Prospective, Split-Face, Randomized, Long-Term Blinded Objective Comparison of the Performance and Tolerability of Two New Hyaluronic Acid Fillers

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BACKGROUND There are requirements for long-term, objective comparisons of hyaluronic acid (HA) dermal fillers.

OBJECTIVE To compare efficacy and tolerability of ART FILLER Universal (AFU) and ART FILLER Fine lines (AFFL) with the existing HA fillers for the treatment of nasolabial folds and crow's feet.

MATERIALS AND METHODS Prospective, randomized, rater- and patient-blind, split-face comparison of AFU with JUVEDERM Ultra 3 (JUV) and AFFL with FIRST LINES PureSense (FLPS). The severity of nasolabial folds and crow's feet was assessed by independent blinded evaluators using the Lemperle scale at baseline, day (D) 30/D45, D90, and D180. Tolerability, Global Aesthetic Improvement Scale (GAIS), wrinkle volumes, and skin thickness and density were also measured at D30/D45, D90, and D180.

RESULTS At D30 and D180 respectively, 61 and 67 patients were assessed. Scores for nasolabial folds and crow's feet showed statistically significant improvements at D30, D90, and D180. AFU and AFFL were noninferior to JUV and FLPS, respectively. Most patients showed GAIS improvements, maintained until at least D180 and significant increases of collagen synthesis in crow's feet and nasolabial folds. Treatments were well tolerated.

CONCLUSION AFU and AFFL are noninferior to comparators. The methodology used represents a novel approach to augment existing clinical assessment of HA fillers.

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Hyaluronic acid (HA), an essential component of the dermis,[1–3] is highly hydrophilic, which accounts for the effectiveness of HA dermal fillers.[4–6] Commercial HA dermal fillers are chemically stabilized by cross-linking, which produces a highly viscose, insoluble gel with a long duration of action. The rheological characteristics of the HA, the volume injected, and the area treated directly influence the clinical improvement and duration of skin effect, produced by the HA filler.[7,8]

This study evaluated the long-term efficacy and safety of 2 new HA gel fillers that contain lidocaine hydrochloride, which reduces injection pain, without compromising safety, tolerability, or immediate and long-term efficacy.[9–11] Furthermore, this study used a novel approach to augment the current gold-standard clinical assessment (split-faced, blinded evaluation) with objective measurements using instrumental methods.

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Materials and Methods

Study Products

ART FILLER Universal filler (AFU; Laboratoires FILORGA, Paris, France) is a new synthetic HA gel (25 mg/mL) for the treatment of mid-to-deep wrinkles, such as nasolabial folds. ART FILLER Fine lines (AFFL; Laboratoires FILORGA) contains 20 mg/mL synthetic HA and corrects fine superficial wrinkles, such as crow's feet. AFU and AFFL both include 0.3% lidocaine hydrochloride.

This study evaluated the long-term efficacy and safety of these 2 new fillers against existing HA fillers: JUVEDERM Ultra 3 (JUV; Allergan) and FIRST LINES PureSense (FLPS; Teoxane), respectively.[7,8] These controls were selected based on several criteria. First, they have comparable gel behavior and properties including similar HA (JUV contains 24 mg/mL HA and FLPS contains 20 mg/mL HA) and lidocaine (0.3%) concentrations. Second, all the fillers have comparable indications and are injected using similar gauge needles. Finally, the control fillers are used to treat the same facial areas with similar market reference points and, where possible had Food and Drug Administration approval (JUV is the same as JUVEDERM Ultra which is available in the United States, the other 3 fillers in this study are not available in the United States).

Study Design

The first part of this study was a prospective, randomized, rater- and patient-blind evaluation using a split-face design comparing AFU with JUV for the treatment of nasolabial folds and AFFL with FLPS for the treatment of crow's feet. After the initial treatment (described below), additional filler could be injected after 14 days to optimize the cosmetic result. Results were evaluated centrally by a blinded evaluator after day (D)30 or D45 in patients who received touch-up at D14 (referred to as D30/45), D90, and D180.

An on-going, second open-label phase enrolled patients who agreed to be followed for an additional 12 months.

Patient Population

A dermatologist from the Group for Research and Evaluation in Dermatology and Cosmetology (GREDECO, Paris, France) invited female or male patients, aged at least 19 years, presenting for nasolabial folds or crow's feet to participate in the study and obtained written informed consent. There was no upper age limit. Patients had a Fitzpatrick phototype of I to IV, with the Lemperle score[12] on both sides of the face of 3 or 4 for nasolabial folds and 2 for crow's feet. Patients had not received any corrective cosmetic procedure (surgery, botulinum toxin, or filler) for at least 12 months before the study and had never received a nonresorbable filler. Patients did not have contraindications for HA injections.

Patients selected the most convenient aesthetic practitioner for injections and follow-up visits. Other injectable cosmetic procedures were not permitted during the study. Patients could use facial emollients or hydrating creams, if recommended by the practitioners.

Treatment

The practitioner injected AFU or AFFL into one randomly selected side of the face and JUV or FLPS respectively into the other. Additional fillers could be injected 14 days after the initial injection. No further HA injections were permitted.

For nasolabial folds, AFU and JUV were injected into the mid-to-deep dermis with the Magic Needle 27G/37-mm cannula into a starter-hole made with a 26G/13-mm needle. Filler was injected slowly using the retrotracing technique in a fan-like distribution. The maximum quantity was 1 mL per side for the initial injection with a further 1 mL per side for patients who received touch-up.

Crow's feet were treated by slow injection of AFFL or FLPS into the upper dermis using 30G1/2″ needles, depending on the depth of the wrinkle and the practitioner's usual approach. The treated area was massaged to facilitate distribution and prevent micropapules.

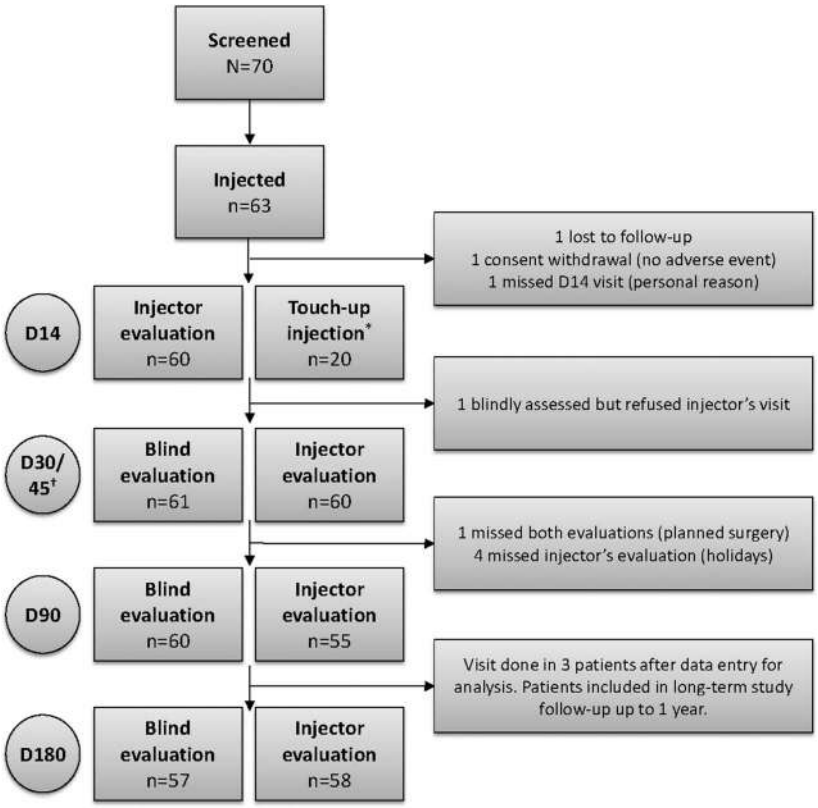

Figure 1. Patient disposition. *Additional fillers could be injected at D14 to optimize the cosmetic result. †Results were evaluated centrally by a blinded evaluator after D30 or D45 in patients who received touch-up at D14.

Blinding

The products' presentations precluded blinded injections. Patients' eyes were covered with compresses during injections. Neither the patient nor the central GREDECO evaluator knew which product was injected into each side. Packaging identified the patient's number and side to be injected. Treatment side allocation was generated in blocks of 4 using SPSS 18.0 (SPSS, Inc.).

Assessments and Evaluations

Centralized evaluations were performed by an independent blinded evaluator at GREDECO who assessed the Lemperle score[12] at baseline for crow's feet and nasolabial folds and took standardized high-definition photographs of the target areas. Profilometry determined the volume of wrinkles (V/mm^2; Skinstation). Dermal high-frequency ultrasound (20 MHz; HFUS; Monaderm) produced 3D visualizations and measurements of dermal thickness and density (collagen formation)[13] as well as early detection of possible inflammatory nodules.

The practitioner scored wrinkles using the Lemperle scale before the first injection. Patients completed a diary at each visit and were asked to score each of the following each day from 0 (absent) to 3 (severe): bruising; redness; swelling; spontaneous pain; pain on pressure; itching; or any other adverse event (AE).

Practitioners contacted patients by telephone approximately 72 hours after the injection and evaluated the patient at D14. Patients who received touch-up at D14 were asked to complete another diary, received another 72-hour call, and were evaluated at D45.

At D30 or D45 (the latter for patients who received an injection at D14), patients were seen by the central evaluator, who assessed any late-onset AE, scored wrinkles, performed HFUS and profilometry, and took photographs. Within 24 to 72 hours of this evaluation, the practitioner independently scored

TABLE 1. Demographics and Baseline Characteristics

Age, yr	55.3 ± 8.5 (range: 36–72)
Body mass index, kg/m²	23.4 ± 3.9 (range: 15.6–34.5)
Phototype, n (%)*	
II	11 (17.7)
III	35 (56.5)
IV	16 (25.8)
Previous aesthetic treatment†	
Any	14 (22.2)
BTX	8 (12.7)
HA	6 (9.5)
BTX + HA	1 (1.6)
Other	3 (4.8)

Blinded Assessment	*AFU/AFFL*	*JUV/FLPS*
Lemperle score‡		
Nasolabial folds		
Mean ± SD	3.36 ± 0.52	3.36 ± 0.48
Score 3	58.7%§	61.3%§
Score 4	39.7%§	38.7%§
Crow's feet		
Mean ± SD	2.02 ± 0.13	2.02 ± 0.13
Score 2	2: 98.4%§	98.4%§
Score 3	3: 1.6%§	1.6%§
Wrinkle volume, V/mm²‖		
Nasolabial folds	39.0 ± 10.3	31.5 ± 6.6
Crow's feet	31.3 ± 5.9	31.5 ± 6.6
Skin thickness, mm¶		
Nasolabial folds	1.7 ± 0.3	1.8 ± 0.3
Crow's feet	1.5 ± 0.2	1.5 ± 0.2
Dermal density¶#		
Nasolabial folds	59.42 ± 8.28	62.03 ± 9.16
Crow's feet	62.15 ± 8.16	63.40 ± 8.58

*Data missing in one case.

†Latest procedure at least 2 years before inclusion.

‡According to treatment side injection.

§Lemperle score 2 = shallow wrinkles; score 3 = moderately deep wrinkle; score 4 = deep wrinkle with well-defined edges.

‖Measured with profilometry.

¶Measured with dermal HFUS.

#N = 59.

AFFL, ART FILLER Fine lines; AFU, ART FILLER Universal; BTX, Botox; FLPS, FIRST LINES PureSense; HA, hyaluronic acid; HFUS, high-frequency ultrasound; JUV, JUVEDERM Ultra 3; SD, standard deviation.

wrinkles and recorded late-onset AE. The procedures were repeated at D90 and D180. The central evaluator and the patient recorded Global Aesthetic Improvement Scale (GAIS) at each visit to GREDECO.

Sample Size Calculation

A minimum of 60 patients was required, assuming a noninferiority margin of 10% for the primary outcome with a 5% alpha risk, 80% power and that 95% of patients would show at least a 1-point reduction in the Lemperle score.[11,12]

Analysis of Efficacy

Efficacy was assessed by change from baseline in the Lemperle score at D30 or D45, the latter in patients who received an additional injection at D14. A 1-point decrease was considered to be a clinically significant aesthetic improvement.[14,15]

Baseline Lemperle scores were compared using the nonparametric Mann–Whitney *U* test. Wrinkle volumes and skin thickness were compared for crow's feet and nasolabial folds separately for each side using univariate analysis of variance (ANOVA). As differences in baseline values between the 2 sides of the face were not statistically significant, the analysis compared each side.

Unless otherwise specified, results are presented as mean ± standard deviation or as frequencies and percentages. SPSS 18.0 was used for analyses. Differences between AFU and JUV, and AFFL and FLPS were calculated as percentages, and the unilateral 97.5% confidence interval (CI) inferior limits were determined using the Miettinen method.[16] If this limit did not include or exceeded the −10% predefined margin, noninferiority was deemed to be established.

Two sensitivity analyses were performed on the efficacy assessment. The first analysis considered unevaluated patients as failures for AFU or AFFL and JUV or FLPS, respectively. The second analysis considered unevaluated patients as failures for AFU or AFFL and successes for JUV or FLPS, respectively.

Secondary efficacy criteria compared with baseline at D90 and D180 were analyzed using univariate ANOVA or Mann–Whitney *U* nonparametric tests. Emergent AEs were analyzed. Mean daily scores for each item in patient diaries were estimated.

TABLE 2. Blind Rating of Lemperle Score Up to Day 180

	Day 30/45		Day 90		Day 180	
Nasolabial Folds	*AFU*	*JUV*	*AFU*	*JUV*	*AFU*	*JUV*
≥1-point decrease from baseline (n, %)	61/61, 100.0	61/61, 100.0	60/60, 100	60/60, 100	55/57, 96.5	55/57, 96.5
AFU-JUV (95% CI)	0.0% (−5.97 to 5.97)		0.0% (−6.06 to 6.06)		0.0% (−8.92 to 8.92)	
Mean change from baseline	−2.26 ± 0.77	−2.26 ± 0.79	−2.53 ± 0.73	−2.50 ± 0.73	−1.91 ± 0.83	−2.07 ± 0.88
Crow's Feet	*AFFL*	*FLPS*	*AFFL*	*FLPS*	*AFFL*	*FLPS*
≥1-point decrease from baseline (n, %)	58/61, 95.1	57/61, 93.4	59/60, 98.3	58/60, 96.7	43/57, 75.4	44/57, 77.2
AFFL-FLPS (95% CI)	1.64% (−7.90 to 11.52)		1.67% (−5.92 to 9.95)		−1.75% (−17.5 to 14.41)	
Mean change from baseline	−1.20 ± 0.51	−1.20 ± 0.54	−1.28 ± 0.49	−1.27 ± 0.52	−0.93 ± 0.68	−0.96 ± 0.65

Results expressed as mean ± SD.

95% CI: limits of the bilateral 95% confidence interval.

All differences at each time: $p < .001$.

AFFL, ART FILLER Fine lines; AFU, ART FILLER Universal; FLPS, FIRST LINES PureSense; JUV, JUVEDERM Ultra 3; SD, standard deviation.

Ethical Approval

This study complies with the 1975 Declaration of Helsinki guidelines on human biomedical research. The study was approved by the local Ethics Committee (Comité de Protection des Personnes, Ile-de-France VI [Pitié Salpêtrière University Hospital, Paris, France]). The study was registered with and approved by the L'Agence Nationale de Sécurité du Médicament et des Produits de Santé (RCB: 2014-A00306-41) and conducted in full accordance with French and European regulations.

Results

Patient Disposition, Demographics, and Baseline Characteristics

Seventy patients were screened by GREDECO between May 7, 2014, and June 3, 2014; 6 males and 57 females were included and injected by aesthetic practitioners at 6 centers. Overall, 61 and 67 patients were blindly assessed by GREDECO at D30/45 and D180, respectively (Figure 1). Groups were well matched (Table 1). No inflammatory nodules were detected at baseline.

At D30 or D45, total HA injected volumes were similar for AFU and AFFL, and JUV and FLPS respectively. For nasolabial folds, mean volumes (±SD) were 0.958 ± 0.381 mL for AFU and 0.970 ± 0.386 mL for JUV (Mann–Whitney *U* test; $p = .933$). For crow's feet, mean volumes were 0.235 ± 0.125 mL for AFFL and 0.233 ± 0.169 mL for FLPS ($p = .526$).

Touch-up for nasolabial folds at D14 was given to 21.7% of the JUV group and 25.0% of the AFU group. Touch-up for crow's feet was given to 13.3% of the AFFL and FLPS groups.

Study Outcomes

The primary outcome was the proportion of patients in whom the severity of nasolabial folds and crow's feet at D30 decreased by at least 1 point on the Lemperle scale[12] compared with baseline when one side of the face was injected with AFU or AFFL and the other side with JUV or FLPS, respectively. Secondary outcomes were tolerability and changes in the following: the Lemperle score assessed by the aesthetic practitioner that injected the filler; GAIS; wrinkle volumes; and skin thickness compared with baseline at D30 or D45 in patients who received touch-up at D14 (referred to as D30/45), D90, and D180.

Lemperle Scores

The mean Lemperle scores assessed by the blinded central evaluator for nasolabial folds and crow's feet

TABLE 3. Patient and Central Assessment GAIS at Days 30/45 and 180

	Day 30/45 (n = 61), %		*Day 180 (n = 57), %*	
	AFU/AFFL	*JUV/FLPS*	*AFU/AFFL*	*JUV/FLPS*
GAIS patient				
Crow's feet				
Much/very much worse	0.0	0.0	0.0	0.0
Worse	1.6	1.6	0.0	0.0
No change	6.6	4.9	22.8	21.1
Improved	57.4	52.5	43.9	47.4
Much/very much improved	34.4	41.0	33.3	31.6
Nasolabial folds				
Much/very much worse	0.0	0.0	0.0	0.0
Worse	1.6	0.0	0.0	0.0
No change	8.2	4.9	8.8	7.0
Improved	32.8	31.1	57.9	47.4
Much/very much improved	57.4	63.9	33.3	45.6
GAIS GREDECO evaluator				
Crow's feet				
Much/very much worse	0.0	0.0	0.0	0.0
Worse	0.0	0.0	0.0	0.0
No change	3.3	3.3	24.6	22.8
Improved	62.3	59.0	54.4	56.1
Much/very much improved	34.4	37.7	21.1	21.1
Nasolabial folds				
Much/very much worse	0.0	0.0	0.0	0.0
Worse	0.0	0.0	0.0	0.0
No change	1.6	0.0	3.5	3.5
Improved	27.9	21.3	52.6	40.4
Much/very much improved	70.5	78.7	43.9	56.1

AFFL, ART FILLER Fine lines; AFU, ART FILLER Universal; FLPS, FIRST LINES PureSense; GAIS, Global Aesthetic Improvement Scale; JUV, JUVEDERM Ultra 3.

TABLE 4. Dermal Density: Relative Change From Baseline at Days 90 and 180

	Change (%) at Day 90 From Baseline (n = 59)	*Change (%) at Day 180 From Baseline (n = 58)*
Nasolabial folds		
AFU	+19.19	+27.33
JUV	+19.56	+27.42
Crow's feet		
AFFL	+28.70	+32.54
FLPS	+29.98	+32.26

AFFL, ART FILLER Fine lines; AFU, ART FILLER Universal; FLPS, FIRST LINES PureSense; JUV, JUVEDERM Ultra 3.

improved significantly ($p < .001$) between baseline and D30/45, and the improvement was maintained at D90 and D180 (Table 2). Based on the blinded assessment, all patients showed at least a 1-point decrease in Lemperle scores for nasolabial folds with AFU and JUV. The lower limit of the unilateral 97.5% CI of the difference between the fillers (−5.97%) exceeded the prespecified noninferiority margin ($p < .01$).

For crow's feet, 95.1% of sides treated with AFFL and 93.4% of the FLPS sides showed at least a 1-point decrease in Lemperle scores based on the blinded assessment. The lower limit of the unilateral 97.5% CI of the difference between the fillers (−7.90%) was above the prespecified non-inferiority margin ($p < .01$).

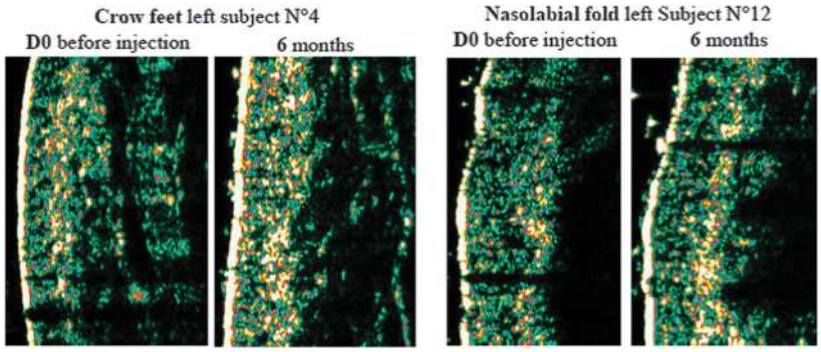

Figure 2. Collagen synthesis in the crow's feet area and nasolabial fold areas after injection of fillers assessed with HFUS. Figures indicate collagen density in the dermis between Day 0 (pretreatment) and Day 180 (green points for mature fibers of collagen and yellow points for newly synthetized fibers). HFUS, high-frequency ultrasound.

Lemperle scores recorded by practitioners and the patients were very similar to the centrally assessed results (data not shown). AFU and AFL remained noninferior to JUV and FLPS respectively ($p < .01$).

Global Aesthetic Improvement Scale

Most patients and central evaluations showed improvements in GAIS irrespective of the filler. Very low numbers of patients reported a worsening in the aesthetic appearance (Table 3). Benefits were generally maintained until at least D180.

Dermal Density, Wrinkle Volume, and Skin Thickness

Mean dermal density showed a statistically significant increase for AFU, AFFL, JUV, and FLPS for nasolabial folds and crow's feet at D90 and D180 versus baseline (Table 4). Volume reductions of nasolabial folds and

TABLE 5. Adverse Events Types Recorded During Follow-up Until Day 30/45 Assessment

	*Day 0**		*Day 3†*		*Day 14‡*		*Day 30/45*		*Total*	
Event Type	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Bruise	2	28.6	10	25.6	3	37.5	1	11.1	16	25.4
Edema	0	0	9	23.1	1	12.5	3	33.3	13	20.6
Hematoma	2	28.6	4	10.3	0	0	0	0	6	9.5
Pain	0	0	3	7.7	1	12.5	2	22.2	6	9.5
Skin heterogeneity at palpation	0	0	4	10.3	0	0	1	11.1	5	7.9
Erythema	0	0	4	10.3	0	0	1	11.1	5	7.9
Dysesthesia	0	0	0	0	0	0	1	11.1	1	1.6
Erosion	0	0	2	5.1	0	0	0	0	2	3.2
Malaise	2	28.6	0	0	0	0	0	0	2	3.2
Toothache	0	0	0	0	2	25.0	0	0	2	3.2
Headache	0	0	1	2.6	0	0	0	0	1	1.6
Nausea	1	14.3	0	0	0	0	0	0	1	1.6
Pruritus	0	0	1	2.6	0	0	0	0	1	1.6
Skin thickness	0	0	1	2.6	0	0	0	0	1	1.6
Whitlow	0	0	0	0	1	12.5	0	0	1	1.6
Total	7	100	39	100	8	100	9	100	63	100

*Immediately after first injection.
†Phone call to patient.
‡Events detected at Day 14 and immediately after additional injection (touch-up).

crow's feet and increases in skin thickness showed similar changes between baseline and D30/45 ($p < .001$) irrespective of the filler, which were maintained up to D180. High-frequency ultrasound showed significant increases in collagen and new collagen density with all fillers until at least D180. New collagen synthesis was more rapid and more marked for crow's feet than for nasolabial folds (Figure 2).

Tolerability and Adverse Events

There were no deaths or serious AEs (Table 5). Between the first injection and D30 or D45, practitioners noted 64 events in 35 patients (55.6%). The nature of one event was not specified. Thirty-nine events were reported at the 72-hour postinjection phone call. Fifty-eight (92.1%) AEs concerned the face and injection sites. The remaining 5 AEs were malaise, nausea, or headache immediately after the injection, and a whitlow. Slight to moderate bruising or edema at the injection site accounted for 60.3% of local events. No unexpected AE emerged, and no differences between the fillers were apparent.

Redness, swelling, and pain on palpation were the most frequently self-reported AE during the first 5 to 6 days after injection based on patients' diaries. Overall, 87.1% of patients reported at least 1 event in crow's feet areas treated with AFFL and 90.3% treated with FLPS. For nasolabial folds, the corresponding figures were 85.5% with AFU and 80.6% with JUV. Including the first injection and touch-up, 11.3% of crow's feet areas were associated with severe AE with both AFFL and FLPS. For nasolabial folds, 17.7% and 16.1% of AFU- and JUV-treated areas, respectively, were associated with severe AE.

Patient-reported scores were highest on D1 after injection, and then declined rapidly. By D6 the scores were close to zero (Tables 6 and 7). No general or local AE occurred between D30/45 and D180, except for one patient who was hospitalized for elective surgery of a diskal hernia. No inflammatory nodules or granulomas were detected on HFUS.

TABLE 6. Mean Diary Scores by Day in the CF Area After Injection of Fillers

	Treatment			
	AFFL		*FLPS*	
	Global Score CF		*Global Score CF*	
Day Postinjection	*Mean*	*Median*	*Mean*	*Median*
Day 1	2.63	2.00	2.39	2.00
Day 2	1.82	1.00	1.73	1.00
Day 3	1.39	1.00	1.28	1.00
Day 4	1.42	1.00	1.02	0.00
Day 5	0.75	0.00	0.47	0.00
Day 6	0.56	0.00	0.37	0.00
Day 7	0.36	0.00	0.26	0.00
Day 8	0.36	0.00	0.28	0.00
Day 9	0.31	0.00	0.19	0.00
Day 10	0.31	0.00	0.23	0.00
Day 11	0.27	0.00	0.12	0.00
Day 12	0.23	0.00	0.15	0.00
Day 13	0.25	0.00	0.17	0.00
Day 14	0.18	0.00	0.16	0.00
Total	0.77	0.00	0.62	0.00

AFFL, ART FILLER Fine lines; CF, crow's feet; FLPS, FIRST LINES PureSense.

Discussion

This study shows that AFU and AFFL are noninferior to JUV and FLPS, respectively. The benefits of AFU and AFFL on nasolabial folds and crow's feet were maintained until at least D180. The on-going study will extend these results until 18 months. Objective measurements of skin thickness and wrinkle volume as well as secondary parameters confirmed the efficacy of AFU and AFFL.

No patient developed a serious AE. Injection site bruising and edema were mainly transitory and occurred immediately after treatment. Adverse events were not apparent between D30/45 and D180.

This study greatly improves, in the authors' view, the existing assessment of HA fillers in aesthetic settings and encompasses several validated approaches, both subjective (scoring by a blinded evaluator) and objective (profilometry and HFUS).[17] For example, interindividual variability in HA assessment is very high, and the split-face design addresses this variability by making each patient their own control.[18] Most

TABLE 7. Mean Diary Scores by Day in the NL Fold Areas After Injection of Fillers

	Treatment			
	AFU		JUV	
	Global Score NL		Global Score NL	
Day Postinjection	Mean	Median	Mean	Median
Day 1	2.55	2.00	2.63	2.00
Day 2	2.29	1.00	2.02	1.00
Day 3	1.88	1.00	1.79	1.00
Day 4	1.45	0.00	1.17	0.00
Day 5	1.25	0.00	1.09	0.00
Day 6	1.08	0.00	0.96	0.00
Day 7	0.74	0.00	0.78	0.00
Day 8	0.61	0.00	0.64	0.00
Day 9	0.31	0.00	0.48	0.00
Day 10	0.24	0.00	0.41	0.00
Day 11	0.18	0.00	0.40	0.00
Day 12	0.19	0.00	0.33	0.00
Day 13	0.19	0.00	0.37	0.00
Day 14	0.20	0.00	0.40	0.00
Total	0.93	0.00	0.95	0.00

AFU, ART FILLER Universal; JUV, JUVEDERM Ultra 3; NL, nasolabial.

controlled trials of HA fillers included in a systematic review used the split-face design.[19]

However, this study further allowed precise and independent evaluation of 2 types of injection in anatomically distinct areas. Clinical improvement was assessed using the scale developed by Lemperle and colleagues,[12] which is widely used, well validated, with good inter- and intra-observer consistency.[14,15]

As the practitioner injecting the filler could not be blinded, the main outcomes were evaluated centrally by blinded clinicians. The study used a robust comparator arm: several randomized studies show that JUV and FLPS are effective and well tolerated.[4–6,14,20–25] The D30/45 evaluation represents the time of optimal cosmetic correction, whereas the D180 follow-up allows an assessment of wrinkle corrections and long-term tolerability.

Finally, centrally performed profilometry and HFUS offer objective support for the clinical evaluations. They further assess how the fillers have been incorporated in situ and how they have reacted with the tissue, independent of assessor evaluation. Profilometry was used to directly measure wrinkle depth before and after treatment, providing a more precise assessment than clinical rating. High-frequency ultrasound was used to measure both the interaction of the filler with the tissue (to assess if there is any reaction around the filler, granuloma, etc.) and the density of the dermis (directly correlated to the neocollagenesis).[26–31] This methodology offers insights that are not usually available in a clinical study. For example, inflammatory nodules are the most common late AE associated with resorbable HA fillers. The prevalence is only, however, around 0.1% and most studies are inadequately powered to detect changes in the incidence of inflammatory nodules. This study used centralized and blinded HFUS evaluation of each injection site. The sensitivity and specificity of HFUS to detect inflammatory nodules is well established.[26–31]

Between D30/45 and D180, mean dermal thickness increased whereas mean wrinkle volume decreased. New collagen synthesis induced by the filler, as assessed by HFUS, might account for this effect. AFFL contains a higher percentage of free HA compared with cross-linked HA than AFU, which might account for the more rapid and marked synthesis in the crow's feet. Furthermore, AFFL is injected into the superficial dermis with a needle and is more likely to stimulate collagen production than AFU injected into the deep dermis with a cannula.[32–34]

In conclusion, AFU and AFFL are well suited for moderate-to-deep and fine line corrections, respectively, and are noninferior to CE-marked comparators. The method used in this study encompasses several validated and objective instrumental approaches and represents, in the authors' view, a significant enhancement to the assessment of HA fillers.

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