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Evaluating Perceived Naturalness of Facial Expression After Fillers to the Nasolabial Folds and Lower Face With Standardized Video and Photography

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BACKGROUND Hyaluronic acid (HA) fillers are commonly used in treating facial wrinkles and folds but have not been studied with standardized methodology to include assessment of standard facial expressions.

OBJECTIVE To assess perceived naturalness of facial expression after treatment with 2 HA fillers manufactured with XpresHAn Technology (also known as Optimal Balance Technology).

MATERIALS AND METHODS Treatment was directed to the nasolabial folds (NLFs) and at least 1 additional lower face wrinkle or fold. Maintenance of naturalness, attractiveness, and age at 1 month after optimal treatment were assessed using video recordings and photographs capturing different facial animations. Global aesthetic improvement, subjects' satisfaction, and safety were also evaluated.

RESULTS The treatment was well tolerated. Naturalness of facial expression in motion was determined to be at least maintained in 95% of subjects. Attractiveness was enhanced in 89% of subjects and 79% of subjects were considered to look younger. Most subjects assessed their aesthetic appearance as improved and were satisfied with their treatment.

CONCLUSION Naturalness and attractiveness can be assessed using video recordings and photographs capturing different facial animations. XpresHAn Technology HA filler treatments create natural-looking results with high subject satisfaction.

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Hyaluronic acid (HA) is a naturally occurring constituent of the extracellular matrix, connective tissue, synovial fluid, and other tissues. Hyaluronic acid fillers have been in clinical use for some 20 years and have a well-documented safety profile.[1,2]

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Restylane Refyne (HA-Ref) and Restylane Defyne (HA-Def) (Galderma, Uppsala, Sweden) are injectable soft tissue fillers containing 20 mg/mL stabilized HA and 3 mg/mL lidocaine. These gels are manufactured with XpresHAn Technology (also known as Optimal Balance Technology). By varying the degree of cross-linking and gel particle size, a range of flexible HA gels with distinct properties suited for different treatment areas are obtained. Both HA-Ref and HA-Def are softer gels that integrate into the dermis where flexibility of gel can adapt to the movement of the tissue during facial expression. Compared with HA-Ref, HA-Def has a higher degree of cross-linking resulting in greater gel firmness to give structural support suitable for treatment of more severe wrinkles and folds.[3] These products have both been studied in active-controlled, split-face design studies investigating safety and effect when treating moderate-to-severe nasolabial folds (NLFs).[4–7]

Many patients desire reassurance of a natural look when seeking facial aesthetic treatments. An example is to avoid the frozen look after botulinum toxin treatment. Considering that facial expressions are integral psychosocial interactions, some propose that assessment of impact of treatment on facial dynamics ought to become part of evaluation of an optimal treatment.[8] Although it is common in clinical studies to use validated photographic scales to evaluate effect of filling of wrinkle with the face in a neutral position, there is as yet no standard methodology on assessing naturalness of facial expression.

A desire for natural-looking results is often described but assessment of naturalness is still subjective. For some, naturalness may be defined as facial expression that is without telltale signs of treatment, characterized by visibility of product, abnormal surface contour, or incomplete movement of the facial area. An improved appearance would be suggested by better symmetry of the facial expression, a more youthful appearance, or reduction in aging signs.

In this prospective study, naturalness of facial expression was assessed from video recordings that captured subjects' lower facial animations (in motion) as well as maximal facial contractions in photographs. A set of standard facial expressions and facial movements used in this study were chosen based on published literature[9] and an attempt to capture common expressions of happiness, joy, and sadness. Reading a standard text was selected as an activity. In addition, kissing and blowing out a candle were included to allow assessment of exaggerated expressions to bring out possible "unnaturalness."

Materials and Methods

Study Design

This was a multicenter, open study (ClinicalTrials.gov ID: NCT02573337) conducted at 3 sites in Germany between October 2015 and January 2016. Efficacy and safety were assessed after achieving optimal correction of NLFs (approximately 6 weeks after baseline treatment). Subjects were thereafter asked to participate in an optional extension study lasting 12 months (data analysis in progress). The study protocol conformed to the Declaration of Helsinki and was approved by independent local ethics committees. All subjects provided signed informed consent.

Study Objectives

The primary objective was to evaluate perceived naturalness of facial expression (in motion) after correction of NLFs and lower face wrinkles and folds. The primary end point was the proportion of subjects perceived by the treating investigators to have at least maintained naturalness of facial expression. Secondary objectives included: perceived attractiveness and age of the subject; NLF severity; lower face aesthetic improvement; subject's satisfaction with the appearance of the NLFs and lower face treatment outcome; treating investigator's satisfaction with lower face aesthetic outcome; and safety.

Eligibility Criteria

Eligible subjects were between 35 and 65 years having moderate-to-severe NLFs (Wrinkle Severity Rating Scale [WSRS] Grade 3–4) and at least 1 other lower face wrinkle or fold suitable for treatment. Subjects with previous treatment area surgery or permanent

filler were excluded, as well as subjects with any lower face neurotoxin or non–permanent filler treatment within 6 and 12 months, respectively.

Study Treatment

Subjects' NLFs were treated to optimal correction (at least 1 grade WSRS improvement) with HA-Ref and HA-Def in mid-to-deep dermis using the supplied needles. At least 1 additional lower face wrinkle or fold was also treated. Product choice and injection technique was at investigators' discretion; however, only 1 product was allowed for each wrinkle or fold. Touch-up treatment was performed after 2 weeks if optimal correction had not been achieved or if lower face appearance could be further improved, as assessed by the treating investigator.

Assessments

Photography and Video Recordings
Photographs and videos were captured in standardized settings using IntelliStudio with a Canon 6D camera (Canfield Imaging Systems, Inc., Parsippany, NJ) and recorded subjects smiling; performing various facial animations, including simulating the emotions of happiness and sadness; and reading a prescribed text. See Figure 1 for paired baseline and post-treatment photographs in different poses.

Nasolabial Fold Wrinkle Severity and Aesthetic Improvement
Wrinkle severity was assessed live by the treating investigators using the WSRS, a 5-point validated scale ranging from 1 (absent) to 5 (extreme).[10]

An independent evaluating investigator performed additional WSRS assessments by comparing follow-up and baseline visit photographs. The treating investigators and subjects independently rated lower face aesthetic changes on the 5-point Global Aesthetic Improvement Scale (GAIS)[11] at the follow-up from photographs showing the subject's face at rest and with a big smile. Photographs were rated by responding to: "How would you describe the aesthetic appearance of your/the subject's lower face compared to the photos taken before first treatment?" Possible responses were: worse, no change, somewhat improved, much improved, or very much improved. Subjects somewhat improved, much improved, or very much improved were defined as *improved*.

Facial Expression (in Motion) and at Full Contraction
The treating investigators and an independent evaluator assessed if naturalness of facial expression and attractiveness of the lower face (in motion) were enhanced, maintained, or reduced by assessing video recordings from the follow-up visit. Subjects with enhanced or maintained naturalness were defined as *at least maintained*. Subjects' perceived age was also assessed as younger, their current age, or older. In addition, treatment impact on naturalness of facial expression at full contraction was evaluated from photographs by the treating investigators. All follow-up videos and photographs were compared with their corresponding baseline capture.

Subject and Investigator Satisfaction
Subjects' satisfaction with their NLF appearance was assessed using the FACE-Q appraisal of nasolabial folds,[12] a questionnaire scoring how bothered subjects

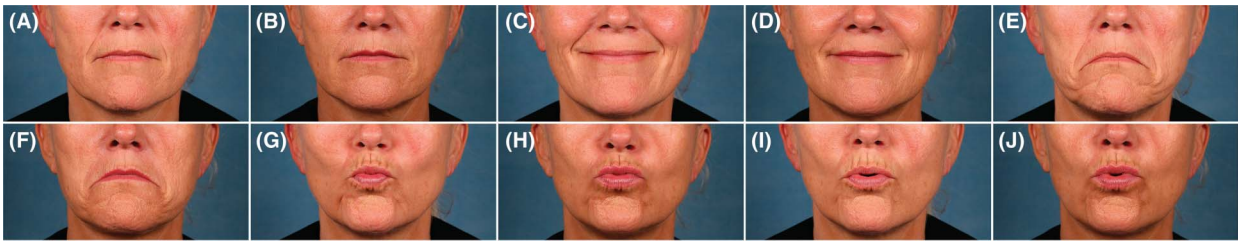

Figure 1. Photographs of a representative subject illustrate 5 selected views at baseline (relaxed face (A), closed big smile (C), grimace (E), pursed kiss (G), blowing out candle (I)) and at the follow-up 1 month after touch-up (relaxed face (B), closed big smile (D), grimace (F), pursed kiss (H), blowing out candle (J)). The nasolabial folds, radial cheek folds, marionette lines, and oral commissures were treated either with HA-Ref or HA-Def.

were by the appearance of their NLFs before and after treatment. Subject satisfaction questionnaires (SSQs) were used to evaluate treatment expectations and results. In addition, treating investigators' satisfaction with the aesthetic appearance of subject's lower face was assessed at the follow-up visit.

Safety

Safety was evaluated by adverse event (AE) monitoring with intensity, causality, and seriousness assessments. Subjects also recorded presence of any local tolerability events (e.g., bruising, redness, swelling, and pain) in diaries for 14 days after treatment and events ongoing at Day 15 onward were reported as AEs.

Statistical Analysis

Assuming 70% of subjects with at least maintained naturalness, 60 subjects were determined sufficient to give ≥80% power to reject a null hypothesis of ≤50% subjects with at least maintained naturalness with 95% confidence. Changes in FACE-Q scores were evaluated with paired *t*-tests and assessments on the agreement between video and photographs using weighted kappa analyses. All tests were 2-sided with a significance level of 5% and were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Demographics and Injection Treatments Used

Sixty female and 3 male Caucasian subjects with a mean age of 52 years (range 35–65 years) participated in the study and completed all study visits up to (and including) Week 6. Forty percent of subjects had undergone previous facial procedures including fillers (24%), neurotoxin (19%), and aesthetic eyelid surgery in 1 subject; all procedures were in compliance with the eligibility criteria.

Equal proportions of subjects had NLFs of WSRS Grade 3 (moderate) and 4 (severe) 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, with 62% of subjects having 6 or more wrinkles and folds treated. An average of 2.9 mL of product was injected at first treatment and for the 43 (68%) subjects receiving touch-up treatment, an average of 1.0 mL was used. Both study products were used in 94% of subjects at the first treatment session and in 63% of subjects at touch-up. Investigators used the linear threading or serial puncture techniques for the injections.

Nasolabial Fold Wrinkle Severity and Aesthetic Improvement

All subjects improved at least 1 grade on the WSRS as determined by the treating investigator assessments of subjects' NLFs at the follow-up visit. This was confirmed by the evaluating investigator assessments (97% of subjects were assessed as improved). Both subjects and treating investigators assessed aesthetic improvement using the GAIS. The treating investigators assessed that 98% of subjects showed aesthetic improvements in the lower face both when at rest and when smiling. Similarly, at least 97% of subjects assessed themselves as aesthetically improved when at rest and when smiling.

Facial Expression (in Motion) and at Full Contraction

Based on video recordings, the treating investigators assessed that naturalness of facial expression (in motion) was enhanced in 24% of subjects and maintained in 71% of subjects. Thus, 95% (confidence interval 87%–99%) were rated at least maintained, thereby fulfilling the primary objective of the study. The independent evaluator found that naturalness was at least maintained in all subjects. Attractiveness was considered to be enhanced in 89% of subjects and 79% of subjects were considered to look younger compared with before treatment, as assessed by the treating investigators. Evaluation of facial expression at full contraction by the treating investigators from photographs showed that naturalness was either unaffected, or affected in a positive way in most subjects compared with before treatment (Table 1). The overall proportion of observed agreement between photographs and videos regarding naturalness was over 80% for each of the

TABLE 1. Treatment Impact on Naturalness of Facial Expression at Full Contraction—Photograph Assessments

	*Treating Investigators' Response**			
Expression	*No*	*Yes, in a Positive Way*	*Yes, in a Negative Way*	*Total* (n)
Blowing out candle	48 (76)	14 (22)	1 (1.6)	63
Closed big smile	46 (74)	15 (24)	1 (1.6)	62†
Pursed kiss	46 (73)	16 (25)	1 (1.6)	63
Grimace	44 (70)	17 (27)	2 (3.2)	63
Big smile—right	40 (65)	19 (31)	3 (4.8)	62†
Big smile	40 (65)	19 (31)	3 (4.8)	62†
Big smile—left	38 (62)	19 (31)	4 (6.6)	61‡

Responses are n (%) unless otherwise stated.

*Assessments were performed by responding to the question: Compared with baseline, is the naturalness of this expression affected by injection treatment of wrinkles and folds?

†Not performed by 1 subject(s).

‡Not performed by 2 subject(s).

expressions and the weighted kappa indicated moderate-to-substantial agreement (0.50–0.62). Paired photographs and a video recording from a representative subject at baseline and 1 month after touch-up are shown in Figure 2 and **Supplemental Digital Content**, Video, http://links.lww.com/DSS/A83.

Subject and Investigator Satisfaction

At baseline, 95% of subjects wished to have improved overall facial appearance, 70% desired that the treatment would prevent signs of aging, and 52% wanted to look younger. At 1 month after touch-up, 40% of subjects agreed with the statement that they looked younger than their age compared with 18% at baseline and no subject thought that they looked older than their age. The FACE-Q assessment showed that subjects were significantly less bothered by their NLFs 1 month after optimal treatment. In addition, 97% of subjects were satisfied with the treatment result and all treating investigators were satisfied with the aesthetic outcome of all subjects.

Local Tolerability and Safety

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, and the majority were of

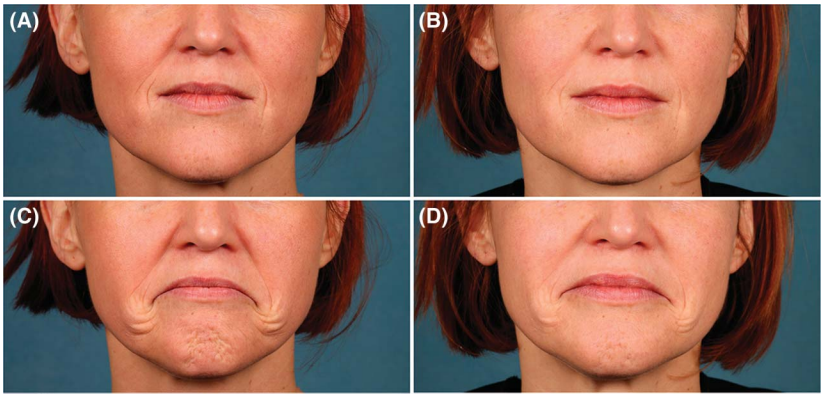

Figure 2. To illustrate improvement in relaxed face expression and negative facial expression of grimace at (A and C) baseline and (B and D) 1 month after touch-up. The nasolabial folds, radial cheek folds, marionette lines, oral commissures, and the mental crease were treated using either HA-Def or HA-Ref.

TABLE 2. Treatment-Related Adverse Events

					Maximal Intensity†		
Adverse Event	*Subjects,* n (%)	*Events,* n	*Time to Onset**	*Duration**	*Mild*	*Moderate*	*Severe*
Implant-site bruising	2 (3.2)	2	5	11	2	0	0
Implant-site induration	1 (1.6)	1	8	13	1	0	0
Implant-site pain	1 (1.6)	2	0	19	2	0	0
Implant-site swelling	1 (1.6)	1	1	7	1	0	0
Total	5 (7.9)	6	0.5	13.5	6	0	0

*Median number of days.
†Number of events.

mild-to-moderate intensity and resolved spontaneously. Six events in 5 subjects were reported as AEs assessed to be related to the study product or injection procedure (Table 2). All AEs were mild in intensity and resolved without any intervention.

Discussion

This study aimed to evaluate whether natural-looking results could be achieved when treating multiple moderate and severe wrinkles and folds in the lower face with 2 HA fillers manufactured with XpresHAn Technology. The study included a standardized set of video recordings and photographs of dynamic facial expression to evaluate facial movements in the treated area in addition to accepted assessments (WSRS, GAIS, SSQ, and FACE-Q). One month after optimal treatment was chosen for assessment of naturalness because the effect of treatment is more visible than at later time points.

Investigators primarily used HA-Def in areas requiring more support, for example the NLFs, whereas more often choosing HA-Ref for treating areas with thinner skin or where a more subtle effect was desired. A mean volume of 3.6 mL of products was used to treat a mean of 6.5 wrinkles and folds. The key finding was that naturalness of facial expression was at least maintained in 95% of subjects. The independent evaluator confirmed that naturalness was maintained. Furthermore, the observation of "enhanced" naturalness in 24% subjects was unexpected. These subjects, assessed to have enhanced naturalness, were also assessed to be more attractive and younger-looking, suggesting that a more attractive youthful appearance could be interpreted as enhanced naturalness. Similarly, those subjects assessed to have enhanced naturalness by the independent evaluator were assessed to look more attractive. All but one subject were assessed to look younger than their age compared with baseline.

A noteworthy observation is that fillers treatment can have an effect on certain facial expressions that represent more than filling wrinkles and folds. For example, reduction of overexpressiveness of negative expressions, as illustrated by the animation of the "grimace" in 2 subjects (Figure 1E, F and Figure 2C, D). It would be interesting to explore further whether the naturalness of the face may be perceived as enhanced if the negative overexpressiveness that tends to be more visible as we age is reduced by the treatment.

In the absence of a scale to define naturalness, considerable efforts were made to minimize assessment variation through use of standardized photographs and videos. We found the use of standardized photographs to capture a range of standard facial expressions and movements very useful in demonstrating the benefits of treatment other than flattening of wrinkles. In addition to photographs, video recordings were included to capture the rich dynamics of facial expression. Both methods provided useful information. Video recordings offer a unique and important way of analyzing treatment effects by capturing the face in movement, whereas photographs have the advantage of making direct comparisons at one single time point. The use of video recordings for baseline and post-treatment comparisons entails both

methodological and technological challenges. One such example was the synchronization of each standard expression so that the movements in the face could be compared. Recognizing that assessment of naturalness ideally should encompass the entire face and possibly the use of other testing methods, a limitation of this study is that the study protocol restricted treatment to only the NLFs and wrinkles and folds in the lower face.

Another limitation of the study is the known subjectivity in assessment of attractiveness, naturalness, and not looking one's age, thus a potential source of investigator bias. Despite this concern, separate evaluations by the independent evaluator and the treating investigators came to similar conclusions that all 3 parameters were at least maintained in almost all or all subjects.

Conclusion

In summary, treatment with HA-Ref and HA-Def was safe, effective, and resulted in natural-looking results with high subject satisfaction. To the best of the authors' knowledge, this is the first study describing the use of a standard set of facial expressions to show that naturalness of the face is maintained and even enhanced after HA filler treatment. We propose inclusion of photographs and video to study facial animation as a means to assess naturalness after aesthetic treatment.

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