

Safety and Effectiveness of Hyaluronic Acid Filler, VYC-20L, via Cannula for Cheek Augmentation: A Randomized, Single-Blind, Controlled Study

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BACKGROUND Using cannulas to deliver facial fillers may reduce adverse events (AEs) compared with needle injection.

OBJECTIVE To evaluate the safety and effectiveness of VYC-20L (20 mg/mL hyaluronic acid gel with lidocaine) via cannula for midface age-related volume deficit.

MATERIALS AND METHODS This multicenter, evaluator-blind, randomized, within-subject, controlled study enrolled adults with moderate to severe Mid-Face Volume Deficit Scale (MFVDS) scores. VYC-20L was administered in one cheek via cannula (with optional needle use in the zygomaticomalar region) and in the other cheek via needle. The primary effectiveness end point was the mean (95% confidence interval [CI]) paired difference between treatments in MFVDS score change from baseline to Month 1; an upper CI limit of less than 0.5 determined noninferiority. Injection-site responses (ISRs), procedural pain, and AEs were assessed.

RESULTS Of 60 randomized and treated subjects, the mean change in MFVDS score from baseline to Month 1 was -1.8 with cannulas and -1.9 with needles, providing a mean (95% CI) paired difference of 0.1 (-0.05 to 0.25). Most ISRs were mild/moderate and resolved within 2 weeks. Procedural pain was minimal, and no serious AEs were reported.

CONCLUSION VYC-20L for cheek augmentation was safe and effective using a cannula and noninferior to needle injection.

The face loses fat and skin elasticity with age, contributing to progressive deepening of facial wrinkles and folds.¹ The current approach for achieving a youthful-looking face has diverged from treating discrete wrinkles and folds to focusing on panfacial volumizing and structural support. Injectable fillers are useful to customize

the shape and size of the various cheek zones. Several hyaluronic acid (HA) injectable gels are available for correction of wrinkles and folds. One such product, VYC-20L (Juvéderm Voluma XC; Allergan Aesthetics, an AbbVie Company, Irvine, CA), has demonstrated effectiveness and safety in restoring age-related volume deficit of the midface in adults using needle injection.^{2,3}

Cannulas have recently become a viable alternative to needles because cannulas seem to be associated with fewer adverse effects.^{4,5} Unlike the sharp beveled tip of needles, cannulas have a blunt rounded end and can be flexible, allowing a greater ability to fill the varying contours of the face.^{5,6} Cannulas may be associated with fewer injections and less pain during the procedure, a reduction in post-injection bruising and swelling, faster recovery, and a decreased risk of intra-arterial injection compared with needle delivery.^{4,6,7} The current study assessed the safety and effectiveness of VYC-20L using cannulas in subjects seeking correction of age-related volume deficit in the midface.

Methods Subjects

Eligible subjects were aged 35 to 65 years and in good general health. The severity of volume deficit in the midface, in addition to the zygomaticomalar, anteromedial, and submalar regions, was assessed by the blinded evaluating investigator using the validated 6-point photonic Mid-Face Volume Deficit Scale (MFVDS; 0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = significant, and 5

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= severe). Study enrolment required the overall midface severity for both cheeks to be at least moderate (3). Per the treating investigator, the subject must be able to achieve at least a 1-grade improvement on the overall MFVDS for both cheeks, given the allowed injection volume of VYC-20L. Subjects were excluded if they had ever received permanent facial implants or fat injection, had a history of facial surgery in the midface, had undergone temporary dermal filler treatment in the treatment area within 24 months of enrolment, had undergone semipermanent dermal filler treatment within 36 months, had substantial skin laxity, or had undergone any cosmetic treatment (including botulinum toxin) in the treatment area within 6 months before enrolment.

Study Design

This multicenter, evaluator-blind, randomized, within-subject, controlled, paired-comparison study assessed the safety and effectiveness of VYC-20L using a cannula versus needle for cheek augmentation. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and was approved by the institutional review boards at each of the 7 study centers. All subjects provided written informed consent.

Study treatment was VYC-20L injected with a 25-gauge 1.5-inch cannula and an optional 25-gauge 1-inch needle (to provide lift only in the zygomaticomalar region with periosteal depot injection if deemed necessary). Optional needle use in the zygomaticomalar region of the cannula cheek was included in this study to encompass key real-world practices and investigator preference. This was discussed with the US FDA and the treating investigators before study initiation. Control treatment was VYC-20L injected with a 25-gauge 1-inch needle. Treatment investigators selected injection volume based on clinical experience, with a maximum permitted dose of 3.0 mL per cheek. On randomization/treatment day, subjects had one cheek treated with VYC-20L using a cannula and the contralateral cheek treated using a needle with the goal of achieving at least a 1-grade improvement in MFVDS score (considered a clinically significant difference²). The side of treatment (e.g., side of face for needle or cannula) was randomized and blinded to the evaluating investigator. An anesthetic agent (topical or injectable lidocaine) was used on the treatment area before making the cannula entry point with the introductory needle and was an option for needle use (control treatment).

Effectiveness Assessments

On treatment day, the treating investigator evaluated ease of injection on a 4-point scale (1 = very difficult, 2 = difficult, 3 = easy, and 4 = very easy). Subjects returned for a visit at 1 and 3 months after treatment. During these visits, the evaluating investigator rated subjects on the MFVDS for the overall midface area and the zygomaticomalar, anteromedial, and submalar regions of each cheek. Subjects also completed the validated 5-item Satisfaction with Cheeks module of the FACE-Q questionnaire⁸ at screening and

Months 1 and 3 (see **Supplemental Digital Content 1**, Text 1, <http://links.lww.com/DSS/A921>).

The primary effectiveness end point was the mean (95% CI) paired difference in MFVDS score change from baseline (screening) to Month 1 for treatment with cannula and treatment with needle based on evaluator assessment. Secondary effectiveness end points included MFVDS responder rate (percentage of subjects with ≥ 1 -point improvement) at Month 1 and change from baseline to Month 1 on subject-rated responses to the FACE-Q Satisfaction with Cheek module.

Safety Assessments

Procedural pain during injection was assessed by the subject for each cheek using an 11-point scale (0 = no pain; 10 = worst pain imaginable). Subjects completed a daily safety diary for 30 days post-treatment, and a safety follow-up call was conducted 3 days after treatment. The presence and severity of injection-site responses (ISRs) were recorded by subjects in 30-day diaries. Adverse events (AEs) observed by the treating investigator or reported by the subject were recorded.

Statistical Analyses

For change from baseline to Month 1 in overall MFVDS score (primary effectiveness end point), the mean paired difference between treatment with a cannula and a needle and its 95% CI based on the paired *t*-test was calculated. Statistical noninferiority was concluded if the upper confidence limit was less than 0.5. Within-treatment overall MFVDS responder rates (and 95% CI) at Month 1 for the cannula and needle sides were displayed separately, using relevant paired-comparison response categories (i.e., responder rate for cannula and needle, cannula only, and needle only). To calculate the difference in MFVDS responder rates at Month 1, a 2-sided 95% unmodified Wald CI was calculated. The primary and secondary effectiveness end points for MFVDS were analyzed by subgroups for each baseline overall MFVDS severity score (moderate, significant, and severe). Separate post hoc analyses for subjects with/without needle use in the cannula-treated cheek were conducted.

Results

Subject Disposition and Baseline Characteristics

Sixty subjects were randomized and treated; all 60 subjects completed the study, constituting the modified intent-to-treat population and safety population. There were 2 protocol deviations: 1 subject missed the window for the Month 1 visit and 1 subject received hyaluronidase to treat an AE. Most subjects were female (81.7%) and White (98.3%); the median age at study entry was 56 years (range, 37–65 years; **Supplemental Digital Content 1**, Table S1, <http://links.lww.com/DSS/A921>).

Treatment Administration

Anesthesia

Before treatment, 1 or more types of anesthesia were administered to all subjects on the cannula side and 76.7% of subjects (46/60) on the needle side. Topical/injectable anesthesia only was the type most commonly administered during initial treatment (93.3% [56/60] of subjects treated with a cannula and 91.3% [42/46] of subjects treated with a needle), whereas the remaining subjects received both ice and topical/injectable anesthesia.

Volume

The total median volume of VYC-20L injected was the same (2.0 mL) for cannula and needle, with similar quantities in each region: anteromedial cheek median, 0.5 mL and 0.6 mL, respectively; zygomaticomalar region median, 1.0 mL for both sides; and submalar region median, 1.0 mL for both sides. One-third of subjects received treatment with a needle (median, 0.65 mL [included in total volume]) in the zygomaticomalar region on the cannula side to obtain optimal correction.

Injection Plane and Technique

The most common plane of injection was subcutaneous (71.7% for both sides) followed by supraperiosteal (36.7% for both sides). The most common injection techniques were tunneling (cannula, 83.3%; needle, 68.3%) and fanning (cannula, 81.7%; needle 63.3%). Serial puncture was performed in a majority of needle procedures (73.3%) but less frequently with a cannula (33.3%). Cross-hatching was used in 18.3% of both treatments. Multiple injection techniques could be used in a single subject.

Administration and Injection Ease

The cannula and needle sides had the same median number of injections per cheek (3.0). The treating investigators reported that 85.0% of cannula treatments and 96.6% of needle treatments were “easy” or “very easy” to inject. The mean score on the 4-point ease-of-injection scale was 3.6 for cannula and 3.8 for needle.

Effectiveness

The mean absolute change in MFVDS score from baseline to Month 1 was 1.8 with cannulas and 1.9 with needles. The mean paired difference between treatments was 0.1, and the 95% CI was -0.05 to 0.25 , indicating noninferiority (Figure 1). For MFVDS score change from baseline to Month 3, the mean paired difference between treatment with a cannula and treatment with a needle was also 0.1 (95% CI, -0.01 to 0.28). Mid-Face Volume Deficit Scale responder rates at Month 1 were similar between treatment groups with a paired absolute difference of 1.7 (95% CI, -7.31 to 3.98 ; Figure 2). At Month 3, MFVDS responder rates were also similar, with a mean absolute paired difference of 5.0 (95% CI, -10.51 to 0.51 ; Figure 2).

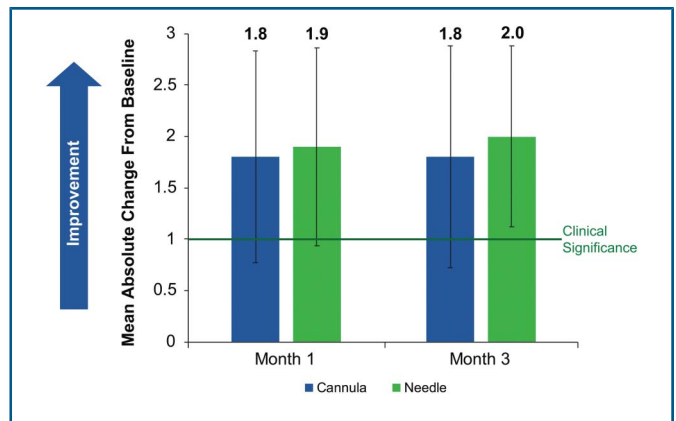


Figure 1. Mean absolute change from baseline in Mid-Face Volume Deficit Scale score. Error bars are standard deviations. Month 1 is the primary end point.

Subjects also reported improvements from baseline on the FACE-Q Satisfaction with Cheeks module (see Text 1 **Supplemental Digital Content 1**, Figure S1 **Supplemental Digital Content 1**, <http://links.lww.com/DSS/A921>).

Subgroup Analyses

Post hoc analyses of MFVDS for subjects with ($n = 20$) or without ($n = 40$) needle use in the zygomaticomalar region of the cannula-treated cheek were conducted. For the 40 subjects who did not receive needle use, the mean paired difference at Month 1 between the cannula-treated and needle-treated cheek was the same as the primary analysis (0.1), with a 95% CI of -0.2 to 0.12 . The MFVDS responder rates at Month 1 were 95% for the cannula side and 97.5% for the needle side. For the 20 subjects who received needle use in the zygomaticomalar region, the mean paired difference at Month 1 was 0.2 (95% CI, -0.25 to 0.65), and the MFVDS responder rate was 90% for both cheeks.

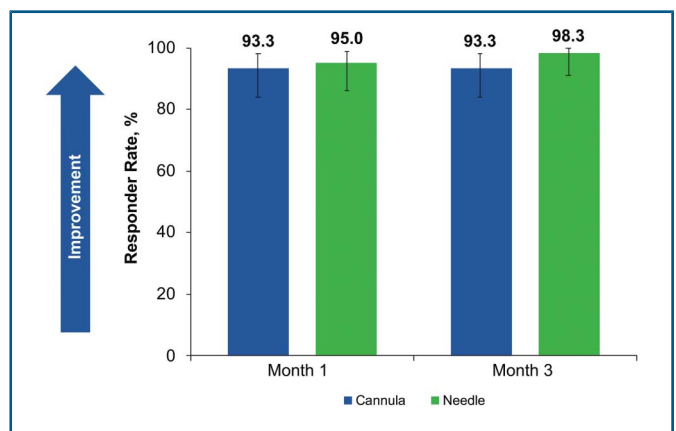


Figure 2. Mid-Face Volume Deficit Scale responder rates (%), defined as the proportion of subjects with at least a 1-point improvement in cheek severity. Error bars are 95% confidence intervals.

Safety

Procedural Pain

Subjects reported minimal procedural pain for treatment with either a cannula (mean pain score, 2.3) or a needle (mean pain score, 3.1). The paired difference in pain scores between cannula and needle treatment was -0.8 (95% CI, -1.32 to -0.35) and favored cannulas. There was no significant difference in the mean procedural pain reported between the 40 subjects (2.3) who did not receive needle treatment on the cannula cheek versus the 20 subjects (2.4) who did receive needle treatment.

Injection-Site Responses

All subjects experienced at least 1 ISR with both treatments. As shown in **Supplemental Digital Content 1**, Table S2, <http://links.lww.com/DSS/A921>, tenderness to touch (91.7% for cannulas and 96.7% for needles), firmness (83.3% and 90.0%, respectively), and swelling (81.7% and 85.0%, respectively) were the most common ISRs. For each individual ISR type, more subjects reported an ISR only on the needle side than only on the cannula side, with the largest differences between injection methods observed for pain after injection (18.3% for needles vs 1.7% for cannulas), lumps or bumps (15.0% vs 1.7%), and bruising (20.0% vs 8.3%). There was a distinct difference in pain after injection with cannulas compared with needles as shown by the nonoverlapping CIs (9.52–30.44 for needles vs 0.04–8.94 for cannulas). The severity of ISRs was similar for cannulas and for needles. Most of the ISRs were mild or moderate in severity, with only 10% of cheeks having severe ISRs (see **Supplemental Digital Content 1**, Table S2, <http://links.lww.com/DSS/A921>). Most ISRs resolved within 2 weeks after initial treatment for both cannulas and needles based on subject diaries. A comparable ISR profile was observed for patients who did not receive needle use on the cannula cheek versus those who did receive needle treatment (data not shown).

Adverse Events

Treatment-emergent AEs (TEAEs) were reported for 1.7% (1/60) and 3.3% (2/60) of cheeks treated with cannulas and needles, respectively, in 2 subjects. These TEAEs were considered treatment-related, had onset within 3 weeks, and resolved without sequelae. One subject developed indurated, red, injection-site plaques of moderate severity measuring 20×20 mm on both cheeks 19 days after treatment on the cannula cheek and 21 days after treatment on the needle cheek. Antinuclear antibody (ANA) tests yielded positive results. The subject was treated with hyaluronidase, oral corticosteroids, and colchicine, and the plaques resolved 122 days (cannula cheek) and 31 days (needle cheek) after injection. The other treatment-related TEAE, mild injection-site mass, occurred on the day of needle injection and resolved 26 days after treatment. No serious AEs (SAEs) or deaths were reported, and no subjects discontinued the study due to an AE.

All TEAEs that occurred at body parts other than the cheeks were considered unrelated to treatment; headache was the most common of these TEAEs (3/60; 5.0%).

Discussion

In this study evaluating the effectiveness of cannula and needle treatments of VYC-20L for age-related midface volume deficit, the primary end point was met and indicated noninferiority of cannula treatment. Dramatic improvements in midface volume were observed with more than 90% of subjects responding by 1 point or more on the MFVDS. Along with FACE-Q results showing that subjects were satisfied with the symmetry, youthfulness, smoothness, attractiveness, and contour of their cheeks at Months 1 and 3, these results demonstrate that the performance of the 2 injection modalities (cannula and needle) were comparable. Subgroup analyses of MFVDS demonstrated that outcomes were similar regardless of whether subjects did or did not receive needle use in the zygomaticomalar region of the cannula-treated cheek, which is consistent with a recent study reporting effectiveness of microcannula-only administration of HA fillers.⁹

Minimal procedural pain was reported by subjects for both the cannula and the needle treatments. Most ISRs were mild to moderate in severity for both treatments, and the most common ISRs were tenderness to touch, firmness, and swelling. These responses generally resolved within 2 weeks of treatment. Anesthesia was required on the cannula side to avoid the pain associated with the introductory needle. The use of anesthesia on the needle side was optional but was used in over three-quarters of needle procedures. Treatment-related TEAEs with either cannulas or needles occurred in less than 5% of subjects and there were no SAEs.

The effectiveness and safety results observed in this study were consistent with results reported in the pivotal study of VYC-20L for midface volume deficit.² Using an average initial treatment volume of 5.07 mL, 85.6% of subjects receiving VYC-20L had improved by at least 1 point on the MFVDS at Month 6 and the effect was sustained for 73.9% of subjects at 1 year. Among the 282 subjects treated in the pivotal study, 2 required treatment with hyaluronidase to reverse delayed inflammatory reactions. In the current study, 1 subject developed injection-site plaques on both cheeks approximately 3 weeks after treatment; the plaques resolved after hyaluronidase treatment. The subject's positive ANA may be indicative of a heightened host immune system. Although the precise cause of this TEAE cannot be determined with certainty, it was deemed unlikely to be related to contamination because the subject's skin was prepared preinjection by washing with soap, preprocedure cleanser, and local disinfectant; aseptic technique was used throughout the procedure.

Needles should be used with caution in areas of the face prone to vascular complications.^{10,11} Intravascular injection of fillers into the facial artery or its branches can cause SAEs, including tissue necrosis and blindness.^{10,11} Blunt cannulas may be more appropriate in high-risk areas

because they may be less likely to penetrate arteries. In a study assessing the force needed to penetrate the facial artery vasculature, results showed that greater force was needed for arterial penetration with 22- and 25-gauge cannulas compared with 22- and 25-gauge needles, but there was no difference between 27-gauge cannulas and needles.¹² Knowledge of facial anatomy can minimize the risk of adverse reactions with filler injections.¹⁰ It should be noted that fewer than half of facial arteries and their branches follow the “textbook course.”¹¹ Special attention should be paid to the angular and infraorbital arteries in the medial cheek, both of which are at risk of intravascular injection causing potential blindness (see **Supplemental Digital Content 1**, Figure S2, <http://links.lww.com/DSS/A921>).^{11,13,14} The course of both arteries is variable, and intravascular injection is possible in the medial cheek in either the subcutaneous (angular artery) or the periosteal planes (infraorbital artery foramen).¹⁵ A 25-gauge cannula (or larger) may minimize the risk of intravascular injection in this high-risk area.¹⁵

Complications may also develop as a result of insufficient experience.¹⁰ In the current study, it is worth noting that treating investigators were skilled at injecting using either needle or cannula (rating at least 85.0% of treatments with both methods easy or very easy to inject). Some investigators preferred using needles, perhaps because cannula injection is slower and technically more challenging than needle injection.¹⁶ The learning curve for cannula treatments is steep, but once the skill is acquired, no differences in injection difficulty are expected using a cannula versus a needle. Knowledge of facial anatomy, adequate training, and appropriate technique will help avoid vascular accidents. Several injection techniques were used in the current study, with tunneling and fanning most commonly employed. Injection using fanning and threading techniques has been shown to result in more frequent bruising than injection using the depot technique. However, these techniques, which limit the number of skin punctures, may reduce postinjection erythema and consequently post-inflammatory hyperpigmentation.¹⁷

This study was subject-controlled using a split-face design to determine the effectiveness and safety of VYC-20L treatment using cannula and needle injections. The evaluating investigator was blinded to treatment, reducing potential bias. The study is limited by the relatively small number of subjects and short duration of follow-up. However, 3 months was deemed appropriate because no difference in product duration was expected relative to the mechanism of delivery, and it was a sufficient length of time to characterize the safety of cannula treatment. Another

limitation was the option to use a needle in the zygomaticomalar region of the cannula cheek. However, separate subanalyses of subjects who did or did not receive needle use on the cannula side indicated that results were similar to those in the primary analysis. Furthermore, the option to use a combination of needles and cannulas more likely approximates real-world practices.

References

1. Bass LS. Injectable filler techniques for facial rejuvenation, volumization, and augmentation. *Facial Plast Surg Clin North Am* 2015;23:479–88.
2. Jones D, Murphy DK. Volumizing hyaluronic acid filler for midface volume deficit: 2-year results from a pivotal single-blind randomized controlled study. *Dermatol Surg* 2013;39:1602–11.
3. *Juvéderm Voluma XC [package Insert]*. Irvine, CA: Allergan; 2016.
4. Fulton J, Caperton C, Weinkle S, Dewandre L. Filler injections with the blunt-tip microcannula. *J Drugs Dermatol* 2012;11:1098–103.
5. Hertzog B, Andre P. The flexible needle, a safe and easy new technique to inject the face. *J Cosmet Dermatol* 2010;9:251–2.
6. DeJoseph LM. Cannulas for facial filler placement. *Facial Plast Surg Clin North Am* 2012;20:215–20. vi–vii.
7. Hexsel D, Soirefmann M, Porto MD, Siega C, et al. Double-blind, randomized, controlled clinical trial to compare safety and efficacy of a metallic cannula with that of a standard needle for soft tissue augmentation of the nasolabial folds. *Dermatol Surg* 2012;38:207–14.
8. Klassen AF, Cano SJ, Scott AM, Pusic AL. Measuring outcomes that matter to face-lift patients: development and validation of FACE-Q appearance appraisal scales and adverse effects checklist for the lower face and neck. *Plast Reconstr Surg* 2014;133:21–30.
9. Jones DH, Hessler J, Chapas A, Jonas B, et al. Microcannula injection of large gel particle hyaluronic acid for cheek augmentation and the correction of age-related midface contour deficiencies. *Dermatol Surg* 2020;46:465–72.
10. Signorini M, Liew S, Sundaram H, De Boule KL, et al. Global Aesthetics Consensus: avoidance and management of complications from hyaluronic acid fillers—evidence- and opinion-based review and consensus recommendations. *Plast Reconstr Surg* 2016;137:961e–71e.
11. Pils U, Anderhuber F, Neugebauer S. The facial artery—the main blood vessel for the anterior face?. *Dermatol Surg* 2016;42:203–8.
12. Pavicic T, Webb KL, Frank K, Gotkin RH, et al. Arterial wall penetration forces in needles versus cannulas. *Plast Reconstr Surg* 2019;143:504e–12e.
13. Kim YS, Choi DY, Gil YC, Hu KS, et al. The anatomical origin and course of the angular artery regarding its clinical implications. *Dermatol Surg* 2014;40:1070–6.
14. Lazzeri D, Agostini T, Figus M, Nardi M, et al. Blindness following cosmetic injections of the face. *Plast Reconstr Surg* 2012;129:995–1012.
15. Cotofana S, Gotkin RH, Frank K, Koban KC, et al. The functional anatomy of the deep facial fat compartments: a detailed imaging-based investigation. *Plast Reconstr Surg* 2019;143:53–63.
16. Humphrey S, Carruthers J, Carruthers A. Clinical experience with 11,460 mL of a 20-mg/mL, smooth, highly cohesive, viscous hyaluronic acid filler. *Dermatol Surg* 2015;41:1060–7.
17. Funt D, Pavicic T. Dermal fillers in aesthetics: an overview of adverse events and treatment approaches. *Plast Surg Nurs* 2015;35:13–32.