1 | INTRODUCTION

While enhanced facial symmetry and a more youthful appearance are sought among facial aesthetic patients, it is also important to achieve natural-looking results. A patient survey has revealed that fear of losing natural expressiveness is a concern regarding facial treatment outcome.\(^1\) Evaluation of treatment effect in clinical studies often includes photographic scales displaying a resting facial position. There is no standard methodology available to determine naturalness of facial expressions, although assessment of facial dynamics has been suggested to become part of treatment evaluation.\(^1\) Assessment of naturalness is subjective, but may be defined

Abstract

**Background:** In addition to having a younger and more attractive appearance after facial aesthetic treatment, patients desire natural-looking and long-lasting results.

**Objective:** To evaluate perceived naturalness of dynamic facial expressions after treatment with hyaluronic acid fillers in nasolabial folds (NLFs) and lower face wrinkles and folds.

**Methods:** Subjects requiring treatment of moderate-to-severe NLFs and at least one other lower face indication were treated with hyaluronic acid fillers. Assessments included perceived naturalness, attractiveness and age, NLF severity, aesthetic improvement, satisfaction, and safety.

**Results:** Sixty-three subjects were enrolled. Six months after treatment, naturalness of facial expression was maintained or enhanced for ≥98% of subjects, attractiveness was enhanced for ≥61% of subjects, and ≥34% of subjects looked younger, as assessed by investigators and an independent evaluator. Wrinkle severity had improved at least 1 grade for ≥54% of subjects at Month 12. Aesthetic improvement was reported for ≥92% of subjects 12 months after treatment. Satisfaction with treatment outcome was high. Local tolerability events and adverse events were mainly mild or moderate and resolved spontaneously.

**Conclusion:** Hyaluronic acid treatment in NLFs and lower face was well tolerated and achieved natural-looking results, long-lasting aesthetic improvement, and high satisfaction with treatment outcome.

**Keywords**

hyaluronic acid, lower face, nasolabial fold, naturalness

Perceived naturalness of facial expression after hyaluronic acid filler injection in nasolabial folds and lower face

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as a facial expression without signs of treatment, such as product visibility, abnormal surface contour, or incomplete movement of the facial area.

Restylane® Refyne [HA-Ref] and Restylane Defyne [HA-Def] (Galderma) are injectable soft tissue fillers containing 20 mg/mL stabilized hyaluronic acid (HA) and 3 mg/mL lidocaine. HA-Ref and HA-Def are manufactured with the Optimal Balance Technology™, making these products soft and flexible, with ability to adapt to the movement of the tissue during facial expression. HA-Def has a higher degree of cross-linking than HA-Ref, resulting in a firmer gel suitable for treatment of more severe wrinkles and folds. Both products have been investigated for safety and effectiveness for treatment of moderate-to-severe nasolabial folds (NLFs). In this prospective study, optimal treatment of the lower face with HA-Ref and HA-Def was followed by assessment of naturalness of facial expressions, from video recordings and photographs. A set of facial expressions and movements were chosen based on published literature including expressions to capture happiness and sadness. Reading a standard text was also selected as a facial expression assessment. In addition, pursed lips as if to kiss and blow out a candle were included to allow assessment of exaggerated expressions to bring out possible “unnaturalness.”

2 | MATERIALS AND METHODS

2.1 | Study design

This study (ClinicalTrials.gov ID: NCT02573337) was conducted at three sites in Germany between October 2015 and January 2017. After participating in the main study during 1 month after optimal treatment of the lower face, subjects were asked to participate in an optional extension study lasting 12 additional months. The study protocol conformed to the Declaration of Helsinki and was approved by independent local ethics committees. All subjects provided signed informed consent for participation in the study. Data for the main study have previously been reported.

2.2 | Study objectives

The focus of the main study was to evaluate perceived naturalness of facial expression in motion following correction of wrinkles and folds in the lower face. In the extension study, durability of the treatment effect was evaluated. In addition to naturalness, assessments of the lower face included perceived attractiveness and age; NLF severity; aesthetic improvement; subjects’ satisfaction with NLF appearance and with treatment outcome; investigators’ satisfaction with aesthetic outcome; and safety. No comparisons of efficacy or safety between the study products were made.

2.3 | Eligibility criteria

Eligible subjects were 35-65 years old and had moderate-to-severe NLFs (grade 3 or 4 on the Wrinkle Severity Rating Scale [WSRS]).

2.4 | Study treatment

After baseline assessments, subjects were treated to achieve optimal correction as defined by at least one-grade improvement on the WSRS. At least one additional wrinkle or fold in the lower face was also treated. HA-Ref and HA-Def were injected into the mid- to deep dermis using supplied needles. The choice of product and injection technique was at the discretion of the investigators. However, only one product was allowed for each wrinkle or fold. Touch-up was performed after 2 weeks if optimal correction of the NLFs had not been achieved or if lower face appearance could be further improved, as assessed by the investigator.

2.5 | Efficacy assessments

2.5.1 | Photography and video recordings

Full-face photographs and videos were captured in standardized settings with a Canon 6D camera (Canfield Imaging Systems, Inc). The photographs included subjects smiling (big smile—right, frontal, left, and closed big smile); performing various facial animations (corners of mouth pulled down, pursed kiss, and blowing candle). The video recordings included the same facial expressions and also expressions of happiness, sadness, and anger, and reading two prescribed texts aloud. The photographs were to be used in the assessment of WSRS, GAIS, and treatment impact on facial expressions at full contraction. The video recordings were used in assessment of facial expressions in motion. Photographs and video for facial expression assessments were taken at baseline, 1 month after optimal treatment, and 6 months after first treatment. Additional photographs for WSRS and GAIS assessments were taken 9 and 12 months after first treatment. All videos and photographs obtained at follow-up visits were compared to their corresponding baseline capture.

2.5.2 | Facial expression in motion and at full contraction

The treating investigators and an independent evaluator assessed from video recordings whether naturalness and attractiveness of the lower face in motion were enhanced, maintained, or reduced. Also, the subject’s perceived age was assessed as younger, current, or older. The independent evaluator knew that each subject had received treatment in NLFs and at least one other wrinkle or fold but had no information on product or volume.

Treatment impact on naturalness of facial expression at full contraction was evaluated from photographs by investigators.
2.5.3 | Nasolabial fold wrinkle severity and aesthetic improvement

Wrinkle severity was assessed live by the investigators using the WSRS, a validated scale ranging from 1 (absent) to 5 (extreme).9 The independent evaluator performed additional WSRS assessments from photographs. The investigators and subjects independently rated lower face aesthetic changes on the 5‐point Global Aesthetic Improvement Scale (GAIS)10 from photographs showing the subject’s face at rest and with a big smile.

2.5.4 | Subject and investigator satisfaction

Subject satisfaction with NLF appearance was assessed with the FACE‐Q© Appraisal of Nasolabial Folds,11 a questionnaire comprising five questions scoring how bothered subjects were by the appearance of their NLFs. Subject Satisfaction Questionnaires (SSQs) were used to evaluate treatment expectations and outcome. Investigators’ satisfaction with the aesthetic appearance of subjects' lower face was also assessed.

2.6 | Safety assessments

Subjects recorded the presence of any local tolerability events, that is, bruising, redness, swelling, pain, tenderness, and itching in diaries for 14 days after treatment. Any local tolerability events ongoing at Day 15 onwards were reported as AEs. Investigators assessed all AEs for intensity, causality, and seriousness.

2.7 | Statistical analyses

The intention‐to‐treat (ITT) study population included all subjects who were injected in both NLFs. The modified ITT was the primary population for efficacy analyses and included all subjects from the ITT who had achieved an improvement by at least 1 grade on the WSRS in both folds and that were injected in at least one other wrinkle or fold in the lower face. Safety analyses were based on the safety population which included all subjects who were injected in at least one wrinkle or fold. Demographic and treatment data, treatment impact on facial expressions at full contraction and in motion, GAIS, and WSRS improvement were summarized descriptively. Satisfaction questionnaires and treatment impact on facial expressions were presented descriptively and using Student’s paired t test (FACE‐Q). All statistical analyses were performed using SAS® 9.4 (SAS Institute Inc).

3 | RESULTS

3.1 | Demographic data, subject disposition, and injection information

Sixty female and three male Caucasian subjects with a mean age of 52 years (range 35–65 years) completed the main study. One subject was lost to follow‐up and did not participate in the extension study. One additional subject withdrew from the extension study due to professional reasons, resulting in a total of 61 subjects completing the extension study. All 63 subjects were included in all analysis sets. Forty percent of subjects had undergone previous facial procedures including fillers (24%), neurotoxin (19%), and aesthetic eyelid surgery (2%), all in compliance with eligibility criteria.

Equal proportions of subjects had moderate or severe NLFs at study entry. The overall mean treatment volume was 3.6 ml (range 1.6–8.1 ml) to treat a mean of 6.5 (range 4–10) wrinkles or folds. Investigators used the linear threading or serial puncture techniques for the injections. Treatment volumes by product and indication are provided in Table 1.

3.2 | Facial expression in motion and at full contraction

3.2.1 | Naturalness

Based on video recordings from 1 month after optimal correction was achieved, the investigators assessed that naturalness of facial expression in motion was enhanced in 24% of subjects and maintained in 71% of subjects. Recordings from Month 6 showed similar levels of assessed naturalness; 32% of subjects were assessed as having enhanced naturalness and 66% as having maintained naturalness. The independent evaluator found that naturalness was maintained or enhanced in all subjects at both timepoints (Figure 1). Video recordings of a representative female subject aged 39, displaying various facial expressions, at baseline, 1 month after treatment, and 6 months after treatment are shown in Supplemental Digital Content (Video S1). The subject was treated with a total of 4 mL HARef in NLFs, radial cheek folds, marionette lines, oral commissures, and sulcus mentalis. The subject provided informed consent for publication of the recordings in a scientific journal.

For the majority of subjects (92%‐100%), the naturalness of a specific facial expression at full contraction, 1 and 6 months after treatment, was either not affected by treatment or affected in a positive way, according to investigators. Photographs from a representative subject showing a big smile at baseline, 6, and 12 months are shown in Figure 2.

3.2.2 | Attractiveness

At 1 month, the investigators assessed that the attractiveness of subjects’ lower face in motion was enhanced in 89% of subjects and maintained in 10% of subjects. At 6 months, attractiveness was assessed as enhanced in 71% of subjects and maintained in 27% of subjects. The independent evaluator assessed that attractiveness was enhanced in 63% of subjects and maintained in 37% at 1 month. At 6 months, the independent evaluator perceived attractiveness as enhanced and maintained in 61% and 39% of subjects, respectively (Figure 1).
3.2.3 | Age assessment

At 1 month, the investigators assessed that 79% of the subjects looked younger and 17% his/her current age compared to baseline. At 6 months, 69% of subjects were perceived as looking younger and 26% his/her current age. The independent evaluator assessed that 35% of subjects looked younger and 65% his/her current age at 1 month and that 34% looked younger and 66% his/her current age at 6 months (Figure 1).

3.3 | Nasolabial fold wrinkle severity and aesthetic improvement

At 1 month, all subjects were improved at least one grade on the WSRs as determined by the investigator. At 6, 9, and 12 months after first treatment, 89%, 64%, and 54% of subjects were still improved, respectively. This was confirmed by the independent evaluator showing similar results (Figure 3). Both subjects and investigators assessed aesthetic improvement of the lower face using the GAIS; investigators assessed that ≥92% of subjects showed improvement both at rest and when smiling during the whole study. Similarly, ≥95% of subjects assessed themselves as aesthetically improved at rest and when smiling (Figure 4).

3.4 | Subject and investigator satisfaction

Subjects were less bothered by their NLFs at all timepoints up to 12 months after treatment (P < .001). In addition, ≥87% of subjects were satisfied with the treatment result at all timepoints and ≥95% would do the treatment again. Investigators were satisfied with the aesthetic outcome for all subjects at 1 month and for ≥84% of subjects at remaining visits. Investigators were satisfied with the treatment duration for 82% of subjects at 6 months and for 92% of subjects at 12 months.
Local tolerability and adverse events

The most common local tolerability events were bruising, tenderness, and swelling, reported by approximately half of the subjects at some point up to 14 days after treatment; the majority were of mild-to-moderate intensity and resolved spontaneously. Severe complaints were most commonly reported for bruising. Seven AEs in six subjects (10%) were related to study product, injection procedure, or both; these included implant site bruising, induration, nodule, pain, and swelling. All related AEs were mild in intensity and resolved within approximately 2 weeks without intervention, except one event of implant site nodule rated as moderate that lasted for 64 days.

DISCUSSION

This study presents a new way to assess the impact of facial aesthetic treatment of the lower face by introducing facial contraction patterns, static and in movement, in terms of both natural-looking results and long-term aesthetic improvement.

The study included video recordings and photographs of dynamic facial expressions in addition to standard assessments (WSRS, GAIS, SSQ, and FACE-Q). In addition to a similar study performed by the sponsor, this is to our knowledge the first study to use video recordings to evaluate aesthetic treatment results. Data up to 1 month after optimal treatment have previously been published. Here, the durability of treatment up to 12 months is presented.

In accordance with the degree of HA gel cross-linking, investigators primarily used HA-Def in areas requiring more support, for example, the NLFs, while choosing HA-Ref for areas with thinner skin such as oral commissures and radial cheek folds. A mean volume of 3.6 mL of product was used to treat a mean of 6.5 wrinkles and folds.

Naturalness of facial expression was enhanced or maintained in ≥95% of subjects up to 6 months after treatment, as assessed by investigators and the independent evaluator. These data show that naturalness of facial movement was achieved after optimal treatment with HA fillers and that it was maintained over time. These data are also in line with a previous study where HA-Ref and HA-Def were used for correction of moderate-to-severe nasolabial folds, in

FIGURE 1  Perceived naturalness, attractiveness, and age based on assessment of facial expression in motion

FIGURE 2  Subject photographs; big smile. A, Baseline; female subject aged 56 with no previous procedure. The subject provided informed consent for publication of the photographs in a scientific journal. B, 6 mo after treatment with: Initial treatment: HA-Ref (1.5 mL) and HA-Def (1.9 mL) in NLFs, radial cheek folds, marionette lines, oral commissures, and left side sulcus mentalis. Touch-up: HA-Ref (0.45 mL) in marionette lines, oral commissures, and left side radial cheek fold. C, 12 mo after treatment
which 90% of subjects agreed that their face looked natural 1 month after treatment, both at rest and when smiling. In most subjects, the naturalness of facial expression at full contraction was either unaffected by treatment or affected in a positive way, according to investigators. Enhanced naturalness of facial expression in motion and reduction of exaggerated expressions show how filler treatment may diminish how with aging we become caricatures of ourselves. There was no obvious correlation between reduced naturalness, reduced attractiveness, and being perceived as older-looking.

Compared to the investigators, the independent evaluator assessed more subjects as maintained than enhanced in terms of attractiveness. Also, the independent evaluator assessed a larger proportion of subjects as looking their current age, whereas the investigators assessed more subjects as younger-looking. The reasons for these discrepancies may include the inevitable differences in performing assessments from photographs/video presentations as compared to live assessment with the patient. Still, the video recordings were valuable to capture the dynamics of facial expressions, and photographs were, in addition to demonstrating wrinkle reduction, useful to evaluate whether the subject looked restricted when performing a facial expression.

A single treatment including touch-up (mean volume 1.6 mL to both NLFs) provided subjects with both immediate and long-term improvement in wrinkle severity; 1 year after treatment, a majority of subjects (54%-56%) had reduced wrinkle severity in both NLFs compared to baseline, as assessed by investigators and the independent evaluator. These results are in line with other studies investigating WSRS improvement after HA filler treatment of the NLFs. In one split-face study treating moderate NLFs with a mean volume of 0.9 mL HA filler to a single NLF, WSRS improvement was observed in approximately 75% of subjects after 6 months, compared to 82%-89% in the current study. In another split-face study by Ascher et al., where severe NLFs were treated with a mean HA filler volume of 1.3 mL, approximately 90% were improved after 6 months and 80% after 12 months. This is higher than corresponding 12-month WSRS data from the current study; however, Ascher and colleagues presented data from a split-face study comparing two HA fillers, where improvement in both NLFs was not applicable for the study design. Furthermore, that study only included subjects with severe NLFs, whereas the current study also enrolled subjects with moderate NLFs, which can explain the observed differences in WSRS improvement.

The validated FACE-Q Appraisal of Nasolabial Folds instrument was included in the subject questionnaire to highlight the subjects’ views on their NLFs; the results showed that subjects were less bothered by their NLFs at all timepoints up to 12 months after treatment compared to baseline (P < .001). Nearly all subjects (≥95%) found themselves to be aesthetically improved on the GAIS 12 months after optimal treatment, both at rest and when smiling. Other comparable NLF trials examining long-term effects on the GAIS are relatively limited; nevertheless, results are similar to those in a full-face study with HA filler, where 98% of subjects showed GAIS improvements after 12 months. In the current study, satisfaction with the treatment result was high and long-lasting; at least 87% of subjects were satisfied with the treatment result up to 12 months after receiving treatment, and the investigators reported being satisfied with the overall aesthetic outcome for at least 84% of subjects. In line with this, investigators were satisfied with the duration of treatment effect for 82% of subjects at 6 months and for 92% at 12 months.

HA-Ref and HA-Def were well tolerated following injection. Subjects were asked to record any expected, posttreatment events in a 14-day diary; bruising, tenderness, and swelling were the most commonly reported local tolerability events in all treatment areas. As anticipated for these products, most events were mild to moderate in severity and resolved within approximately 2 weeks without any intervention. The related AEs reported by 10% of subjects were mostly mild in intensity and all resolved spontaneously.

Limitations with the study include that assessment of naturalness ideally should involve a full-face evaluation, whereas this study protocol restricted treatment to NLFs and lower face. Also, there is subjectivity in assessment of naturalness, attractiveness, and age and therefore a source of potential evaluator bias.
CONCLUSION

HA-Ref and HA-Def treatment in NLFs and lower face was well tolerated and achieved natural-looking results, long-lasting aesthetic improvement, and high satisfaction with treatment outcome. Photographs and video recordings are valuable tools for evaluation of naturalness and efficacy after aesthetic treatment.

ACKNOWLEDGMENTS

The authors would like to thank Maria Norberg, PhD, for medical writing assistance.

CONFLICT OF INTEREST

Galderma funded the study and provided the study product and was responsible for study design; collection, analysis, and interpretation of data; writing of clinical study report; and the decision to submit the data for publication. Dr Philipp-Dormston has given lectures, consulted and participated in advisory board meetings and clinical studies, and has received honorariums for those by Allergan, Beiersdorf, Biofrontera, Galderma, Leo Pharma, L’Oréal, Merz, and SkinCeuticals. Dr Podda has consulted, lectured, or participated in advisory board meetings for AbbVie, Allergan, Galderma, Janssen-Cilag, La-Roche-Posay, Leo Pharma, L’Oréal, MSD, Novartis, and SkinCeuticals. Dr Schuster reports no further financial interest with Galderma besides involvement in the study. The FACE-Q© is owned by Memorial Sloan Kettering Cancer Center.

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REFERENCES

1. Michaud T, Gassia V, Belhaouari L. Facial dynamics and emotional expressions in facial aging treatments. J Cosmet Dermatol. 2015;14(1):9-21.
2. Segura S, Anthonioz L, Fuchez F, Herbage B. A complete range of hyaluronic acid filler with distinctive physical properties specifically designed for optimal tissue adapttions. J Drugs Dermatol. 2012;11(1 Suppl):55-8.
3. Rzany B, Bayerl C, Bodokh I, et al. Efficacy and safety of a new hyaluronic acid dermal filler in the treatment of moderate nasolabial folds: 6-month interim results of a randomized, evaluator-blinded, intra-individual comparison study. J Cosmet Laser Ther. 2011;13(3):107-112.
4. Ascher B, Bayerl C, Brun P, et al. Efficacy and safety of a new hyaluronic acid dermal filler in the treatment of severe nasolabial lines-6-month interim results of a randomized, evaluator-blinded, intra-individual comparison study. J Cosmet Dermatol. 2011;10(2):94-98.
5. Rzany B, Bayerl C, Bodokh I, et al. An 18-month follow-up, randomized comparison of effectiveness and safety of two hyaluronic acid fillers for treatment of moderate nasolabial folds. Dermatol Surg. 2017;43(1):58-65.
6. Ascher B, Bayerl C, Kestemont P, Rzany B, Edwartz C, Podda M. A 12-month follow-up, randomized comparison of effectiveness and safety of two hyaluronic acid fillers for treatment of severe nasolabial folds. Dermatol Surg. 2017;43(3):389-395.
7. Ekman P. Emotions in the Human Face. New York, NY: Cambridge University Press; 1982.
8. Philipp-Dormston WG, Wong C, Schuster B, Larsson MK, Podda M. Evaluating perceived naturalness of facial expression after fillers to the nasolabial folds and lower face with standardized video and photography. Dermatol Surg. 2018;44(6):826-832.
9. Day DJ, Littler CM, Swift RW, Gottlieb S. The wrinkle severity rating scale: a validation study. Am J Clin Dermatol. 2004;5(1):49-52.
10. Narins RS, Brandt F, Leyden J, Lorenc ZP, Rubin M, Smith S. 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(6):586-595.
11. Klassen AF, Cano SJ, Scott A, Snell L, Pusic AL. Measuring patient-reported outcomes in facial aesthetic patients: development of the FACE-Q. Facial Plast Surg. 2010;26(4):303-309.
12. Solish N, Bertucci V, Percec I, Wagner T, Nogueira A, Mashburn J. Dynamics of hyaluronic acid fillers formulated to maintain natural facial expression. J Cosmet Dermatol. 2019;18(3):738-746.
13. Swift A, von Grote E, Jonas B, Nogueira A. Minimal recovery time needed to return to social engagement following nasolabial fold correction with hyaluronic acid fillers produced with XpresHAn technology. Clin Cosmet Investig Dermatol. 2017;10:229-238.
14. Talarico S, Meski AP, Buratini L, et al. High patient satisfaction of a hyaluronic acid filler producing enduring full-facial volume restoration: an 18-month open multicenter study. Dermatol Surg. 2015;41(12):1361-1369.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Philipp-Dormston WG, Schuster B, Podda M. Perceived naturalness of facial expression after hyaluronic acid filler injection in nasolabial folds and lower face. J Cosmet Dermatol. 2020;19:1600–1606. https://doi.org/10.1111/jocd.13205