Volumizing Hyaluronic Acid Filler for Midface Volume Deficit: 2-Year Results from a Pivotal Single-Blind Randomized Controlled Study

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BACKGROUND Hyaluronic acid (HA) gels are commonly used to correct age-related midface volume deficit (MVD), yet the Food and Drug Administration has not specifically approved them for this purpose.

OBJECTIVE To study the safety and effectiveness of a new 20-mg/mL HA gel (VYC-20L) specifically formulated and optimized for mid-face volumizing.

METHODS AND MATERIALS A multicenter, single-blind, controlled study randomized 235 subjects aged 35 to 65 with MVD to a treatment group and 47 to a no-treatment control group. Responders were defined as subjects who achieved improvement of 1 point or more on the validated 6-point Mid-Face Volume Deficit Scale (MFVDS) at 6 months as rated live by two blinded independent evaluators. The primary endpoint required a 70% or greater treatment group response and a statistically significant difference ($p < .001$) between the treatment and control group responder rates.

RESULTS The primary endpoint was met, with 85.6% of the treatment group improving by 1 point or more on the MFVDS at month 6 and a statistically significant difference ($p < .001$) between the treatment and control group responder rates. Subjects tolerated VYC-20L well, with no unanticipated adverse device effects. Nearly half of subjects maintained correction for 24 months.

CONCLUSION VYC-20L is safe and effective for age-related MVD, with correction lasting up to 2 years.

The authors have indicated no significant interest with commercial supporters.

Hyaluronic acid (HA) gels are the leading injectable fillers worldwide, with an established record of safety and effectiveness.[1] The Food and Drug Administration (FDA) has approved several for correction of wrinkles and folds such as nasolabial folds,[1] with more than 1.4 million procedures performed in the United States in 2012.[2]

Volume loss of skin, bone, and the subcutaneous fat of the face contribute to the visible signs of aging, with areas of facial atrophy and sagging skin appearing by age 35 in many individuals.[3] Given this, there has been an evolution over the past decade away from treating specific discrete wrinkles and folds in isolation and toward panfacial volumizing to achieve facial harmony and improved aesthetic results.[3] In particular, midface volumizing to correct age-related volume deficits is often performed using a variety of injectable fillers, although the FDA has not specifically approved them for this indication.[3]

Juvéderm Voluma XC (VYC-20L; Allergan, Goleta, CA) is a newer HA gel developed specifically for this

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Allergan designed and funded this study. Dr. Jones is a consultant for Allergan and received research support for conducting this study. Ms. Murphy is an Allergan Employee and stockholder.

ISSN: 1076-0512 • Dermatol Surg 2013;39:1602–1612 • DOI: 10.1111/dsu.12343

purpose, is approved in many countries outside of the United States, and has an established record of safety and effectiveness.[4–9] It consists of a 20-mg/mL mixture of low- and high-molecular-weight HA, which allows for efficient crosslinking, resulting in a highly cohesive gel with greater hardness (G′) than other Juvéderm products, greater lift capability, and long in vivo duration optimized for midface volumizing. Like other HA gels, it has the advantage of being reversible with hyaluronidase if needed for treating adverse events (AEs).[1] The pivotal study reported herein was designed to support FDA approval of VYC-20L.

Methods

Study Design

A single-blind randomized controlled study was designed to assess the safety and effectiveness of VYC-20L in treating moderate to severe age-related mid-face volume deficit (MVD). Because no dermal fillers were approved for this indication in the United States, the study made use of a no-treatment control group of subjects who did not receive treatment but were assessed for effectiveness. Subjects were randomized to treatment or control using a 5.3:1 ratio. As an incentive to remain in the study through the 6-month primary endpoint assessment, control subjects were allowed to receive VYC-20L treatment after 6 months.

The study was conducted at 15 sites (13 U.S. and 2 Canadian sites), each of which had a treating investigator (11 dermatologists, 4 plastic surgeons) and two blinded evaluating investigators. The treating investigators discussed treatment goals with the subjects, performed the treatments, and monitored subject safety throughout the study, and the blinded evaluating investigators performed all effectiveness assessments.

At the FDA's request, three facial subregions for treatment were defined: the zygomaticomalar region, the anteromedial cheek, and the submalar region

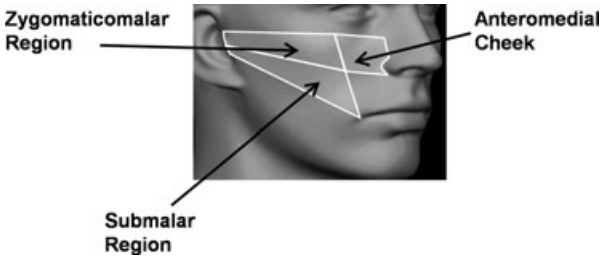

Figure 1. Mid-face treatment areas.

(Figure 1). Subjects were treated in one or more of these regions and then returned 30 days later for a touch-up treatment, which was performed as necessary to achieve optimal correction. Subjects completed 30-day diaries after each treatment to record incidence, severity, and duration of prespecified common treatment site responses and attended follow-up visits at months 1 and 3 and then quarterly for up to 24 months. Between 12 and 24 months, subjects could receive an optional repeat treatment if they had lost their correction in all regions; any subject who did not receive the treatment by month 24 was eligible to receive it at that time regardless of the correction maintained at that visit.

Subjects were required to be aged 35 to 65 and to desire cheek augmentation to correct moderate, significant, or severe age-related MVD. They were ineligible if they had undergone cosmetic facial plastic surgery (with the exception of rhinoplasty more than 2 years before enrollment), tissue grafting, or tissue augmentation with silicone, fat, or permanent or semipermanent dermal fillers. Mandatory facial treatment washout periods before study entry were 24 months for porcine-based collagen fillers, 12 months for HA fillers, and 6 months for neuromodulator injections, mesotherapy, or resurfacing (laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, chemical peel, or other ablative or nonablative procedures).

The study was registered at www.clinicaltrials.gov (NCT #00978042) and approved by the applicable institutional review boards, and all subjects signed informed consent.

Response Measures and Statistics

The primary endpoint was based on the blinded independent evaluating investigators' live assessments of subjects' overall MVD on the validated 6-point Mid-Face Volume Deficit Scale (MFVDS) (Figure 2). Scale grades were severe (5), significant (4), moderate (3), mild (2), minimal (1), and none (0).

To be considered a "responder," the average of the two evaluating investigators' month 6 assessments had to be improved (reduced) by 1 point or more from the average pretreatment assessments. VYC-20L was considered to be clinically effective if 70% or more of the treatment group subjects were responders at month 6 based on a two-sided exact binomial test at 2.5% significance level and if their responder rate was statistically superior to the control group responder rate using a two-sided, two-group Fisher exact test at 2.5% significance level.

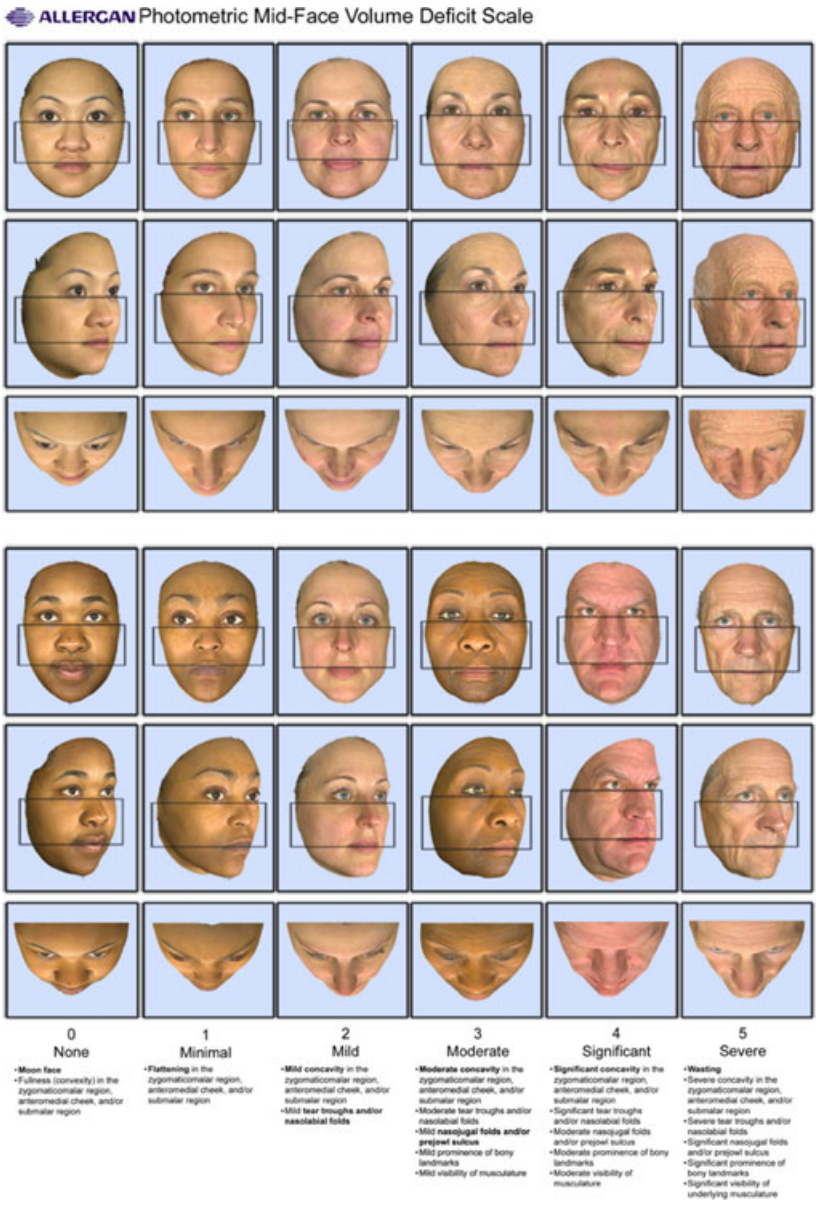

Figure 2. Allergan Mid-face Volume Deficit Scale.

Secondary endpoints were the MFVDS responder rate in each facial subregion and the responder rate on the 5-point Global Aesthetic Improvement Scale (GAIS), both based on the average of the evaluating investigators' assessments at month 6. For GAIS ratings, evaluating investigators and subjects compared the live post-treatment face with a baseline photograph and assigned the level of improvement in cheek volume as much improved (2), improved (1), no change (0), worse (−1), or much worse (−2).

Duration of effectiveness of the product was determined using a Kaplan–Meier estimate of the probability of retaining a 1-point or greater improvement in MFVDS score since baseline based on evaluating investigator assessment. It is a more-conservative methodology than a responder rate analysis and takes study drop-outs into consideration because it is based on the first time point when a subject loses correction. Responder rates are based on subjects observed at a particular time point and can be inflated at later time points because only the subjects who have improvement at earlier time points remain in the study for later time points.

Subjects also underwent three-dimensional digital imaging at pre- and post-treatment visits, and an image analysis technician at Canfield Scientific, Inc. calculated volume changes from baseline to provide an objective measurement of change in cheek volume after treatment.

Subjects

Investigators enrolled 345 subjects, with an average of 23 (range 14–37) per investigational site. Of these, 16 were screen failures, 30 were run-in subjects (2 allowed at each site), and 17 discontinued after randomization but before treatment, resulting in 282 subjects: 235 (83.3%) in the treatment group and 47 (16.7%) in the control group. All initial treatments for the treatment group occurred between August 26, 2009, and June 17, 2010. Safety results are based on 270 randomized and treated subjects: 235 treatment group and 35 control group.

Subjects were primarily female (80.1%) and of Caucasian descent (58.5%), with a median age at study entry of 55 (Table 1). All Fitzpatrick skin types were represented, and characteristics were similar for the treatment and control groups. Most subjects had overall moderate (51.5% treatment, 51.1% control) or significant (41.7% treatment, 44.7% control) MVD.

Treatment

Anesthesia was administered to 66.0% of subjects in preparation for their initial treatment (Table 2), with the most common being topical agents applied an average of 27 minutes before treatment (range 5–-121 minutes) and ice applied for an average of 23 minutes (range 2–107 minutes). More than 90% of subjects received treatment in all three facial subregions, and 86.6% were treated in the subcutaneous and supraperiosteal planes. (See Video S1 for an example of treatment techniques.) Three-quarters of subjects were treated using tunneling, serial puncture, and fanning and half with crosshatching. Approximately half of the subjects were treated using a 27G 0.5-inch ultra-thin-wall needle (52.1%) and half using a 25G 1-inch ultra-thin-wall needle (47.5%). Postinjection massage was performed for 90% of subjects (gentle 45.0%, moderate 33.6%,

TABLE 1. Subject Characteristics (*N* = 282)

Characteristic	*Value*
Sex, *n* (%)	
Female	226 (80.1)
Male	56 (19.9)
Age, median (range)	55.0 (35–65)
Race, *n* (%)	
Caucasian	165 (58.5)
Hispanic	39 (13.8)
African-American	56 (19.9)
Asian	12 (4.3)
Other	10 (3.5)
Fitzpatrick skin type, *n* (%)	
I	8 (2.8)
II	72 (25.5)
III	78 (27.7)
IV	57 (20.2)
V	53 (18.8)
VI	14 (5.0)

vigorous 16.0%) to mold or sculpt the product into proper placement for restoring cheek contour.

The majority of subjects (81.9%) received a touch-up 30 days after initial treatment to achieve optimal correction, and all effectiveness assessments were based on time since last treatment (initial or touch-up). Average injection volume for initial and touch-up treatments combined was 6.65 mL (range 1.2–13.9 mL), with an average total of 2.38 mL (range 0.1–7.0 mL) injected in the zygomaticomalar region, 2.11 mL (range 0.4–5.7 mL) in the anteromedial cheek, and 2.41 mL (range 0.2–10.0 mL) in the submalar region. The volumes for the subregions reflect the total for the right and left sides of the face. Average treatment volume was 5.07 mL for initial and 1.93 mL for touch-up treatment. Subjects rated pain after initial treatment as an average of 3 on a standard pain scale (0 = no pain, 10 = worst pain imaginable).

TABLE 2. Treatment Characteristics for Initial Treatment (*N* = 238)

Characteristic	*Value*
Anesthetic administered, *n* (%)	157 (66.0)
Type of anesthesia, *n* (%) (*n* = 157)	
Topical	123 (78.3)
Ice	87 (55.4)
Nerve block	23 (14.6)
Local	22 (14.0)
Treatment site, *n* (%)	
Zygomaticomalar region	230 (96.6)
Anteromedial cheek	228 (95.8)
Submalar region	220 (92.4)
Injection plane, *n* (%)	
Subcutaneous and supraperiosteal	206 (86.6)
Only subcutaneous	21 (8.8)
Only supraperiosteal	10 (4.2)
Injection technique, *n* (%)	
Tunneling	185 (77.7)
Serial puncture	183 (76.9)
Fanning	180 (75.6)
Crosshatching	118 (49.6)
Ferning	10 (4.2)
Injection volume, mean (range)	
Initial treatment	5.07 (1.0–12.0)
Touch-up treatment	1.93 (0.1–7.0)
Initial plus touch-up	6.65 (1.2–13.9)

Results

Effectiveness

The primary endpoint was met in that 85.6% of the treatment group had improved by 1 point or more on the MFVDS at month 6, and there was a statistically significant difference ($p < .001$) between the treatment and no-treatment control group responder rates. The control group response includes two subjects who were treated in error at study outset. Examining responders at higher MFVDS thresholds shows a dramatic decrease in the control group response, whereas the treatment group response remained strong (Figure 3). Month 6 MFVDS responder rates were also high for the facial subregions: 75.5% for zygomaticomalar, 83.2% for anteromedial, and 76.9% for submalar.

Duration of effectiveness calculated using Kaplan–Meier analysis based on evaluating investigators' assessments of overall MFVDS showed that 73.9% of subjects were still responders at 1 year and that 44.6% were responders at 2 years (Figure 4).

On the GAIS, 82.2% of investigators and 92.8% of subjects rated midface volume as improved or much improved at 6 months, and Kaplan–Meier analysis of long-term results showed a pattern similar to that for MFVDS (Figure 5). The fact that 105 of 125 subjects (85.6%) receiving repeat treatment received it after month 24 also supports the long-term effectiveness of the product. Examples of aesthetic outcomes after treatment are provided in Figures 6–8.

Analyses of three-dimensional digital images to calculate volumetric change provided further support for the effectiveness of VYC-20L. At month 6, mean increase in midface volume was 6.8 mL for the treatment group and 0.8 mL for the control group.

Safety

Treatment site responses most frequently reported in subject diaries after initial treatment were tenderness (92.1% of subjects), swelling (85.7%),

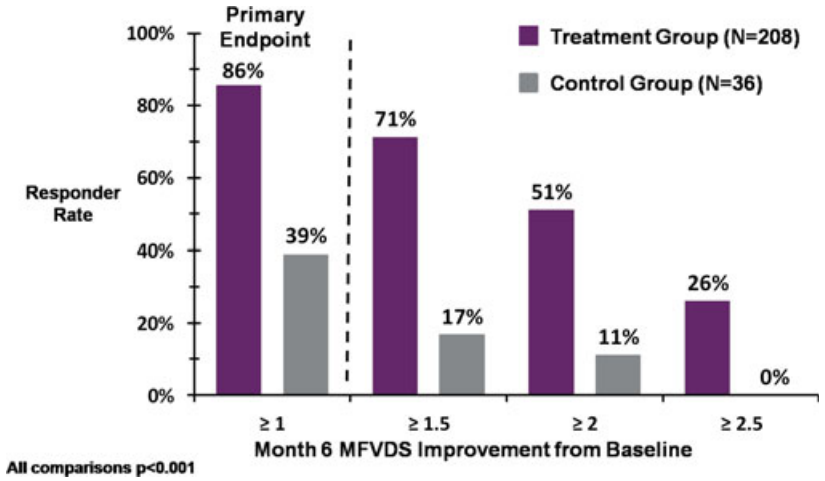

Figure 3. Month 6 Mid-face Volume Deficit Scale responder rates at increasing thresholds based on evaluating investigator assessments.

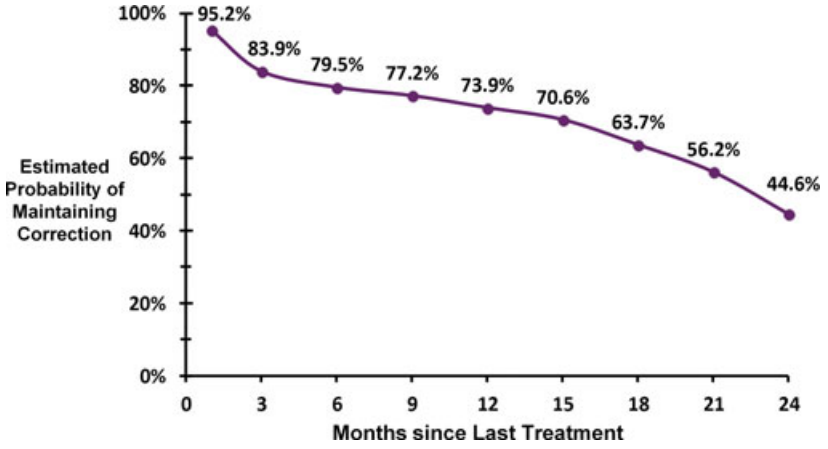

Figure 4. Duration of effectiveness based on Kaplan–Meier analysis of evaluating investigator Mid-face Volume Deficit Scale assessments.

firmness (82.3%), and lumps or bumps (81.1%). Most of the subjects (80.7%) had responses that were mild to moderate in severity and lasted 2 weeks or less (55.4%). For moderate and severe events, median duration was 6 days, and median time that events were moderate or severe was 2 days.

Any treatment site responses ongoing at the end of the 30-day diary were classified as AEs, and treating investigators could report any other AEs throughout the study. Treatment-related AEs reported in more than 5% of subjects were injection site mass (lumps or bumps, 18.9% of subjects), injection site induration (firmness, 14.1%), injection site swelling (7.0%), and injection site pain (5.9%). These were predominantly mild to moderate in severity (87.7%), and all but one resolved. (One subject had mild ongoing firmness but reported that she was satisfied with her treatment outcome.) No treatment was required for 94.3% of these AEs, with most of the rest treated with medication. Four subjects received treatment for moderate AEs: ice and smelling salts for syncope, Tylenol 3 for 4 days for

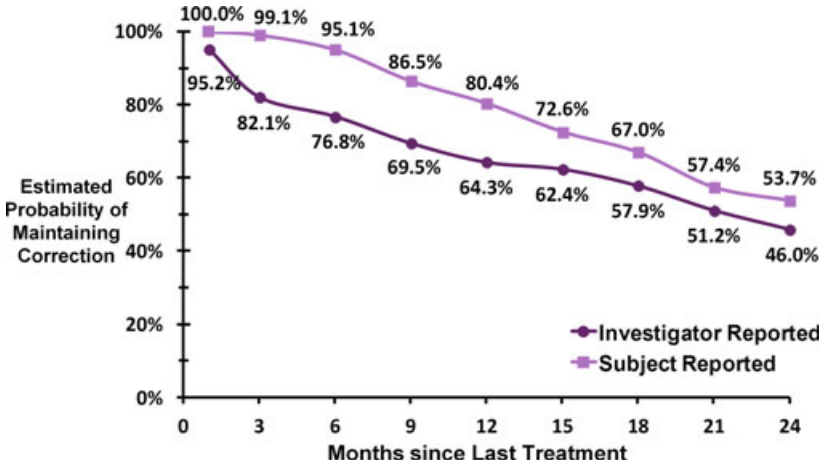

Figure 5. Duration of effectiveness based on evaluating investigator and subject Global Aesthetic Improvement Scale assessments.

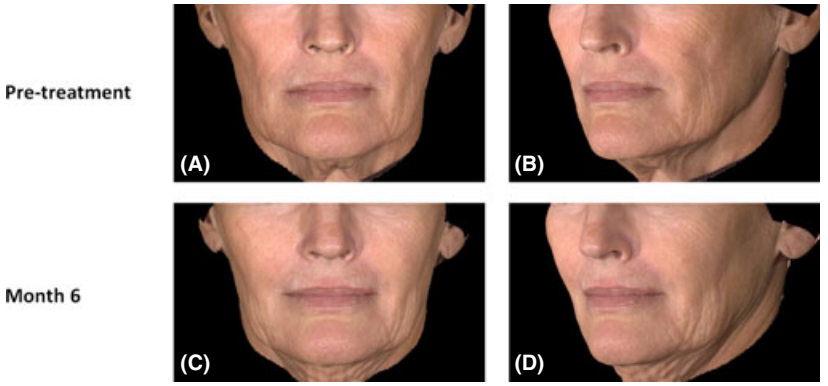

Figure 6. Aesthetic outcomes for a 64-year-old woman before treatment (A,B) and 6 months (C,D) after treatment with 5.8 mL of a 20-mg/mL hyaluronic acid gel in the midface. The subject's Mid-face Volume Deficit Scale score improved from mild or moderate to minimal.

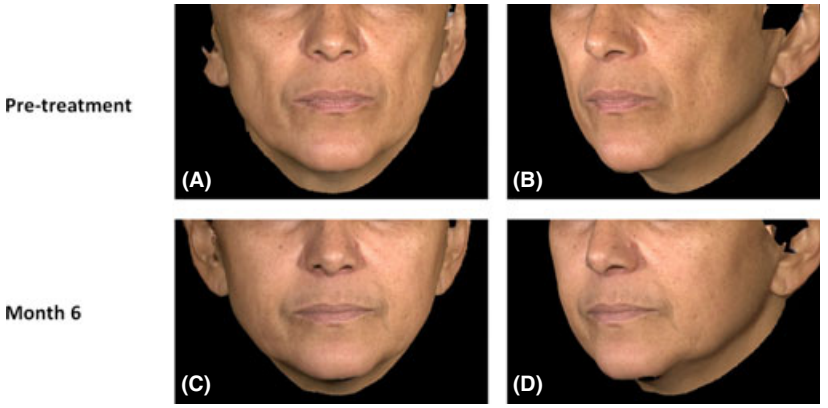

Figure 7. Aesthetic outcomes for a 56-year-old woman before treatment (A,B) and 6 months (C,D) after treatment with 6.9 mL of a 20-mg/mL hyaluronic acid gel in the mid-face. The subject's Mid-face Volume Deficit Scale score improved from moderate or significant to minimal or mild.

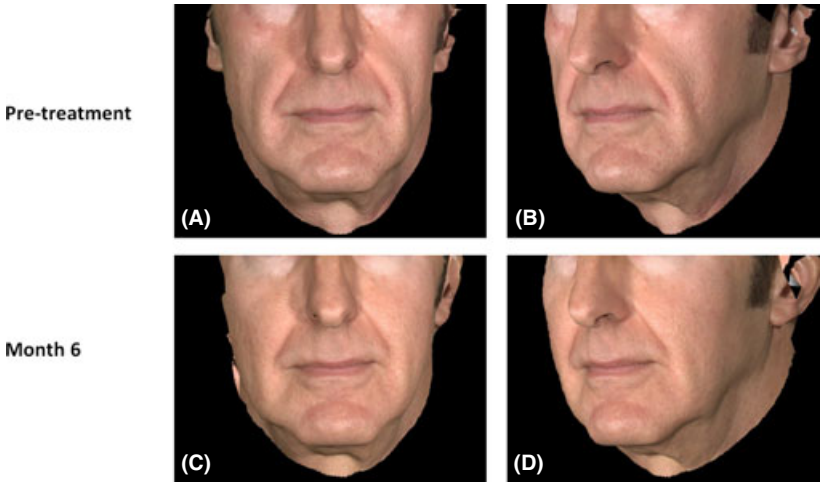

Figure 8. Aesthetic outcomes for a 59-year-old man before treatment (A,B) and 6 months (C,D) after treatment with 8.0 mL of a 20-mg/mL hyaluronic acid gel in the mid-face. The subject's Mid-face Volume Deficit Scale score improved from significant to minimal.

aching, and hyaluronidase for two subjects for lumps or bumps and overcorrection.

Two subjects with severe AEs required treatment. The first subject reported lumps 7 months after the last treatment. Biopsy showed microscopically near-normal skin, and the subject was treated with antibiotics, anti-inflammatories, and hyaluronidase, which resolved the event. The second subject suffered a scratch from a tree branch under the left eye while playing golf. The next day it was diagnosed as cellulitis, and as the event progressed, the subject reported nodularity in the right cheek area. Treatment consisted of antibiotics, anti-inflammatories, and hyaluronidase, and the events resolved without sequelae.

There were no occurrences of scarring or keloids, and the product was found to be safe and effective for all Fitzpatrick skin types.

Discussion

Volumizing with injectable fillers to correct MVD is a common treatment worldwide, but the FDA has not approved any injectable filler specifically for age-related MVD. An injectable option is needed for MVD that is capable of producing immediate, long-lasting results; is effective and safe as judged by physicians and patients; and is reversible if needed to treat AEs.

In this study comparing VYC-20L with no-treatment control for moderate to severe age-related MVD, the primary endpoint was met, with 85.6% of the treatment group improving by 1 point or more on the MFVDS at month 6 and a statistically significant difference ($p < .001$) between the treatment and no-treatment control group responder rates. One might initially be surprised at the control group response (38.9%), but control group response is common in trials of this type in which subjective scales are used to measure subtle yet clinically meaningful change. A similar control group response (37%, vs 70% in the treatment group) was seen in the Restylane lips trial, which led to FDA approval of Restylane for lips in 2011.[10] The VYC-20L protocol anticipated the possibility of as much as a 40% control response, which supported the requirement to prove statistical significance between treatment and control as part of the primary endpoint assessment. In addition, two subjects randomized to the control group received treatment in error at study initiation before the 6-month

primary endpoint assessment, yet data from these treated control subjects remained in the control group for analysis, which inflated the control group response.

Although a 1-point response on the MFVDS is subtle, it results in statistically significant aesthetic improvement in the treatment group, as physicians and subjects reported on the GAIS. In the real world, correcting MVD is an art and a science, and subtlety is important. The treatment goal is usually a natural and subtle change. For this reason, in many cases, physicians and patients may not desire more than a 1-point improvement on the MFVDS.

Accurately predicting volume requirements before treatment is an important part of treatment planning and helps to establish expectations regarding volume and treatment cost. The mean volume of VYC-20L injected for the treatment group in this trial was 6.65 mL, with the largest proportion going to the submalar region, but there was clearly variability of response, with some subjects achieving correction with low volumes and others requiring higher volumes. Generally speaking, as baseline severity increases, treatment volumes also increase. Predicting volume accurately is often a matter of physician experience. Volume injected should therefore be customized to the patient, and clinicians and patients should confer to determine what amount of correction is desired and can reasonably be achieved. It is recommended that VYC-20L be injected as it was in this trial, with the physician injecting to optimal correction at the first visit and using a touch-up injection a few weeks later to refine.

Subjects tolerated VYC-20L well. The majority of subjects reported common treatment site responses typical of HA injections, including tenderness, swelling, firmness, and lumps or bumps. The majority of these lasted 2 weeks or less, were considered mild to moderate in severity, and resolved without treatment. Two subjects had severe delayed-onset AEs that required treatment. One reported lumps 7 months after the last treatment, and another developed cellulitis under the left eye at the site of a scratch from a tree branch, with nodularity developing on the right cheek as the event progressed. Both subjects were treated with antibiotics, anti-inflammatories, and hyaluronidase according to the American Society of Dermatologic Surgery guidelines of care for the treatment of AEs with fillers,[11] and both events resolved. As with other currently available HAs, VYC-20L is reversible in rare cases of inflammatory reactions or misplaced or unwanted product.[1] This characteristic of HA fillers is important to physicians and patients.

Regarding injection technique, a variety of injection techniques were employed, using needles to inject into the subcutaneous and supraperiosteal planes. Although cannulas have grown in popularity, further study is needed to compare the safety and effectiveness of injecting VYC-20L using cannulas with that of needles. Intradermal injection should be avoided to prevent dermal contour irregularities. The injecting physician should also have excellent knowledge of the facial anatomy to avoid injury to underlying structures such as vessels, nerves, and the parotid gland and duct.[12] It is hypothesized that delayed inflammatory reactions may be related to an infectious biofilm process. Accordingly, patients' skin should be thoroughly cleansed with antiseptic cleansers or isopropyl alcohol before injection, and the product should not be injected at sites of active infection.[11]

This study directly corroborates a recent, similar 24-month Australian study of VYC-20L in 103 subjects treated for correction of MVD.[9] Results were predefined as clinically meaningful if at least a 1-point improvement was achieved on the MFVDS as rated by physician investigators, in addition to at least a 1-point improvement on the GAIS as rated by physicians and subjects. Of 103 subjects, 96% were MFVDS responders at postinjection week 8, and 98% and 100% were GAIS responders as rated by subjects and investigators, respectively. At week 78,

81.7% of subjects were MFVDS responders, and 73.2% and 78.1% were GAIS responders, respectively. Subjects were given the option of retreatment at week 78 if needed to maintain optimal correction. Seventy-two subjects completed the 24-month study, 45 of whom did not receive a touch-up at week 78. Forty-three of the 45 remained MFVDS responders at week 104, with 82.2% and 91.1% being GAIS responders as rated by subjects and investigators, respectively. Subject satisfaction was high, with 70 of 72 indicating they would recommend the product to others. As with other HA fillers, AEs were infrequent and transient and consisted mostly of injection site bruising and swelling.

In summary, in this FDA registration trial of VYC-20L for the treatment of age-related MVD, both measures of the primary effectiveness endpoint were met; approximately 86% of subjects in the treatment group were responders on the MFVDS, and the difference was statistically significant compared with the control group. Evaluating investigators and subjects rated the vast majority of subjects as responders on the GAIS. Calculations from the objective three-dimensional digital imaging also supported these subjective measures. The Kaplan–Meier estimates demonstrated that nearly half of subjects will see a clinical benefit for 24 months.

Conclusion

VYC-20L is a safe and effective treatment for age-related MVD, with correction lasting up to 2 years.

Acknowledgments Deepali Paradkar, PhD, of Allergan performed statistical analysis of the data. The Voluma U.S. Study Group included Derek Jones, MD, Gregory Mueller, MD, and Naissan Wesley, MD (Los Angeles, CA); Kimberly Butterwick, MD, Mitchel Goldman, MD, and Douglas Keel, DO (San Diego, CA); Vic Narurkar, MD, Kathleen Welsh, MD, and Usha Rajagopal, MD (San Francisco, CA); Rhoda Narins, MD, David Narins, MD, and Robert Bernard, MD (White Plains, NY); Victor Lacombe, MD, Charles Perry, MD, and Keith Denkler, MD (Santa Rosa, CA); Cheryl Burgess, MD, Beverly Johnson, MD, and Valerie Callender, MD (Washington, DC); Julius Few, MD, Michael Lee, MD, and James Platis, MD (Chicago, IL); Sue Ellen Cox, MD, John Soderberg, MD, and J. Charles Finn, MD (Chapel Hill, NC); David Goldberg, MD, Mussarat Hussain, MD, and David Ciocon, MD (Hillsborough, NJ); Leslie Baumann, MD, Heather Woolery-Lloyd, MD, and Brandon Kallman, MD (Miami Beach, FL); Dee Anna Glaser, MD, Natalie Semchyshyn, MD, and Quenby Erickson, DO (Des Peres, MO); Jeffrey Kenkel, MD, Andrew Trussler, MD, and Ron Hoxworth, MD (Dallas, TX); Jean Carruthers, MD, Alastair Carruthers, MD, and Andrew Denton, MD (Vancouver, British Columbia); Arthur Swift, MD, William Papanastasiou, MD, and Andreas Nikolis, MD (Westmount, Quebec); Kenneth Beer, MD, Daniel Kapp, MD, and Richard Schwartz, MD (West Palm Beach, FL).

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Supplementary Material

Additional Supporting Information may be found in the online version of this article:

Video S1. Supplemental video file.