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An Interim 6-Month Analysis of the Dermatologic Effects and Midface Volume Correction With XTR_{CL} Filler in a Prospective, Single-Center Study

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BACKGROUND Hyaluronic acid-based filler injections with parenteral anesthetics have become the standard in treating midface volume deficits. There are currently limited data on the effects of these types of fillers on skin density, thickness, and firmness.

OBJECTIVE This study aimed to assess the efficacy of XTR_{CL} filler in improving skin quality and tissue volume in women with midface volume loss.

MATERIALS AND METHODS In this prospective, noncomparative, single-center study, 50 women aged between 40 and 60 years with midface volume loss were recruited. The primary endpoint was the improvement in investigator-assessed Global Aesthetic Improvement Scores (GAIS) 1 month after treatment. Secondary endpoints include objective measurements of skin density, thickness, and quality measurements, facial and/or cheek volume augmentation, subjective GAIS, and device evaluation from after the first injection until 6 months, and the documentation of injection site reactions and adverse events.

RESULTS XTR_{CL} use led to significant improvement in midface volume deficits, and skin quality and skin thickness. Injector and subject satisfaction with the treatment were documented and only mild-to-moderate adverse reactions were reported.

CONCLUSION XTR_{CL} was shown to be effective in improving volume loss and skin quality at 6 months.

Hyaluronic acid (HA) fillers are considered to be the most popular volumizer for correcting moderate-to-severe age-related deficits of the midface such as tear trough deformities, malar hollowing or loss of cheek definition, and the double convexity at the junction of the eyelid and midface.[1,2] Hyaluronic acid fillers with higher linear elastic or storage modulus (G′) are used to correct these deficits because they tend to maintain their shape when injected and prominently project soft tissue with a minimal amount of product.[3] Studies on fillers have shown the tendency to improve skin density and thickness when introduced into superficial layers of the skin, but these have been limited to intradermally administered low G′ fillers.[4]

This phase IV study was designed to evaluate the performance and safety of the high G′ filler Definisse core + lidocaine (XTR_{CL} [eXcellent Tridimensional Reticulation]), because it is used for midfacial volume restoration or augmentation, and its effects on skin density, thickness, and biomechanical properties through subjective and objective outcomes in healthy female subjects. We present the 6-month interim results of this study.

Materials and Methods

Filler Material

XTR_{CL} filler is a class III CE marked (CE 0120) product [RELIFE S.R.L. (Menarini Group)] for the treatment of moderate-to-severe volume loss of deep subcutaneous and/or supraperiosteal facial tissue, typically at the zygomaticomalar, anteromedial cheek, and submalar regions. It is a biodegradable, viscoelastic, clear, transparent, isotonic, and homogenized injectable gel of cross-linked HA from *Streptococcus equi*. XTR_{CL} is formulated at a concentration of 25 mg/mL in a physiologic buffer supplemented with

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0.3% lidocaine hydrochloride, a common component of modern facial fillers.[5] A box of XTR_{CL} contains 1 prefilled glass syringe with 1.0 mL gel implant, 2 (2) × 27 G 1⁄2" thin wall Terumo needles (CE 0197), with a length of 12 mm +1/−2 mm, and outer diameter 0.4 +0.02/−0.00 mm (RELIFE S.r.l., personal communication, September 2022).

XTR_{CL} has a storage modulus or G′ of about 427 Pa at 0.7 Hz, which is notably higher compared with other fillers used for the same indications, for example, deep volumization, reshaping, contouring, and lifting of sagging facial tissue. Having intermediate cohesivity (i.e., mostly dispersed after 70 seconds), a loss modulus (G″) of 26.9 (intermediate), and a tan δ of 0.063 complements these properties.[3]

Subjects

Fifty healthy women aged 40 to 60 years (an average of 51) with clinically apparent facial tissue volume loss were included in the study. All subjects were adequately counseled and agreed to sign an informed consent form. They each underwent 1 session and a touch-up at 1 month as needed, and were followed up at months 3, 6, and 12 (M3, M6, and M12). The last visit was scheduled for the 18th month (M18).

This investigation was conducted under the ethical principles outlined initially in the 1975 Declaration of Helsinki and EN ISO standard 14155:2012 and their updates and complies with local regulatory requirements as written at the time of the clinical investigation plan. This study was also approved by the National Ethics Committee of France.

Study Design

This was a prospective, noncomparative, single-center study. The Global Aesthetic Improvement Scale (GAIS)[6,7] was the main evaluation tool. Changes in facial volume were recorded using the Facial Volume Loss Scale [FVLS][8] using three-dimensional photographs. These images were taken using a stereophotogrammetry system (3D LifeViz Mini, QuantifiCare).[9] A series of photographs of the front, 45°, right, and left facial profiles was taken.

Measurements of skin density, thickness, and biomechanical properties were performed using a high-frequency 2-dimensional echograph (Dermascan C 2D; Cortex Technology; Denmark)[10] allowing for visualization of the epidermis and dermis with a 13-mm penetration (Figure 1).[10]

The ratio of the nonechogenic surface to the total surface analyzed gives the proportion of nonechogenic tissues and the accompanying software measures the average thickness of the epidermis and dermis.[10] To evaluate the biomechanical properties of the skin, for example, skin elasticity, firmness, tonicity, and suppleness, a suction skin elasticity meter (Cutometer, EnviroDerm) was used.[11]

Study Treatment

XTR_{CL} was injected on V1 (D0) in the midface using a novel 6-point injection method, that is, the *Pegasus technique*. This technique allows for more even distribution of filler material over key sections of the midface and was so-named because of the injection point pattern resembling the wings of the mythological stallion in midflight. Each side of the face was injected with supraperiosteal boluses using a 27 G needle following the sequence below (Figure 2):

- Zygomatic arch (2 boluses, about 0.2–0.3 mL each)
- Malar area (3 boluses, lateral suborbicularis oculi fat (SOOF) pad, medial SOOF, deep malar fat pad, about 0.3–0.4 mL each)
- Deep pyriform fossa (1 bolus, about 0.3–0.4 mL)

A total of 4.0 to 5.0 mL was used to achieve optimal aesthetic results. A touch-up was performed on V2 (M1) at the discretion of the injector.

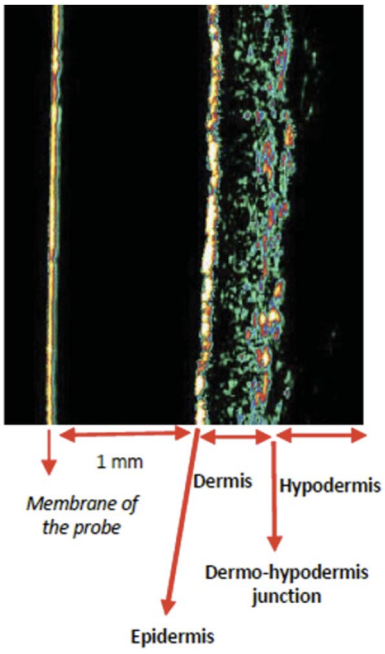

Figure 1. An image captured using the high-frequency Dermascan C 2D echograph.

Study Endpoints

The primary endpoint was the improvement in investigator-assessed GAIS 1 month after treatment. Among the secondary endpoints were the before and after skin density, thickness, and skin biomechanical properties measurements, subject-assessed GAIS, the need for touch-up injection/s, objective evaluation of restoration and/or augmentation of facial volume, with cheekbone volume variation measured by stereophotogrammetry, and evaluation of subject satisfaction using a questionnaire. At each visit, injectors filled out questionnaires about the ease of injection and product positioning, immediate results, and results after massage. Subjects and investigators were required to document injection site reactions (ISRs) and adverse events (AEs).

Statistical Analyses

Because no hypothesis was established using the primary criteria, there was no need for a formal sample size

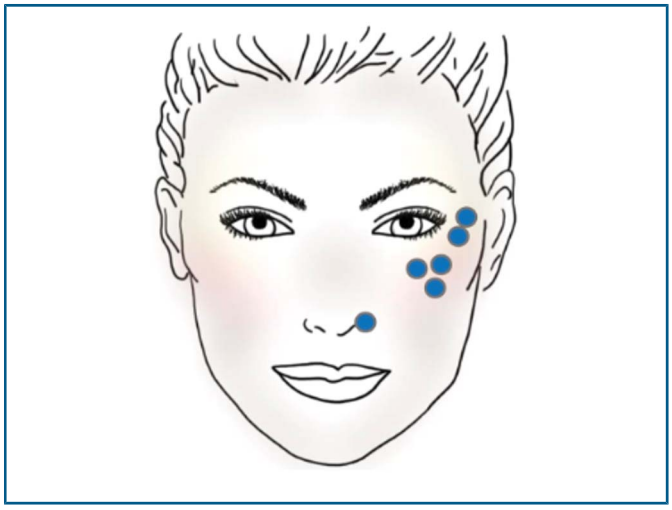

Figure 2. Sites of injection of core filler using the *Pegasus technique*.

calculation. However, a sample size of 42 subjects allowed for a power of 90% to demonstrate a significant difference between a successful proportion in GAIS of 90% compared with a theoretical value of 70% using a 2-sided binomial test, with a type I error set at $\alpha = 0.05$. The computation was performed using SAS software (SAS Institutue, North Carolina).

Considering a 15% drop-out rate, a sample size of 50 subjects was considered. Intermediate analyses were planned for M12, and the final analysis is slated for M18. A statistical analysis plan with detailed statistical methodology was written and approved before the first intermediate data review.

Results

All subjects had mild and moderate-to-severe midface deficits and underwent XTR_{CL} filler injections on day 0. The initial injection comprised an average volume of 1.7 mL per side (between 1.3 and 2.0 mL per side). Most (48/50, 96%) subjects underwent a touch-up, with an average volume of 0.4 mL per side.

Investigator-Assessed and Subjective Global Aesthetic Improvement Scale

All patients were reported to have improved aesthetically according to investigator-assessed GAIS from immediately after the initial injection, at M1, M3, and until M6. About 76% of the subjects immediately after the initial injections and 87.5% immediately after the touch-up injections were rated as "much improved" to "very much improved." At M3 and M6, 86% and 74% of subjects were rated to be "much improved" to "very much improved," respectively (Figure 3). One hundred percent of subjects were noted to have global aesthetic improvement 6 months after the initial injection (See **Supplemental Digital Content 1**, Table, http://links.lww.com/DSS/B297).

Overall subjective GAIS ratings immediately after the first injection were favorable as well. About 98.0% of subjects rated themselves to have global aesthetic improvement. At M6, 94.0% of subjects had improved global aesthetic ratings (See **Supplemental Digital Content 2**, Table, http://links.lww.com/DSS/B297). About 62% of the subjects immediately after the initial injection and 54% immediately after the touch-up injection rated themselves to be "much improved" to "very much improved," respectively. At 3 and 6 months after the initial injection, 54% and 48% rated themselves "much improved" to "very much improved," correspondingly (Figure 4).

Facial Volume, Skin Density, and Thickness Measurements

From M1 to M6, a significant decrease in FVLS score was observed ($p < .0001$), suggesting an improvement of midface volume (average decrease of 0.44 point on M1, −0.44 point on M3, −0.44 point on M6).

The proportion of subjects with a grade 1 on FVLS before injection increased from 38.0% to 64.0% at M1 and 62.0% at M6. Furthermore, the proportion of subjects with grades 2, 3, and 4 (mild to moderate, moderate, and moderate-to-severe) deficits decreased (See **Supplemental Digital Content 1**, Figure, http://links.lww.com/DSS/B297). Forty-four percent of the subjects had improved FVLS ratings at M1 and M6 and 46% at M3. Nonetheless, excluding patients with grade 1 deficit at baseline, there were improved FVLS scores of 71% on M1 and M6, and 74% on M3.

Objective improvements in cheekbone volume were likewise favorable. One month after the initial injection (and before the touch-up), the average cheekbone volume significantly increased by 2.8 mL per side ($p < .001$). Three months after the initial injection (and after touchup), the volume increase was maximal with an average increase of 3.3 mL ($p < .001$). Six months after the initial injection, there was noted to be a 3.0-mL average increase in volume on both sides ($p < .001$) (See **Supplemental Digital Content 2**, Figure, http://links.lww.com/DSS/B297, Figure 5A, B).

At M3 and M6, there was a significant improvement in skin density as measured by high-frequency echography. This improvement was more apparent at M6 (decrease of nonechogenic proportion vs baseline of −0.05 (−13.5%), $p = .0007$ on M3 and -0.09 (−24.3%), $p < .0001$ on M6). At the same time, a mild but significant increase in skin thickness was observed at M6 (+0.07 mm [4.7%], $p = .0389$).

Skin biomechanical properties were also noticeably improved. A significant decrease of Ue and Uf (immediate and final extensibility) and Ur and Ua (immediate and total retractation) was observed 3 and 6 months after injection. These variations can be interpreted as firmer, less lax skin, which are typical of skin findings after HA injections (See **Supplemental Digital Content 3**, Table, http://links.lww.com/DSS/B297).

Subject and Injector Satisfaction Ratings

At the first visit and at M1, 100% of injectors graded a high satisfaction rating (e.g., very satisfied and satisfied) for ease

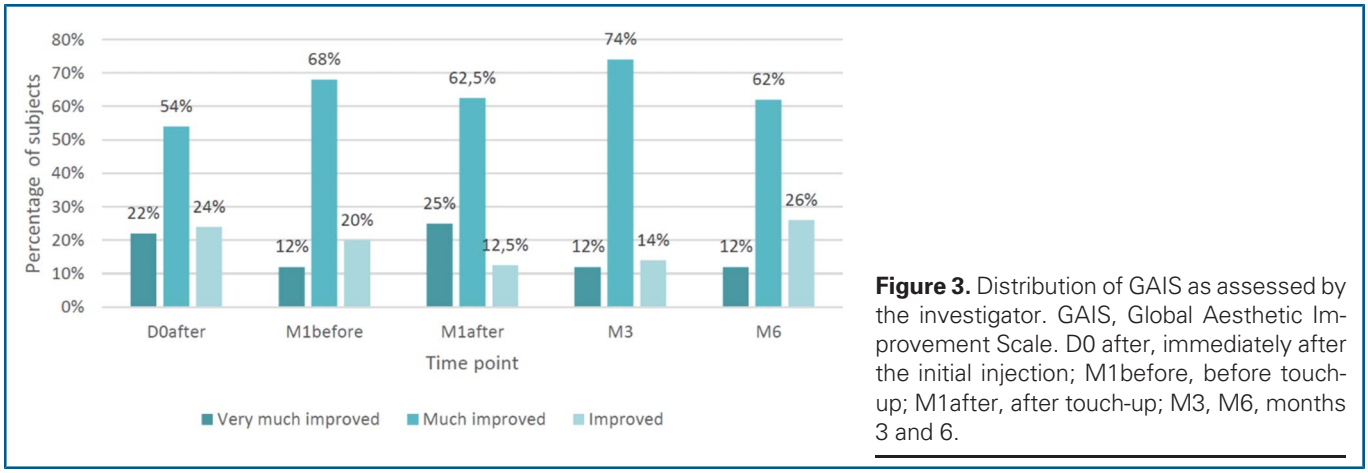

Figure 3. Distribution of GAIS as assessed by the investigator. GAIS, Global Aesthetic Improvement Scale. D0 after, immediately after the initial injection; M1before, before touch-up; M1after, after touch-up; M3, M6, months 3 and 6.

of injection. The corresponding ratings for ease of product positioning, immediate result, and the result after the massage are shown in the figure (See **Supplemental Digital Content 3**, Figure, http://links.lww.com/DSS/B297).

At M6, most subjects expressed that they were satisfied with the treatment from M1 to M6 after the initial injection. Six months after injection, 100% of the subjects stated that the intervention was good for them, were satisfied with the result, found their skin firmer, and more natural-looking, and would recommend the treatment to a friend.

Safety

Injections site reactions observed by the subjects and investigators consisted mainly of low-grade (18 were rated mild and 3, moderate) and transient pain/tenderness, lumps/bumps, skin redness, induration, edema, and bruising/hematoma lasting only a few days after injection. After the initial injection, lumps/bumps lasted an average of 11 days, followed by pain/tenderness (9 days), induration (8 days), bruising/hematoma (7 days), edema and itching (5 days), redness (3 days), and discoloration (2 days after initial injection—1 subject experienced this for 31 days). Device-associated AEs were observed in 15 subjects, namely, headache, injection site pain, oral herpes, gingival pain, injection site mass, injection site inflammation, and injection site paresthesia, and were resolved by M6 with most lasting only a few days (at most lasting 5 days and with 1 outlier reporting a 25-day course of gingival pain). All ISRs and AEs reported during the study were expected and responded well to supportive treatment (required by only 62% of subjects with device-associated AEs), while no severe or serious AEs occurred (Table 1).

Discussion

The subjects who were recruited in this study represent the largest patient demographic traversing 3 generations—Millennials, Generation Xers, and Baby Boomers.[12] Regardless of age, all these subjects recruited were well-informed about the possible outcomes and were considered to have realistic expectations and to be compliant with post-treatment care.

Hyaluronic acid fillers are standard aesthetic and dermatologic devices that are effective and well-tolerated for correcting midface volume deficits.[13] Similarly, we have demonstrated that XTR_{CL} was effective as an HA filler for use in volumization (e.g., subjective improvement rating,

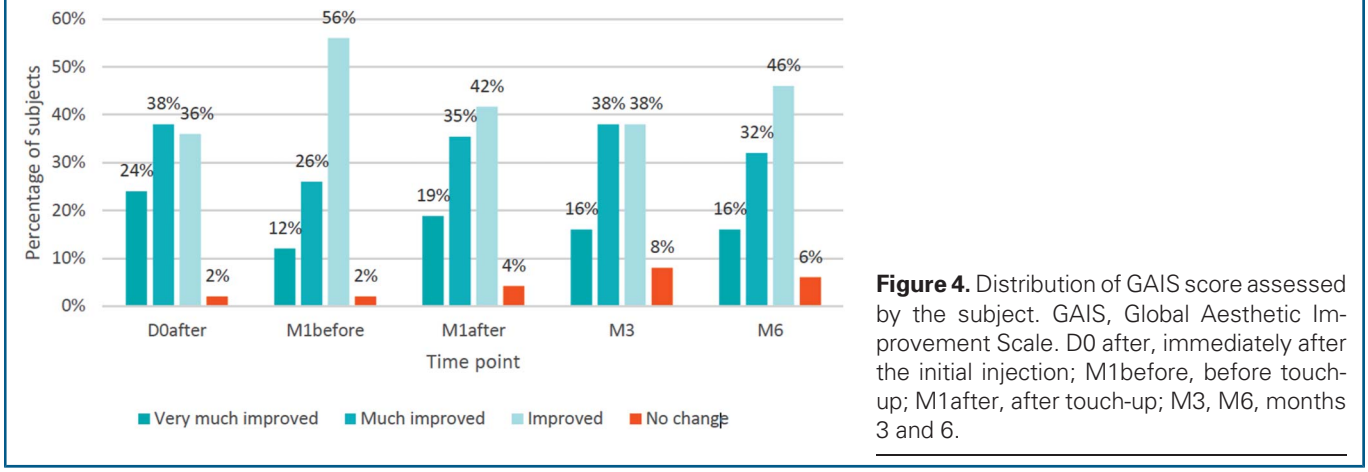

Figure 4. Distribution of GAIS score assessed by the subject. GAIS, Global Aesthetic Improvement Scale. D0 after, immediately after the initial injection; M1before, before touch-up; M1after, after touch-up; M3, M6, months 3 and 6.

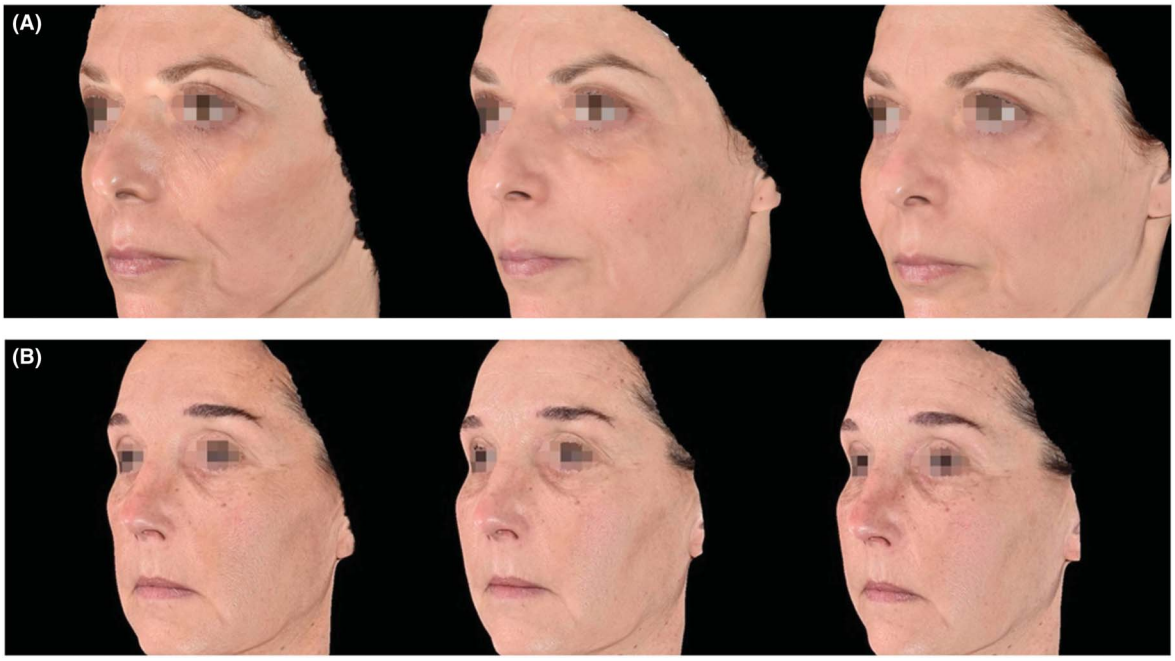

Figure 5. Clinical photographs of 2 subjects showing visually improved midface volume deficits at 3 months (second photo) and 6 months postinjection (third photo). (A) A subject with noticeable increase in malar volume and reduction in the prominence of the nasolabial groove and marionette lines at 3 months persisting at 6 months. (B) A subject with a reduction in the cheek hollows at 3 months also persisting at 6 months.

improvement in volume) and in improving skin quality, (e.g., skin density and thickness, and biomechanical properties) with minimal associated adverse effects.

Improvements in investigator-assessed GAIS and subject-rated GAIS until M6 were consistent with other clinical studies conducted in other facial regions (i.e., cheeks) where XTR_{CL} was demonstrated to have good volumization properties while also improving skin quality with results lasting up to 2 years.[14] The rheologic and physicochemical properties of this high G′ filler have been documented and elaborated in a series of in vitro studies. When compared with high G′ HA fillers of other brands, XTR_{CL} has the advantage of having high volumizing and lifting effects; thus, less amount of product is needed to achieve similar clinical effects.[3]

Significant improvement in FVLS scores confirmed subjective volume improvement. It is interesting to note that this volume was pronounced despite the low volume of injectate; this is likely because of the hygroscopic properties of XTR_{CL}. Similar results were observed in other HA fillers,[15] although a like-for-like comparison of these devices remains to be performed.

TABLE 1. A Summary of Injection Site Reactions and Adverse Reactions With XTR_{CL}

Component	Data Item	Reported Subjects
Subjects with at least 1 AE	—	33/50
Number of AEs	—	84
Number of device-related AEs	—	15/84
Severity (all AEs, %)	Mild	75/84 (89.3)
	Moderate	9/84 (10.7)
	Severe	0/84 (0.0)
Treatment required (overall, %)	No	18/84 (21.4)
	Yes	65/84 (77.4)
	Other	1/84 (1.2)

AE, adverse event.

Improvements in skin density, thickness, and firmness were observed in most patients after M6. Comparable effects are documented in HA gel skin boosters purposely manufactured to improve skin quality through minimal amounts of intradermal or subdermal injections.[16] Authors believe that deep injections of HA fillers with adequate swelling factor, such as those performed in the supraperiosteal layer, can contribute to positive changes in skin density, thickness, and firmness through increased hydration of multiple tissue layers and the possible outflow of minute amounts of filler material to more superficial layers through the injection track. However, more large-scale, prospective studies are needed to support this observation.

Subject and injector satisfaction ratings were rated high in ease of injection and product positioning, immediate results, and results after massage all rated high on the day of treatment and after M1. All subjects were satisfied with the treatment and rated the intervention positively across the board.

The Pegasus technique used in this study was also likely to be instrumental in the outcomes because it covers more midface areas compared with other conventional techniques. More prospective, controlled studies should be able to establish this.

ISRs were expected and mostly resolved spontaneously or with standard supportive measures. Device-associated AEs documented were rated mild-to-moderate and were consistent with HA filler injections with high G′. Most of these reactions lasted for a few days after injection and were managed with standard clinical measures for filler AEs.

Conclusions

XTR_{CL} injected via the Pegasus technique in subjects with mild-to-moderate midface volume deficit produced an improvement in GAIS according to the investigator, skin density, thickness, and firmness, in all subjects until 6 months after the initial injection. Significant improvements in the FVLS scores and objective improvements in cheekbone volume were likewise observed. Injector and subject satisfaction were rated highly, and only mild-to-moderate expected adverse device effects were reported. The data presented in this manuscript are based on interim 6-month results, and further studies describing longer-term outcomes until the end of the study (i.e., 18 months) are underway.

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References

1. Cazzaniga A, Ballin A, Brandt F. Hyaluronic acid gel fillers in the management of facial aging. *Clin Interv Aging* 2008;3:153–9.
2. Ko EJ, Kim H, Park W-S, Kim BJ. Correction of midface volume deficiency using hyaluronic acid filler and intradermal radiofrequency. *J Cosmet Laser Ther* 2015;17:46–8.
3. Salti G, Fundarò SP. Evaluation of the rheologic and physicochemical properties of a novel hyaluronic acid filler range with eXcellent Three-Dimensional Reticulation (XTR™) Technology. *Polymers (Basel)* 2020;12:1644.
4. Nakab L, Hee CK, Guetta O. Improvements in skin quality biological markers in skin explants using hyaluronic acid filler VYC-12L. *Plast Reconstr Surg—Glob Open* 2020;8:e2723.
5. Smith L, Cockerham K. Hyaluronic acid dermal fillers: can adjunctive lidocaine improve patient satisfaction without decreasing efficacy or duration? *Patient Prefer Adherence* 2011;5:133–9.
6. Callan P, Goodman GJ, Carlisle I, Liew S, et al. Efficacy and safety of a hyaluronic acid filler in subjects treated for correction of midface volume deficiency: a 24 month study. *Clin Cosmet Investig Dermatol* 2013;6:81–9.
7. Savoia A, Onori N, Baldi A. Efficacy of Skinfill plus filler in the management of facial aging: a multicenter, post-marketing clinical study. *Biomed Dermatol* 2018;2:2–6.
8. Sparavigna A, La Gatta A, Bellia G, La Penna L, et al. Evaluation of the volumizing performance of a new volumizer filler in volunteers with age-related midfacial volume defects. *Clin Cosmet Investig Dermatol* 2020;13:683–90.
9. Heike CL, Upson K, Stuhaug E, Weinberg SM. 3D digital stereophotogrammetry: a practical guide to facial image acquisition. *Head Face Med* 2010;6:18.
10. Alsing KK, Serup J. High-frequency ultrasound skin thickness: comparison of manual reading and automatic border detection includes assessment of interobserver variation of measurement. *Skin Res Technol* 2020;26:832–8.
11. Dobrev HP. A study of human skin mechanical properties by means of Cutometer. *Folia Med (Plovdiv)* 2002;44:5–10.
12. Berkup S. Working with Generations X and Y in Generation Z period: management of different generations in business life. *Mediterr J Social Sci* 2014;5:218–29.
13. Baumann L, Narins RS, Beer K, Swift A, et al. Volumizing hyaluronic acid filler for midface volume deficit: results after repeat treatment. *Dermatol Surg* 2015;41(Suppl 1):S284–92.
14. Muti GF. Midface 3D restoration with an innovative high G' filler. *J Cosmet Dermatol* 2021;20(Supp 2):7–11.
15. Kerscher M, Agsten K, Kravtsov M, Prager W. Effectiveness evaluation of two volumizing hyaluronic acid dermal fillers in a controlled, randomized, double-blind, split-face clinical study. *Clin Cosmet Investig Dermatol* 2017;10:239–47.
16. Belmontesi M, De Angelis F, Di Gregorio C, Iozzo I, et al. Injectable non-animal stabilized hyaluronic acid as a skin quality booster: an expert panel consensus. *J Drugs Dermatol* 2018;17:83–8.