

Patient-Reported Outcomes following Split-Face Injection of 2 Volumizing Fillers in the Upper Cheeks

Welf Prager, MD*
 Karla Agsten, MD†
 Martina Kerscher, MD‡

Background: Patient-reported outcomes are important measures when assessing the efficacy of aesthetic procedures.

Objective: To compare outcomes between 2 volumizing hyaluronic acid fillers.

Materials and Methods: Subjects with moderate-to-severe volume loss in the cheeks were randomized in a split-face design to malar enhancement with Cohesive Polydensified Matrix 26 mg/ml HA (CPM-26) and Vycross 20 mg/ml HA (VYC-20). The same injection technique and injection volume were applied for both sides of the face. Anesthetics, overcorrection, and touch-ups were not permitted. Blinded subjects assessed aesthetic improvements using the Global Aesthetic Improvement Scale and treatment satisfaction by confirming their willingness to repeat treatment or recommend it to friends. Follow-up was 18 months.

Results: A total of 45 subjects received a single 2 mL injection of CPM-26 on one side and VYC-20 on the contralateral side of the face. The proportion of subjects reporting improvement on the Global Aesthetic Improvement Scale compared with baseline for CPM-26 and VYC-20 was 97.7% and 88.6%, respectively, at 3 months, 73.8% and 71.1% at 12 months, and 61.0% and 56.7% at 18 months. Treatment satisfaction was high, with the majority of subjects stating that they would repeat treatment and recommend it to friends, but at each time point, a higher proportion of subjects was more satisfied with the CPM-26-treated side of the face.

Conclusions: In this first direct comparison of CPM-26 and VYC-20, the majority of subjects were satisfied with both treatments throughout the study. Patient-reported outcome measures identified a trend in favor of CPM-26. (*Plast Reconstr Surg Glob Open* 2017;5:e1412; doi: 10.1097/GOX.0000000000001412; Published online 5 October 2017.)

INTRODUCTION

Defined cheek bones and fullness in the malar region convey a youthful appearance. However, over time, loss of volume in the malar fat pad and increased laxity of the retaining ligaments result in a gradual diminution and descent of malar soft tissue from a position over the zygoma and orbital rim to a lower point in the midface.^{1,2} The loss of volume in one area of the face often leads to

the development of folds in neighboring areas, resulting in sunken cheeks, shadows, and the deepening of nasolabial and other folds. Restoring malar contours with a volumizing filler provides a lifting effect, often reducing or negating the need for treatment in other areas. As a result, consensus recommendations for the midface advise targeting the malar area first when treating multiple facial sites in 1 session.³

Hyaluronic acid (HA) dermal fillers are a popular option for facial volume restoration because of their ef-

From the *Prager & Partner Dermatologische Praxis, Hamburg, Germany; †SCIderm GmbH, Hamburg, Germany; and ‡Department of Cosmetic Science University of Hamburg, Hamburg, Germany. Received for publication September 19, 2016; accepted May 24, 2017.

Copyright © 2017 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of The American Society of Plastic Surgeons. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal. DOI: 10.1097/GOX.0000000000001412

Disclosure: Dr. Prager has acted as a consultant and lecturer for Allergan Inc, Merz Pharmaceuticals GmbH, and Galderma Pharma SA. Dr. Agsten reports no conflicts of interest in this work. Dr. Kerscher has received research support and has conducted clinical trials for Merz Pharmaceuticals GmbH (as Head of the Division of Cosmetic Sciences, University of Hamburg, Germany) and has acted as a speaker and/or investigator for Merz, Kythera, Q-Med/Galderma, and Pierre Fabre. The Article Processing Charge was paid for by Merz Pharmaceuticals GmbH.

fectiveness, safety, and reversibility. Modifications to the crosslinking technology have also resulted in some HA fillers having a longevity of at least 12 months.^{4,5} CPM-26 (Modélis SHAPE, Anteis S.A, Geneva, Switzerland; currently commercialized as Belotero Volume, Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany) and VYC-20 (Juvéderm VOLUMA, Allergan Inc., Pringy, France) are 2 HA fillers that have been specifically developed to provide midface volumization to correct age-related volume loss.

CPM-26 is manufactured with patented Cohesive Polydensified Matrix (CPM) technology. It is composed of 26 mg/ml HA from biofermentation origin crosslinked with 1,4-butanediol diglycidyl ether. The CPM technology creates a product with variable crosslinking densities within the gel, where denser areas ensure a volumizing effect and less dense areas ensure cohesivity of the matrix. These properties allow the gel to be easily extruded through the needle during injection and prevent it from migrating once implanted. CPM-26 is also characterized by its plasticity, which allows the practitioner to mold and sculpt the product easily into the desired shape once injected to achieve optimal aesthetic results. VYC-20 is a 20 mg/ml HA manufactured with patented Vycross technology, which uses a proprietary mix of a majority of low-molecular weight (< 1 mDa) HA and minority of high-molecular weight (≥ 1 mDa) HA to maintain a tightly crosslinked network of HA chains providing the gel with high cohesivity and viscosity.⁶⁻⁸ Both CPM-26 and VYC-20 are designed to be injected subcutaneously or in deeper soft-tissue layers to restore facial volumes. In several clinical trials, both fillers have demonstrated their effectiveness with high patient and physician satisfaction.^{4,5,9,10}

When evaluating dermal fillers for aesthetic use, the perception of results by physicians and patients may differ. Aesthetic procedures are aimed at improving physical appearance, body image, and quality of life. Outcomes measured from a patient's view point are therefore highly relevant due to the fact that the procedures are voluntary and because of the subjective nature of aesthetic perception.¹¹ The U.S. Food and Drug Administration advises that a patient-reported outcome instrument should be used when measuring a concept best known by the patient or best measured from the patient perspective.¹² Therefore, emphasis on the use of patient-reported outcomes that measure patients' perceptions of treatment success is increasing. The current study used a split-face design to compare patient-reported outcomes for CPM-26 and VYC-20 following malar injection in subjects with moderate-to-severe volume loss in the upper cheeks.

METHODS

This single-center, randomized, controlled, split-face study was conducted from June 2013 to March 2015. The study design and methods have been described elsewhere.^{13,14} Briefly, the study enrolled men or women aged ≥ 18 to ≤ 65 years presenting with bilateral, symmetrical, moderate-to-severe sunken upper cheeks (Merz Aesthetics Scale grade 2 and 3), seeking volume enhancement.^{13,14} Subjects could not have been injected with permanent or

semi-permanent fillers or have received any HA filler injection in the face for 2 years before study injection.

Subjects were randomized to injection of CPM-26 into the malar area on one side of the face and VYC-20 into the other side. Injections were performed in a single session to achieve optimal cosmetic results balanced on both sides of the face. Injections were at either a subdermal or epiperiosteal level via 1 entry point using a fanning and/or bolus technique. The use of needles/cannulae, injection depth, and technique were at the discretion of the investigator but were required to be identical for both sides of the face. The products did not contain lidocaine and the use of anesthetics was not permitted. Subjects were blind regarding the assignment of the 2 products to each side. Touch-up injections were not allowed according to the study protocol. An exception was introduced for subjects who complained about asymmetrical cheeks after the month 3 (M3) visit. Upon request, these subjects could have an additional evaluation visit between M3 and M12, at which the site blinded evaluator confirmed asymmetry if there was at least a 1 grade difference on the Merz Aesthetics Scale between the cheeks. A touch-up was offered for the under-corrected side with the same product that was initially injected.

The study was conducted in accordance with the declaration of Helsinki, ISO14155 version 2011 and all applicable regulatory requirements. All patients provided written informed consent before any study-related procedures. Results of the injection techniques and safety aspects of the trial are reported in a separate article.¹³ The current report concerns patient-reported outcomes.

Outcome Measures

Patient-reported outcomes were assessed using a subject satisfaction questionnaire, which was completed at the beginning of visits M3, M12, and M18. They rated overall effectiveness and satisfaction with the tested products using the Global Aesthetic Improvement Scale (GAIS)¹⁵ by comparing their appearance at follow-up visits against photographs taken before treatment on a 5-point scale ranging from "very much improved" (grade 3) to "worse" (grade -1). Subjects gave 1 score for each side of the face based on direct comparison of their face in a mirror versus photographs taken at baseline before injection.

To evaluate treatment satisfaction, subjects were asked a number of questions concerning whether they would repeat the treatment themselves and/or recommend it to friends and relatives, and concerning the effect they believed the treatment had had on their appearance, for example, Would you repeat the treatment? Would you recommend the treatment? Were the results natural? Was there a filling/lifting/smoothing effect? Was there an effect on skin firmness? For each question, subjects responded "yes" or "no" and indicated their side preference, if any.

Statistical Analysis

Analysis was performed on the full-analysis set defined as all subjects who received the treatment and whose endpoint at M3 was available. Data from the asymmetrical subjects referring to the reinjected side were considered as

missing. The distribution of GAIS scores by treatment and visit was calculated. Subject satisfaction questionnaire results at M3, M12, and M18 were summarized by treatment and visit using frequency tables. No statistical tests were performed on the patient-reported outcomes. All statistical analyses were performed by SCIderm GmbH using SAS (Statistical Analysis System) version 9.3.

RESULTS

Demographic Data

Of the 46 subjects enrolled, a total of 45 were randomized to receive injections of CPM-26 and VYC-20 in either upper cheek. For 1 subject among the 45, treatments were interchanged by mistake, and the subject was analyzed as treated and not as randomized. The majority of subjects were female ($n = 43$), white ($n = 44$; 97.8%), and of Fitzpatrick skin type III ($n = 31$; 68.9%). Subject age ranged from 38 to 66 years with a mean of 50.3 ± 6.95 years. Forty subjects completed the study, 3 withdrew consent, and 2 were lost to follow-up.

All subjects received injection with 2 ml of CPM-26 and VYC-20. The products were placed at the epiperiosteal depth in 40 (88.9%) subjects, at the subdermal depth in 4 (8.9%), and at both levels in 1 (2.2%) subject. A detailed description of the injection techniques used has been published separately.¹³

Four subjects complained about facial asymmetry in the cheeks between the M3 and M6 follow-up visits and were confirmed to have a difference of at least 1 MAS grade between the left and right upper cheeks. In all 4 cases, the side previously injected with VYC-20 appeared under-corrected, and the subject was eligible for a touch-up with the same product.

Subject GAIS Scores

At M3 and M12 after treatment, GAIS scores indicated that the majority of subjects were at least improved compared with baseline whether treated with CPM-26 or VYC-20. At M3, 97.7% ($n = 43/44$) of CPM-26 and 88.6% ($n = 39/44$) of VYC-20 subjects were at least improved (grade ≥ 1) compared with baseline, 52.3% ($n = 23/44$) of CPM-26 and 43.2% ($n = 19/44$) of VYC-20 subjects were at least much improved (grade ≥ 2), and 13.6% ($n = 6/44$) and 4.5% ($n = 2/44$), respectively, were very much improved (grade 3; Fig. 1). Only 1 CPM-26-treated subject in contrast to 4 VYC-20 subjects reported no change at M3. At M12, 73.8% ($n = 31/42$) of CPM-26 subjects and 71.1% ($n = 27/38$) of VYC-20 subjects remained at least improved (grade ≥ 1) compared with baseline, 35.7% ($n = 15/42$) and 21.1% ($n = 8/38$) of CPM-26 and VYC-20 subjects, respectively, were at least much improved, and 9.5% ($n = 4/42$) and 5.3% ($n = 2/38$), respectively, remained very much improved. At M18, there was a shift toward lower scores. Nevertheless, for the CPM-26-treated side of the face, 61% ($n = 25/41$) of subjects continued to rate themselves as at least improved, 26.8% ($n = 11/41$) as much improved, and 9.8% ($n = 4/41$) as very much improved. Corresponding figures for the VYC-20-treated side of the

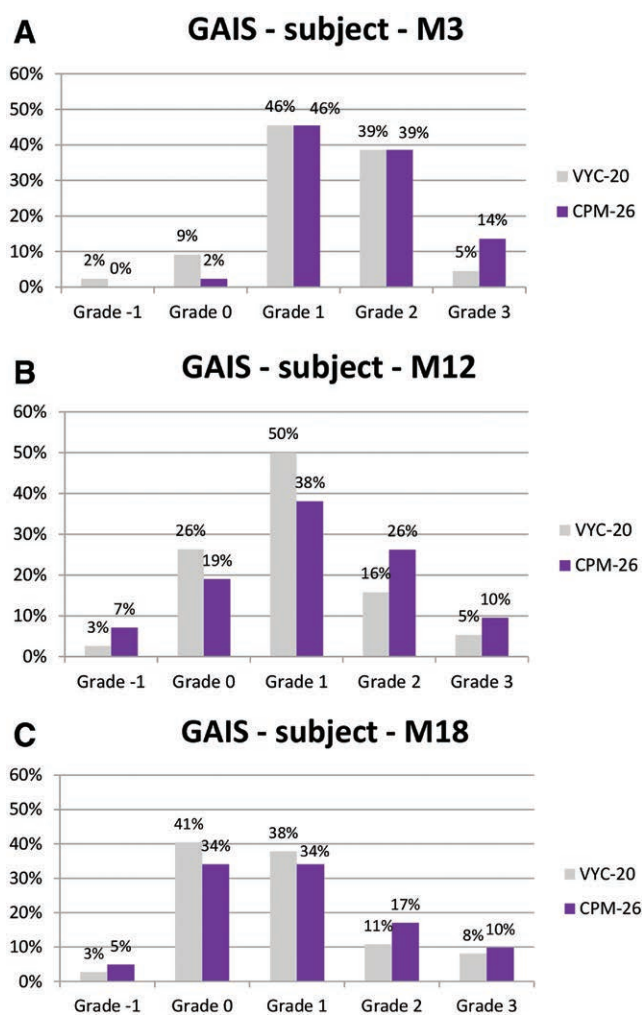


Fig. 1. Subject GAIS results at visits M3 (A), M12 (B), and M18 (C).

face were 56.8% ($n = 21/37$), 18.9% ($n = 7/37$), and 8.1% ($n = 3/37$), respectively. At both the M12 and M18 visits, more CPM-26-treated subjects considered themselves much improved or very much improved compared with VYC-20-treated subjects. Overall, the majority of subjects were satisfied with both treatments throughout the study with a trend in favor of CPM-26. Representative examples of aesthetic outcomes following split-face treatment with CPM-26 and VYC-20 at baseline, M3, M12, and M18 are shown in Figure 2.

Subject Satisfaction Questionnaire

When asked “Would you repeat the treatment?” or “Would you recommend the treatment?,” the majority of subjects indicated that they would do both for both products. However, at each visit, the proportion of subjects that would repeat treatment or recommend it to friends or relatives was always higher with CPM-26 (Fig. 3).

When asked “Do you believe your aesthetic results look natural?” the majority was happy with the appearance on both sides of their face (Fig. 4A). When asked whether they thought treatment had had a volumizing

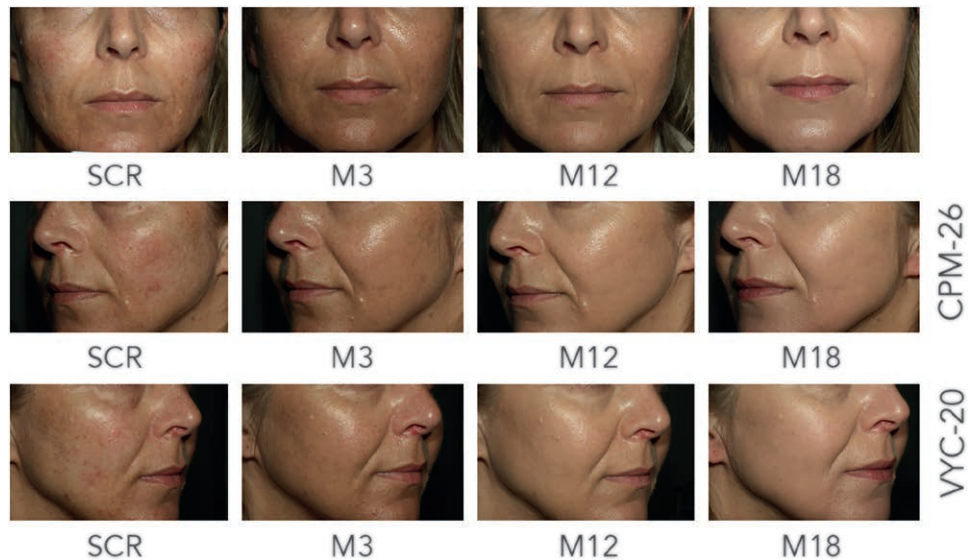


Fig. 2. Representative example of aesthetic outcomes following split-face treatment with CPM-26 and VYC-20 at SCR, M3, M12, and M18. Left side is injected with CPM-26 and right side with VYC-20. SCR, screening visit.

effect, smoothed fine lines, and improved skin firmness, the majority of subjects gave a positive response for both products (Fig. 4B–D). An effect on skin elasticity and softness was detected by approximately 50% of subjects. However, responses were highly variable between visits. Most subjects did not detect an effect in terms of reduction in nasolabial folds, lifting around the lips, and skin hydration for either products.

DISCUSSION

In this split-face comparison of CPM-26 and VYC-20 in subjects with moderate-to-severe volume loss in the upper cheeks, the proportion of subjects reporting improvement on GAIS compared with baseline was high for both products throughout the study. At visit M3, 97.7% and 88.6% of subjects reported they were “at least improved” compared with baseline on the side of their face treated with CPM-26 and VYC-20, respectively. Improvement remained high at visit M12, with 73.8% and 71.1% of CPM-26 and VYC-20 sides rated as “at least improved” compared with baseline. As expected for these degradable fillers, treatment effects had started to decline by the M18 visit, but over half the subjects continued to consider themselves as “at least improved” (61.0% CPM-26; 56.8% VYC-20) demonstrating the longevity of the products.

Blinded physician evaluation of subjects using GAIS scoring is reported in a separate article¹⁴ and demonstrated that at M18, 77.8% of CPM-26 cheeks and 64.5% of VYC-20 cheeks continued to show improvement compared with baseline (grade ≥ 1). In the current article, subjects were more critical in their GAIS scoring than the blinded physician evaluator, but overall results supported the conclusion of a high rate of improvement with both products, but with an overall trend in favor of CPM-26. Subjects tend to have higher expectations from treatment and can be more critical of the results achieved than expe-

rienced investigators, as has been found in other studies with these volumizing fillers.^{5,9,10}

In a separate questionnaire, subjects were asked a number of questions to gauge their overall satisfaction with the volumizing treatments. The majority of subjects indicated that they would repeat treatment with either CPM-26 or VYC-20, and that they would recommend the treatments to family and friends. However, at each visit the proportion of subjects that would do so was always higher with CPM-26. Additional questions enquired whether subjects believed treatment had had a volumizing effect, smoothed fine lines, and improved skin firmness. Again, the majority of subjects gave a positive response for both products, but at each visit subjects’ preference was for CPM-26.

According to the results of the blinded evaluator,¹⁴ a volumizing effect was still present in more than half of the subjects with both products at M18, illustrating the longevity of the products. Based on MAS and GAIS ratings by the blinded evaluator and 3D volume assessment, CPM-26 showed a better performance. This trend was also observed in the subjects’ preference reported here.

Although this is the first study to directly compare CPM-26 and VYC-20, previous studies have examined the volumizing effects of the individual treatments for at least 18 months, albeit in studies that permitted optional touch-up injections and in which investigators determined the appropriate volume to inject based on clinical experience and the severity of the facial depressions.^{5,10,16} In a post-marketing, clinical follow-up study with CPM-26,⁵ the distribution of subject-evaluated GAIS results indicating “at least improved” was similar to that reported in the current study: 100% at M3 and 95% at M12. The value at M18 was also 100%, although this must be interpreted with caution as only 11 of 20 subjects attended this optional follow-up visit. A high level of patient satisfaction was also observed in this study. At 12 months, 95% of subjects reported that

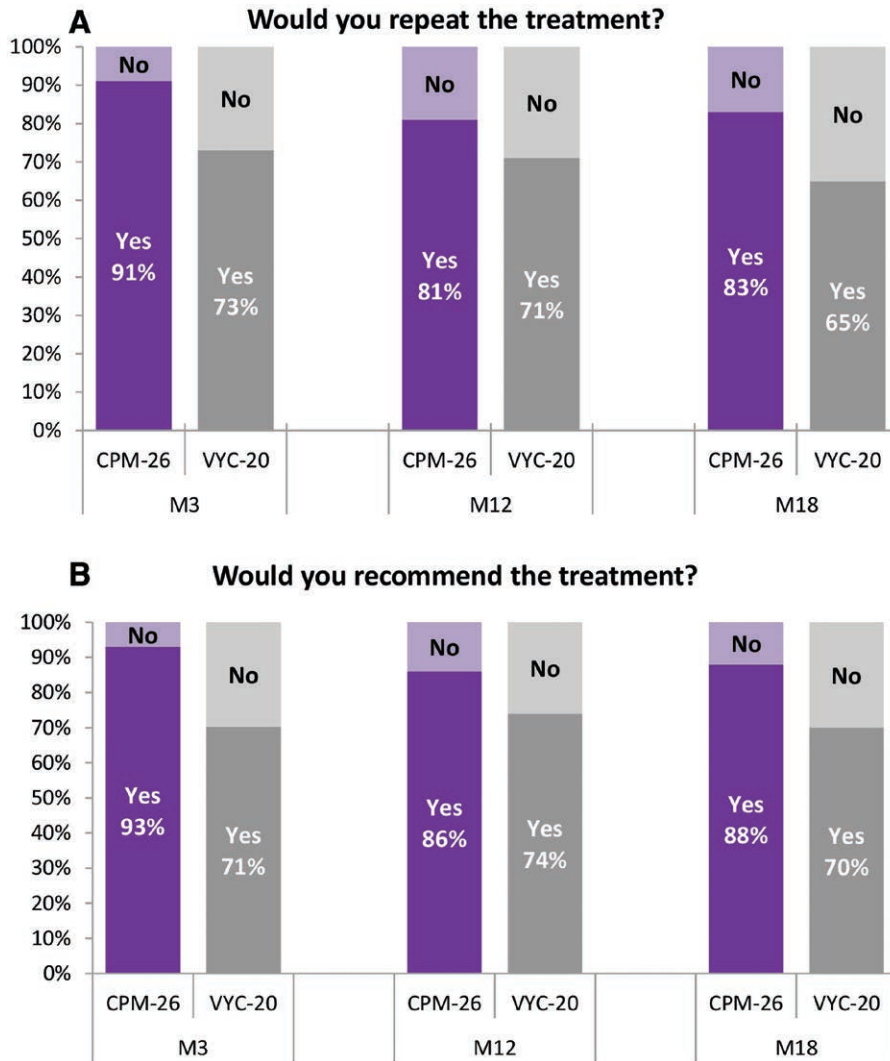


Fig. 3. Subject measures of treatment satisfaction. Subject responses in reply to questions: “Would you repeat the treatment you received on the left/right side?” (A); “Would you recommend the treatment you received on your left/right side to your family/friends?” (B).

they would repeat the treatment themselves and/or recommend it to their friends and relatives as did all of the 11 subjects remaining in the study at 18 months.⁵ In a single-blind, randomized study with VYC-20, 92.8% of subjects rated their cheek volume as at least improved at 6 months, and 79.0% at 2 years¹⁶ for an injection volume of 6.68 mL. In a separate VYC-20 study, 66 (91.6%) of the 72 subjects who completed the 24-month study were either satisfied or very satisfied with the study treatment according to the GAIS scale,¹⁰ and 70 (97.2%) indicated that they would recommend the treatment to others. Of these 72 subjects, 27 were retreated at 18 months with an average of 1.3 mL of VYC-20 per side. Additionally, 28 of the remaining 45 untreated subjects were eligible for retreatment at 24 months (≥ 1 grade loss on midface volume deficit scale). The results from these studies are in agreement with the present findings and support the use of volumizing agents such as CPM-26 and VYC-20 for improving the appearance of subjects with age-associated volume loss in the malar

area. In the majority of subjects, these results were still visible at 18 months even though they presented with moderate-to-severe volume loss at baseline.

The current study presented the patient-reported outcomes data from a single-center, randomized, controlled, split-face study that was also designed to evaluate the effectiveness and safety of CPM-26 compared with VYC-20.^{13,14} The results of live assessment using the Merz Aesthetics Scale showed optimal correction for both products at visit M3 and longevity of the aesthetic effect up to M18.¹⁴ Both products were also well tolerated.¹³

When selecting a dermal filler for aesthetic treatment, physicians should be cognizant of all aspects of the fillers’ behavior including its clinical effects, tolerability, rheological properties, and patient-reported outcome data. Only then can physicians match the individual properties of the filler to its optimal use. Patient-reported outcomes data are particularly relevant for aesthetic procedures because of the subjective nature of perception of beauty.

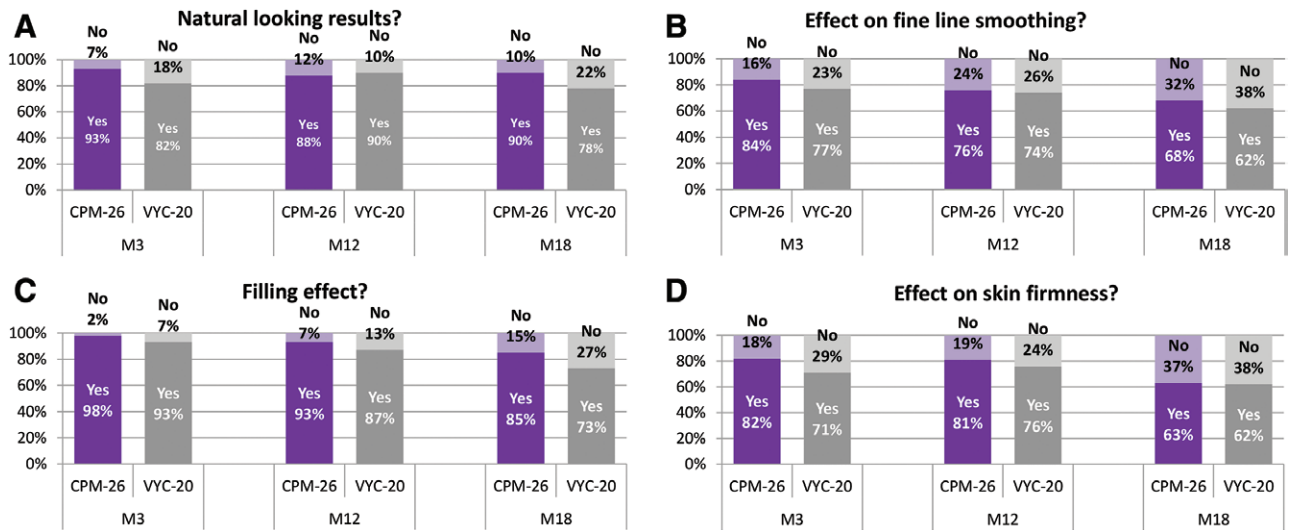


Fig. 4. Subject measures of treatment satisfaction. Subject responses in reply to questions: Do you consider your aesthetic results look natural? (A); Did you detect an effect on fine line smoothing? (B); Did you detect a filling effect? (C); Did you detect an effect on skin firmness? (D).

This study has some limitations. Although GAIS is an accepted secondary outcome measure in studies of aesthetic treatments, it has only 5 rating descriptions, which renders it less sensitive to change than larger scales. GAIS also provides only 1 measurement that characterizes the subject’s overall appearance. It is not specific to a particular facial area and therefore does not necessarily provide any information as to whether a particular treatment improved the severity of sunken cheeks specifically. A more objective technique to measure the volume augmentation observed in this study is reported in a separate article and demonstrated a significant difference in favor of CPM-26 at M3.¹⁴ In the current study, only the malar area was treated, as the aim was to compare 2 specific products. Depending on the extent of aging, level of facial volume loss, and amount of wrinkles in individual subjects, treatment of other facial areas may have been required in some subjects. A global full face aesthetic approach might therefore have led to even higher subject satisfaction.

CONCLUSIONS

In this split-face study of subjects treated with CPM-26 and VYC-20 for moderate-to-severe midfacial volume loss, the majority of subjects reported improvements with treatment at visits M3 and M12, and in over half the subjects an improvement was still visible at M18. At all visits, subjects reported greater improvements with CPM-26 than VYC-20. This trend was also observed for subjects’ satisfaction with treatment, with a greater proportion of CPM-26 treated subjects willing to repeat treatment and recommend it to others.

Welf Prager, MD

Prager & Partner Dermatologische Praxis
 Hemmingstedter Weg 168
 D-22609 Hamburg
 Germany
 Email: info@derma-hamburg.de

ACKNOWLEDGMENTS

The authors thank Maria Kravtsov for support during the course of the study, and Anne Kunz from SCIderm GmbH for the statistical analysis of the results. This study was supported by Anteis SA, a wholly owned subsidiary of Merz Pharmaceuticals GmbH. Editorial assistance was provided by Jenny Grice and funded by Merz Pharmaceuticals GmbH.

REFERENCES

- Coleman SR, Grover R. The anatomy of the aging face: volume loss and changes in 3-dimensional topography. *Aesthet Surg J.* 2006;26:S4–S9.
- Pils U, Anderhuber F, Rzany B. Anatomy of the cheek: implications for soft tissue augmentation. *Dermatol Surg.* 2012;38:1254–1262.
- Carruthers JD, Glogau RG, Blitzer A; Facial Aesthetics Consensus Group Faculty. Advances in facial rejuvenation: botulinum toxin type a, hyaluronic acid dermal fillers, and combination therapies—consensus recommendations. *Plast Reconstr Surg.* 2008;121:5S–30S; quiz 31S.
- Rasaldo H. Volumizing effect of a new hyaluronic acid subdermal facial filler: a retrospective analysis based on 102 cases. *J Cosmet Laser Ther.* 2008;10:134–142.
- Micheels P, Vandeputte J, Kravtsov M. Treatment of age-related mid-face atrophy by injection of cohesive polydensified matrix hyaluronic acid volumizer. *J Clin Aesthet Dermatol.* 2015;8:28–34.
- Carruthers J, Carruthers A, Tezel A, et al. Volumizing with a 20-mg/mL smooth, highly cohesive, viscous hyaluronic acid filler and its role in facial rejuvenation therapy. *Dermatol Surg.* 2010;36:1886–1892.
- Bernardin A, Pierre S, Pather S, et al. Vycross: an innovative dermal filler technology [poster]. In: Presented at: the Anti-Aging Medicine European Congress, October 11–12, 2013; Paris, France.
- Beleznay K, Carruthers JD, Carruthers A, et al. Delayed-onset nodules secondary to a smooth cohesive 20mg/mL hyaluronic acid filler: cause and management. *Dermatol Surg.* 2015;41:929–939.
- Hoffmann K; Juvéderm Voluma Study Investigators Group. Volumizing effects of a smooth, highly cohesive, viscous 20-mg/mL hyaluronic acid volumizing filler: prospective European study. *BMC Dermatol.* 2009;9:9.

10. Callan P, Goodman GJ, Carlisle I, et al. Efficacy and safety of a hyaluronic acid filler in subjects treated for correction of mid-face volume deficiency: a 24 month study. *Clin Cosmet Investig Dermatol*. 2013;6:81–89.
11. Sears ED, Chung KC. A guide to interpreting a study of patient-reported outcomes. *Plast Reconstr Surg*. 2012;129:1200–1207.
12. U.S. Department of Health and Human Services, Food and Drug Administration. *Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. Rockville, MD, 2009. Available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf. Accessed January 8, 2016.
13. Prager W, Agsten K, Kravtsov M, et al. Mid-face volumization with hyaluronic acid: injection technique and safety aspects from a controlled, randomized, double-blind clinical study. *J Drugs Dermatol*. 2017;16:351–357.
14. Kerscher M, Agsten K, Kravtsov M, et al. Effectiveness evaluation of two volumizing hyaluronic acid dermal fillers in a controlled, randomized, double-blind split-face clinical study. *Clin Cosmet Investig Dermatol* 2017;10:239–247.
15. Narins RS, Brandt F, Leyden J, et al. A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. *Dermatol Surg*. 2003;29:588–595.
16. Few J, Cox SE, Paradkar-Mitragotri D, et al. A multicenter, single-blind randomized, controlled study of a volumizing hyaluronic acid filler for midface volume deficit: patient-reported outcomes at 2 years. *Aesthet Surg J*. 2015;35:589–599.