Juvéderm Vollure™ XC Is Safe and Effective for Correcting Nasolabial Folds: Results From a Randomized Controlled Study

Gary Monheit, MD[1]; Kenneth Beer, MD, FAAD[2]; Pearl E. Grimes, MD, FAAD[3]; Bhushan Hardas, MD, MBA[4]; Vince Lin, PhD[4]; Diane K. Murphy, MBA[4]

[1]Total Skin and Beauty Dermatology Center, Birmingham, AL; [2]Beer Surgical, Aesthetic and General Dermatology, West Palm Beach, FL; [3]Pigmentation Institute of Southern California, Los Angeles, CA; [4]Allergan plc, Irvine, CA

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ABSTRACT

Study Objective: To evaluate Juvéderm Vollure™ XC, a hyaluronic acid (HA) gel (17.5 mg/mL) based on the Vycross® technology platform, for correction of moderate to severe nasolabial folds (NLFs).

Design: This was a prospective, within-subject–controlled, double-blind study.

Method: Adults (N=123) were randomized to initial/touch-up treatment with Vollure XC in 1 NLF and control HA filler in the contralateral NLF. Co-primary effectiveness endpoints at Month 6 were difference in improvement in mean NLF Severity Scale (NLFSS) score for Vollure XC versus control and NLFSS responder rate (≥1-point improvement vs baseline) for Vollure XC. Other effectiveness endpoints for Vollure XC included subject-assessed Appraisal of Nasolabial Folds (FACE-Q) and investigator-assessed smoothness and natural look. Subjects reported injection site responses (ISRs).

Results: Co-primary effectiveness endpoints were met. Vollure XC was non-inferior to control (NLFSS scores improved by 1.4 with Vollure XC and 1.3 with control), and responder rates with Vollure XC were 93% at Months 1, 3, and 6. The median volume of initial/touch-up treatment was 1.7 mL for both products. Mean FACE-Q score for Vollure XC was ≥70 at Months 3 and 6 versus 32 at baseline, indicating improvement. When one NLF was rated smoother than the other, the majority (71%) of smoother NLFs had been treated with Vollure XC. From Day 3 to Month 6, a difference in the natural look of each NLF region was reported in 77%–85% of subjects, with Vollure XC providing a more natural look in twice as many cases as control at all timepoints. Fewer severe ISRs were reported with Vollure XC versus control, particularly firmness (19% vs 43%), swelling (17% vs 43%), tenderness to touch (17% vs 34%), and lumps/bumps (14% vs 39%).

Conclusion: Vollure XC demonstrated effectiveness for correcting moderate to severe NLFs in 93% of subjects at Month 6 and was safe and well tolerated.

INTRODUCTION

- Hyaluronic acid (HA) dermal gels can successfully correct nasolabial folds (NLFs) by providing volume to the targeted area, reducing the appearance of folds, and restoring the natural 3-dimensional contour of the treated region[1,2]
- Juvéderm Vollure™ XC (17.5 mg/mL; Allergan plc, Dublin, Ireland) belongs to a family of versatile, highly moldable HA gels based on the Vycross® technology platform (Allergan plc, Dublin, Ireland), which combines low– and high–molecular-weight HA to improve the crosslinking efficiency of the HA chains[3]
- The tightly crosslinked HA network yields a gel with greater lift capacity and improved response durability[2,4]
- Vollure XC also contains lidocaine to make the injection process more comfortable and reduce the need for conventional anesthetics[3,5]
- Multiple clinical studies have demonstrated the safety and effectiveness of Juvéderm products for treating moderate to severe NLFs[6–11]
- The objective of this study was to evaluate the safety and effectiveness of Vollure XC for the correction of moderate to severe NLFs through 6 months compared with control HA filler

METHODS

Study Design

- This was a prospective, multicenter, randomized, within-subject–controlled study evaluating the safety and effectiveness of Vollure XC up to 18 months after treatment at 6 US sites; a planned interim analysis included data through 6 months (www.clinicaltrials.gov; #NCT01976663)
- Each site had a treating investigator (TI) and a blinded evaluating investigator (EI)
- Eligible subjects were randomized to treatment with Vollure XC in either the right or left NLF and control in the contralateral NLF; the order of injections (left or right side) was also randomized
- Optional touch-up treatment was administered 30 days after initial treatment as determined necessary by the TI
- The TI determined injection volumes, with a maximum allowed volume of 4 mL in each NLF for the initial and touch-up treatments combined
- The subjects and EIs remained blinded to the treatment assignment for each NLF throughout the study

Subjects

- Inclusion criteria were age ≥18 years; 2 fully visible NLFs, both with a score of 2 (moderate) or 3 (severe) on the validated 5-point photonumeric NLF Severity Scale (NLFSS) as assessed by the EI; and agreement by the subject to refrain from other antiwrinkle/volumizing treatments in facial regions below the orbital rim for the study duration
- Among the exclusion criteria were tissue augmentation in the lower two-thirds of the face with dermal fillers within the previous 12 months or with fat or botulinum toxin injections within the previous 6 months; cosmetic facial procedures in the face or neck within the previous 6 months; and semipermanent fillers or permanent facial implants in the lower face

Assessments

- The co-primary effectiveness endpoints were the difference in improvement in the mean NLFSS score for Vollure XC versus control at Month 6 and the NLFSS responder rate (≥1-point improvement vs baseline) for Vollure XC
  - EIs evaluated the severity of NLFs using the NLFSS (0=none; 1=mild; 2=moderate; 3=severe; 4=extreme)
- The primary effectiveness analysis determined whether Vollure XC was non-inferior to control in improvement in mean NLFSS scores at Month 6 (prespecified margin of non-inferiority, 0.5 points) and whether the responder rate for Vollure XC was statistically significantly greater than 50% at Month 6
- TIs evaluated the ease of injection and moldability of each product on a 3-point scale (left side easier, both sides the same, right side easier) at the initial treatment
- EIs compared the smoothness of each NLF region using a 3-point scale (left side felt smoother; both sides felt equally smooth; right side felt smoother) at Day 3 after treatment, as well as the natural look of each NLF region using a 3-point scale (left side looked more natural; both sides looked equally natural; right side looked more natural) at Day 3 and Months 1, 3, and 6
- Subject-reported outcomes:
  - Appraisal of Nasolabial Folds scale of the FACE-Q questionnaire for each NLF (screening and Months 3 and 6)
  - Satisfaction with treatment for each NLF (11-point scale: 0=completely dissatisfied; 10=completely satisfied) (Days 3 and 14 and Months 1, 3, and 6)
  - NLF preference (Days 3 and 14 and Months 1, 3, and 6)
  - Injection site responses (ISRs; 30-day safety diary) including ISR ratings of mild, moderate, or severe (initial and touch-up treatment)
  - Procedural pain for each NLF (11-point scale: 0=no pain; 10=worst pain imaginable; rated at initial and touch-up treatment)
  - Recovery Early Symptoms scale of the FACE-Q questionnaire (Day 3)
- Adverse events (AEs) were evaluated and reported by the EI

Statistical Analyses

- Effectiveness analyses were conducted on all randomized subjects who received study treatment
- Because each subject received both products (1 in each NLF), statistical comparisons were made using paired data
- A 1-sided 95% Wald confidence interval (CI) for the mean difference in improvement in NLFSS scores between Vollure XC versus control was constructed to test for non-inferiority; a *P* value was determined using the Wilcoxon signed-rank test
- A 1-sided exact binomial test was used to evaluate whether the responder rate for Vollure XC at Month 6 was significantly greater than 50% and to compare injection characteristics between the products
- The Benjamini-Hochberg method was used to correct for statistical multiplicity
- Other effectiveness endpoints and safety parameters were analyzed descriptively

RESULTS

Subjects

- A total of 126 subjects were enrolled, 123 (97.6%) were randomized and treated, and 63 (51.2%) received optional touch-up treatment
- 117 subjects (95.1%) completed the visit within the analysis window for the Month 6 visit (primary timepoint)
- Subjects were primarily female and white, with a mean baseline NLFSS score of moderate or severe (**Table 1**); all Fitzpatrick skin types were represented

Table 1. Baseline Demographics

Characteristic	Subjects (N=123)
Age, median (range), years	54 (33–83)
Female, n (%)	117 (95.1)
Race	
White	91 (74.0)
Black	26 (21.1)
Other	6 (4.9)
Ethnicity, n (%)	
Hispanic or Latino	29 (23.6)
Not Hispanic or Latino	94 (76.4)
Fitzpatrick skin phototype, n (%)	
I	14 (11.4)
II	27 (22.0)
III	31 (25.2)
IV	20 (16.3)
V	18 (14.6)
VI	13 (10.6)
NLFSS score, mean (SD)	2.6 (0.49)

NLFSS, nasolabial fold severity scale; SD, standard deviation.

Treatment

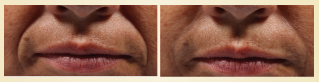
- The median volume injected for the combined initial treatment and touch-up was 1.7 mL for each product
- At the initial treatment, the TI reported that Vollure XC was significantly easier to inject and easier to mold versus control (*P*<0.001) in 73.5% (83/113) of subjects for whom the TI noticed a difference; in 8.1% of subjects (10/123), the TI did not discern a difference in ease of injection and moldability between Vollure XC and control
- A serial puncture technique was used in both NLFs in 92.7% of subjects, with tunneling used in 50.4%, fanning in 31.7%, and cross-hatching in 16.3%

Effectiveness

Difference in Improvement in Mean NLFSS Score

- Mean NLFSS scores improved by 1.4 in the NLFs treated with Vollure XC and by 1.3 in the NLFs treated with control (*P*=0.097)
  - Vollure XC was non-inferior to control (lower 95% CI limit, −0.02)
- **Figure 1** shows photographs representative of the treatment effect with severe NLFs at baseline and improvements evident at Month 6

Figure 1. Representative Photographs of a Subject's NLFs at Baseline and Month 6



Baseline | Month 6

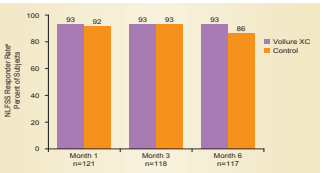
	EI Rating (Baseline to Month 6)	Volume Injected
Right NLF	Severe to Mild	1.6 mL Vollure XC
Left NLF	Severe to Moderate	1.6 mL control

EI, evaluating investigator; NLF, nasolabial fold.

NLFSS Responder Rate

- The NLFSS responder rate at Month 6 with Vollure XC was 93.2% (109/117; *P*<0.001)
- NLFSS responder rates with Vollure XC were equal to or numerically higher than control through Month 6 (**Figure 2**)

Figure 2. NLFSS Responder Rates Based on EI Assessment After Treatment With Vollure XC and Control by Study Visit

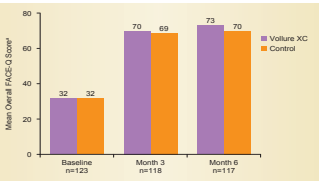


*Responder rate = % of NLFs with ≥1-point improvement from baseline in EI-rated NLFSS score (0=none; 1=mild; 2=moderate; 3=severe; 4=extreme).
EI, evaluating investigator; NLF, nasolabial fold; NLFSS, nasolabial fold severity scale.

FACE-Q Appraisal of Nasolabial Folds

- The mean FACE-Q Appraisal of Nasolabial Folds score for Vollure XC increased dramatically from baseline to Month 6, indicating improvement (**Figure 3**)
- At Month 6, the mean (standard deviation) improvement from baseline in FACE-Q score was 40.6 (23.8) with Vollure XC and 37.8 (23.6) with control
- On the FACE-Q question of how much subjects were bothered by the depth of their NLFs, 87.0% (107/123) of subjects reported being moderately or extremely bothered at baseline and 13.7% (16/117) at Month 6 after Vollure XC treatment

Figure 3. Overall Appraisal of NLF FACE-Q Score After Treatment With Vollure XC and Control by Study Visit

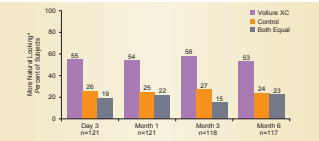


*Subject responses to the 5 FACE-Q questions were combined into an overall score for the NLF ranging from 0 (subject is extremely bothered by appearance of the NLF) to 100 (subject is not at all bothered by the appearance of the NLF). NLF, nasolabial fold.

EI-Assessed Smoothness and Natural Look

- In 91/121 cases (75.2%), the EI rated one NLF smoother than the other at Day 3 after initial treatment, with Vollure XC rated as smoother in 65/91 subjects (71.4%) versus 26/91 subjects for control (28.6%)
- From Day 3 to Month 6, a difference in the natural look of each NLF region was reported in 77%–85% of subjects, with Vollure XC providing a more natural look in twice as many cases as control at all timepoints (**Figure 4**)

Figure 4. Evaluating Investigator Assessments of Natural Look by Study Visit

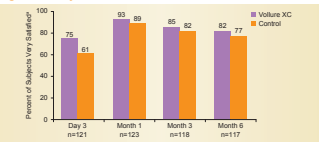


*Blinded assessment on a 3-point scale (right NLF and surrounding region look more natural than the left, both NLFs and surrounding regions look equally natural, or left NLF and surrounding region look more natural than the right). NLF, nasolabial fold.

Subject Satisfaction

- Subjects reported a high level of satisfaction with Vollure XC through Month 6, which was numerically higher than with control from Day 3 through Month 6 (**Figure 5**)
- Among subjects expressing an NLF preference, a numerical preference for Vollure XC over control was evident at Day 3 (70.6% vs 29.4%) and remained evident at Month 6 (62.9% vs 37.1%)

Figure 5. Subject Satisfaction With Treatment



*Percentage of subjects with scores of 7 through 10 on an 11-point scale (0=completely dissatisfied; 10=completely satisfied).

Safety

- Subjects reported lower rates of ISRs in all categories after treatment with Vollure XC than with control, and severity of ISRs was notably lower with Vollure XC compared with control (**Table 2**)
  - Significantly fewer severe ISRs (non-overlapping 95% CIs) were reported with Vollure XC versus control, particularly firmness (19% vs 43%), swelling (17% vs 43%), tenderness to touch (17% vs 34%), and lumps/bumps (14% vs 39%)
- Mean scores for procedural pain assessed by subjects after completion of initial and touch-up injections were 2.3 for Vollure XC and control on initial treatment and 2.2 for Vollure XC and 2.3 for control on touch-up treatment
- The EIs reported AEs for 29 NLFs (23.6%) treated with Vollure XC and 27 NLFs (22.0%) treated with control, with the most common AEs for both products being injection site induration (firmness), injection site mass (lumps/bumps), and injection site swelling
- Most AEs at both NLFs resolved within 60 days and were mild or moderate, and few required treatment
- No serious AEs or deaths related to treatment were reported
- After initial treatment, the majority of subjects reported feeling not at all bothered or a little bothered by the 17 symptoms in the FACE-Q Recovery Early Symptoms scale
  - The proportion of subjects who reported feeling not at all bothered or a little bothered was ≥15% higher for Vollure XC compared with control on 4 questions: discomfort (90.1% vs 74.4%), tenderness (88.4% vs 69.4%), feeling sore (89.3% vs 71.1%), and swelling (84.9% vs 60.0%)

Table 2. Incidence of Injection Site Responses After Initial Treatment

	Initial Treatment	
ISR	Vollure (n=122)*	Control (n=122)
Any ISR, n (%)	116 (95.1)	120 (98.4)
Maximum severity, n (%)		
Mild	22 (19.0)	9 (7.5)
Moderate	58 (50.0)	41 (34.2)
Severe	36 (31.0)	70 (58.3)
ISR category, n (%)		
Firmness	108 (88.5)	113 (92.6)
Swelling	105 (86.1)	113 (92.6)
Tenderness to touch	103 (84.4)	115 (94.3)
Lumps/bumps	100 (82.0)	110 (90.2)
Redness	90 (73.8)	106 (86.9)
Pain after injection	88 (72.1)	97 (79.5)
Bruising	69 (56.6)	72 (59.0)
Itching	38 (31.1)	55 (45.1)
Discoloration	33 (27.0)	36 (29.5)

*Number of subjects who recorded in diaries after the specified treatment.
ISR, injection site response.

CONCLUSIONS

- Vollure XC is safe and effective for correcting moderate to severe NLFs, with treatment benefits lasting at least 6 months in 93% of subjects
- Vollure XC was significantly easier to inject and easier to mold than control in the majority of subjects
- NLFs treated with Vollure XC were rated by investigators as smoother and more natural-looking than NLFs treated with control
- Subjects reported dramatic improvement in NLFs on the FACE-Q and high levels of satisfaction with Vollure XC through 6 months
- Of subjects expressing a preference for overall treatment outcome, most preferred the NLF treated with Vollure XC at every visit
- Subjects treated with Vollure XC reported fewer and less severe ISRs than those treated with control; symptoms were less bothersome with Vollure XC than control, suggesting that subjects recover more quickly after Vollure XC treatment

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DISCLOSURES

G Monheit is an investigator for Allergan plc; Galderma, Alphaeon, and Teoxane and is a consultant for Allergan plc; Galderma, Suneva, and Merz. K Beer is a clinical trial investigator, consultant, and speaker for Allergan plc, Galderma, and Merz. He is a shareholder in Anterios and a partner in The Cosmetic Bootcamp and Theraplex LLC. PE Grimes is an investigator for Allergan plc, Suneva, and Alphaeon, and is a consultant for Procter & Gamble. B Hardas, V Lin, and DK Murphy are employees and stockholders of Allergan plc.

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