on the self-esteem assessment did not improve, which is discordant with the GAIS results. This may show that this scale is not powerful enough to reflect the effects of a facial volume restoring treatment on subjects' self-esteem and other existing scales (such as Rosenberg Self Esteem Scale) may be more appropriate for future studies.

Other studies confirm the long-term ability of HA fillers (including Juvéderm® Voluma®, Belotero® Volume and Emervel HA) to restore facial volume loss and the published data are similar to the data obtained in this study.[1,7,13] One study reported that 3 months and 2 years after HA treatment, 92.8% and 79.0% of subjects, respectively, rated their cheek volume as "improved" or "much improved" on the GAIS; in this study, at 6 months, the investigator rating was 96% and subject rating 86%, while at D540 both were 68%.[1] In another study, a comparison of two HA fillers (Belotero® Volume [CPM-26] and Juvéderm® Voluma® [VYC-20]) found that about half (51% and 54%) of subjects showed an improvement of ≥1 grade on the Merz Aesthetics Scale after 12 and 18 months, respectively.[7] In the current study 61% and 22% subjects showed ≥1 grade improvement in the MMVS score at 12 and 18 months; this difference may be due to differences in average injection volumes, which were 1.1 mL in this study and 2 mL in the previous study.[7] Moreover, 78% and 65% of the subjects in the same study showed an improvement on the GAIS at 18 months which is comparable to the 68% observed in the present study.[7]

Another study published in 2015 on 60 subjects with at least Grade 2 on the 4-point volume loss scale reported that at 18 months, 68.3% of subjects showed ≥1-grade improvement for full face (68.3% of subjects) after injection with a mean volume of 7.4 mL Emervel HA dermal fillers.[12] The improvement was apparent in several facial areas, including 66.6% in the cheeks and 58.6% improvement in the cheekbones. The volume of injection was also higher in this study; the mean volume injected was 7.4 mL for the full face, 2.2 mL in the cheeks, and 1.8 mL in the cheekbones.[13]

Other studies have explored the parallels between assessment of the longevity of clinical outcomes and histological durability of HA fillers in tissues.[14,15] Histologically, HA fillers have been shown to be long lasting and are associated with maintenance of clinically relevant improvement.[14] In addition, da Costa et al. demonstrated that the durability of HA fillers in the dermis varies depending on the class of HA filler (monophasic polydensified, monophasic monodensified, and biphasic).[15] They showed that the durability of the biphasic HA-based filler was superior to both monophasic monodensified filler and monophasic polydensified filler.[15] However, histological observations do not always correlated with a clinical correction improvement. For example, a monophasic HA filler (Juvederm Ultra Plus) has been shown to display greater correction longevity after injection compared to a monophasic HA filler (Perlane®).[16] Although the different classes of HA filler behave differently immediately after their injection into the dermis, their histological patterns are predictable.[17] The intrinsic physicochemical properties of HA fillers, associated with different manufacturing technologies, may also affect HA filler longevity in the dermis.

AFV was well tolerated, which again is consistent with other studies assessing HA fillers used to restore facial volume.[1,7,13] In this study, the investigators respected the "less is more" concept to avoid high volume injections which directly influence the inflammatory reactions of highly cross-linked fillers.[18] The most common adverse events associated with HA injections include erythema, swelling, bruising, tenderness, firmness, and lumps and bumps.[1,8,13] Most adverse events in previous studies were mild to moderate and lasted less than 2 weeks,[1] which is similar to the results of this study.

The study had certain limitations. The study was a post market study aimed to mirror naturalistic practice and blinding investigators and subjects would be difficult. The study was, therefore, non-randomized and open-label and did not include a comparative or placebo arm. Nevertheless, the consistent results across multiple assessment methods and anatomical sites suggest that the findings are robust and clinically meaningful. The study enrolled Caucasians who were predominately female. Future studies could enroll more male subjects and different ethnic cohorts, who have different facial ratios and expectations.[19–23] Facial rejuvenation and aesthetic interventions need to be racially sensitive.[22] Aesthetic outcomes depend on the expertise of the treating practitioner, but the numbers of subjects in each center were inadequate to discern any difference between sites or practitioners.

5 | CONCLUSION

AFV injections produced ≥1 grade improvement in MMVS scores in almost all subjects in the right and left cheeks and overall (both cheeks) after 3 weeks. AFV shows a sustained objective and subjective benefit that persists in some subjects for at least 18 months, often without retouching. The sustained improvement was consistent in both cheeks, and across multiple assessment methods, suggesting the findings are robust and clinically meaningful. AFV was well tolerated. These findings suggest that AFV is a safe and effective filler to rejuvenate cheek volume.

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, Ferial Fanian and Karim Nadra conducted the data analysis. Philippe Kestemont, Ferial Fanian, Philippe Garcia, Anne Grand-Vincent, Laurent Benadiba, Henry Delmar, Isaac Bodokh, Patrick Brun, Karim Nadra, and Patrick Trevidic made substantial contributions to the interpretation of the data. CS was involved in the study conception and design. Philippe Kestemont, Philippe Garcia, Anne Grand-Vincent, Laurent Benadiba, Henry Delmar, Isaac Bodokh, Patrick Brun, Frédéric Braccini, Christophe Desouches, Jérôme Paris, and Patrick Trevidic were all study investigators.

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CONFLICT OF INTEREST STATEMENT

This project was supported by Laboratoires FILLMED. Ferial Fanian and Karim Nadra are the employee of Laboratories FILLMED. The other authors have been paid for their participation in the study. No other potential conflicts of interest were reported.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS STATEMENT

Ethical approval was provided by the committee of "Île-de-France VI Comité de protection des personnes", at Pitié-Salpêtrière Hospital, Paris. Subjects provided informed consent for the study and use of images. The study was conducted in accordance with ISO 14155:2011.

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