Safety and Effectiveness of Juvéderm Ultra Plus Injectable Gel in Correcting Severe Nasolabial Folds in Chinese Subjects

Dong Li, MD*  
Yun Xie, MD†  
Qin Li, MD, PhD‡  
Jiaming Sun, MD, PhD§  
Ping Jiang, MD, PhD¶  
Yi Jia, MD, MSc. PhD∥  
Diane K. Murphy, MBA**  
Qingfeng Li, MD, PhD†

Background: Hyaluronic acid dermal fillers are effective in correcting severe nasolabial folds (NLFs) in non-Asian populations. We assessed safety and effectiveness of Juvéderm Ultra Plus in a Chinese population.

Methods: This double-blind study randomized Chinese subjects with severe NLFs to Juvéderm Ultra Plus (24 mg/mL) in 1 NLF and Restylane injectable gel (20 mg/mL) in the other NLF. NLFs were evaluated using the validated 5-point photometric Allergan NLF Severity Scale (0 is “no wrinkle” and 4 is “very deep wrinkle”). Investigator-assessed responder rates (primary outcome at 6 months), NLF mean improvements, and subject-assessed responder rates and preference were assessed.

Results: Of 124 subjects randomized, 122 completed the 6-month visit. NLFs treated with Juvéderm Ultra Plus required less volume than those treated with Restylane (median [range]: 0.80 [0.3–2.0] vs 1.00 [0.3–1.9]; P<0.001). Investigator-assessed responder rates were 90.4% for Juvéderm Ultra Plus and 89.6% for Restylane, establishing noninferiority of Juvéderm Ultra Plus. Mean (SD) improvements in NLF Severity Scale scores from baseline at 6 months were 1.5 (0.75) for Juvéderm Ultra Plus and 1.6 (0.73) for Restylane. Subject-assessed responder rates were similar to investigator-assessed rates (87.3%, Juvéderm Ultra Plus; 83.9%, Restylane). Of subjects reporting a preference, 62.1% preferred Juvéderm Ultra Plus. The most common treatment site responses were swelling and tenderness; most were mild or moderate in severity and resolved without intervention. Juvéderm Ultra Plus had fewer severe treatment site responses than Restylane.

Conclusion: In this study in Chinese subjects, Juvéderm Ultra Plus was safe and effective for correcting severe NLFs. (Plast Reconstr Surg Glob Open 2017;5:e1133; doi: 10.1097/GOX.0000000000001133; Published online 16 January 2017.)

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The effectiveness of Juvederm Ultra Plus for moderate and severe NLF correction has been reported in a 6-month study showing clinically significant improvement from baseline on the 5-point Wrinkle Assessment Scale (former name of the 5-point photonumeric Allergan NLF severity scale [NLFSS] used in this study) at 6 months. Improvements were maintained beyond 1 year in extension studies including subjects from the 6-month study cohort. Studies of NLF correction have primarily been reported for non-Asian subjects. However, the relationship between perceived age and the severity of aging signs in Chinese female faces has been established in a study that showed that coarse wrinkles were among the signs most strongly predicting perceived age.

Here, we report results from the Chinese registration study evaluating the safety and effectiveness of Juvederm Ultra Plus injectable gel by comparing it with the China Food and Drug Administration-approved Restylane (Medicis Aesthetics Inc., Scottsdale, Ariz.) injectable gel for the correction of severe NLFs in Chinese subjects.

**METHODS**

**Study Design**

This prospective, double-blind, randomized, 2-arm, within-subject–controlled, multicenter study was conducted in adult men and women from 7 Chinese centers. Subjects were randomly allocated to receive Juvederm Ultra Plus (24mg/mL) in 1 NLF and Restylane injectable gel (20mg/mL) in the other (ie, right or left NLF). Treatment was performed with a 27-gauge needle for Juvederm Ultra Plus and a 30-gauge needle for Restylane based on the respective directions for the use of each product. Subjects were allowed 1 touch-up treatment 1 month after initial treatment (maximum total volume, 1.5 and 0.5 mL per NLF for initial and touch-up treatments, respectively). Treatment and safety assessments were performed by the treating investigator, and NLF severity ratings were assessed by an evaluating investigator.

Evaluating investigators and subjects were blinded to treatment assignment. Subjects were blinded during treatment, and treating investigators were instructed to use injection techniques that they deemed suitable based on their clinical experience and to use similar injection techniques on both NLFs.

**Subjects**

Subjects were eligible for inclusion if they were more than 18 years of age and had fully visible, approximately symmetrical NLFs with bilateral severity scores of 3 (evaluating investigator’s assessment) on the NLFSS. Subjects were excluded if they had facial hair that would interfere with visual assessments of NLF severity, noticeable acne scarring, active infection, cancerous or precancerous lesions, or an unhealed wound in the NLF area. Additional exclusion criteria included lipoinjection (fat), facial plastic surgery, or any type of facial or cosmetic procedure (including but not limited to tissue augmentation with temporary dermal fillers) within 6 months before study treatment if treatment was not administered near the NLFs; if treatment was administered near the NLFs, the washout period was at least 12 months before study treatment. The study was approved by individual ethics committees, and subjects signed an ethics committee–approved consent for study participation.

**Assessments and Endpoints**

Follow-up visits for effectiveness occurred at 1, 3, and 6 months after the last NLF treatment (ie, initial or touch-up treatment, if performed). The evaluating investigator and subject independently evaluated NLF severity using the NLFSS (Table 1) before and after treatment. At 6 months, subjects indicated their preferred NLF based on overall treatment outcome.

Safety was evaluated by recording treatment site responses in subject diaries for 28 days after treatment (initial and touch-up, if performed) and adverse events (AEs). AE severity was reported by the treating investigator. A protocol amendment extended safety follow-up assessments to visits at 9 and 12 months after the last NLF treatment.

The primary effectiveness measure was the responder rate at 6 months, with responders defined as the percentage of subjects with a greater than or equal to 1-point improvement for each NLF versus baseline on the NLFSS as assessed by the evaluating investigator. The responder rate based on subject assessments of NLF severity using the NLFSS at baseline and 6 months for Juvederm Ultra Plus and Restylane and subject assessments of preferred NLF for overall treatment outcome at 6 months were secondary effectiveness measures. Additional effectiveness measures included evaluating investigator and subject assessments of NLF severity over time (months 1, 3, and 6). To assess product handling characteristics, treating investigators were asked to evaluate the ease of product handling by selecting “very easy,” “moderately easy,” “not too easy or difficult,” “moderately difficult,” or “very difficult.” Treating investigators were asked to indicate if there were any problems with the device or needle by answering “yes” or “no” to the question: “were there any device/needle problems or malfunctions?”

**Statistical Analyses**

The primary effectiveness endpoint was a noninferiority comparison of Juvederm Ultra Plus versus Re-
stylane based on responder rates at 6 months. Statistical noninferiority was confirmed if the upper limit of a one sided 98.75% confidence interval (CI) for the difference in proportions of NLFs retaining a greater than or equal to 1-point improvement at 6 months was less than 15%. The primary effectiveness analysis was performed in the per-protocol population, defined as all subjects who were randomized, received at least 1 study treatment, provided primary effectiveness assessments at 6 months, and did not have any major protocol violations. The primary effectiveness analysis was also performed in the intent-to-treat (ITT) population (defined as all subjects who were randomized and received at least 1 treatment) as a sensitivity analysis. Other effectiveness analyses were performed in the ITT population. Comparison of injection volume for Juvéderm Ultra Plus versus Restylane was assessed using the paired t test. Comparison of subject treatment preference for Juvéderm Ultra Plus versus Restylane was assessed using the exact binomial test assuming that the preference probability for Juvéderm Ultra Plus was 0.5. Safety was assessed in the safety population, defined as all subjects who received at least 1 treatment based on the actual treatment received for each NLF.

Secondary effectiveness analyses included responder rates with 95% CIs at 6 months for Juvéderm Ultra Plus and Restylane based on subject assessments of NLF severity and summary of subjects’ NLF preference for overall treatment outcome at 6 months. Descriptive statistics were used for analysis of product handling characteristics.

RESULTS

Of the 124 subjects enrolled in the study, all were randomized and treated and thus formed the ITT population (Fig. 1). The per-protocol population comprised 115 subjects. Product distribution was balanced between right and left NLFs (61 subjects [49.2%] in the ITT population received Juvéderm Ultra Plus in the left NLF; 63 subjects [50.8%] received Juvéderm Ultra Plus in the right NLF). Of the 124 ITT subjects, 122 (98.4%) completed the primary effectiveness visit at 6 months (1 subject was lost to follow-up and 1 subject withdrew consent). Eighty-seven subjects (70.2%) consented to follow-up at months 9 and 12, all of whom completed the follow-up. Most subjects who did not consent to the additional follow-up visits had already exited the study before the protocol amendment that added the month 9 and 12 visits.

Demographic, Baseline, and Treatment Characteristics

Subjects were primarily females (95.2%) and of Fitzpatrick skin type III or IV (72.6%; Table 2). Among the ITT population, median age was 46 years, median daily sunlight exposure was 1 hour, and the majority of subjects were nonsmokers.

Treatment

At initial treatment, anesthesia was administered identically for each NLF, with 78.2% of subjects administered pretreatment anesthesia (Table 3). For both products, the most common anesthesia was nerve block, followed by ice and topical anesthesia. No local injectable anesthesia was
Table 2. Demographic and Baseline Characteristics (ITT Population)

| Characteristic       | N = 124 |
|----------------------|---------|
| Age (y), median (range) | 46.0 (23–63) |
| Female               | 118 (95.2) |
| Fitzpatrick skin type |         |
| I                    | 0       |
| II                   | 13 (10.5) |
| III                  | 35 (26.6) |
| IV                   | 57 (46.0) |
| V                    | 21 (16.9) |
| VI                   | 0       |
| Place                |         |
| East China           | 35 (28.2) |
| North China          | 35 (28.2) |
| Central China        | 32 (25.8) |
| South China          | 8 (6.5)  |
| Northeast China      | 8 (6.5)  |
| Northwest China      | 5 (4.0)  |
| Southwest China      | 1 (0.8)  |
| Smoking history      |         |
| Nonsmoker            | 116 (93.5) |
| Current smoker       | 7 (5.6)  |
| Ex-smoker            | 1 (0.8)  |
| Sun exposure estimate (h/d), median (range) | 1.0 (0.0–5.0) |

All data are expressed as n (%) unless otherwise noted.

Table 3. Treatment Characteristics (Safety Population)

| Characteristic | Juvéderm Ultra Plus (N = 124) | Restylane (N = 124) |
|----------------|-------------------------------|---------------------|
| Touch-up treatment, n | 27                            | 29                  |
| Anesthesia administered at initial treatment |         |                     |
| Any          | 97 (78.2)                     | 97 (78.2)           |
| Ice          | 37 (30.1)                     | 37 (30.1)           |
| Topical      | 21 (17.6)                     | 21 (16.3)           |
| Local        | 0                             | 0                   |
| Nerve block  | 39 (32.1)                     | 39 (32.1)           |
| Anesthesia administered at touch-up treatment |         |                     |
| Any          | 21 (77.8)                     | 23 (79.3)           |
| Ice          | 5 (23.8)                      | 5 (21.7)            |
| Topical      | 8 (38.1)                      | 10 (43.5)           |
| Local        | 0                             | 0                   |
| Nerve block  | 8 (38.1)                      | 8 (34.8)            |
| Treatment volume (mL), median (range) |         |                     |
| Initial treatment† | 0.80 (0.3–1.5)              | 1.00 (0.3–1.5)     |
| Touch-up treatment† | 0.40 (0.1–0.8)              | 0.30 (0.2–0.9)     |
| Total†       | 0.80 (0.3–2.0)                | 1.00 (0.3–1.9)     |

*No. of nasolabial folds receiving treatment. Percentages for anesthesia based on the number of subjects receiving treatment.
†Juvéderm Ultra Plus vs Restylane (P < 0.001).
‡Juvéderm Ultra Plus vs Restylane (P = 0.876).

All data are expressed as n (%) unless otherwise noted.

administered in the study. NLFs treated with Juvéderm Ultra Plus required significantly less total volume and volume at initial treatment (both P < 0.001) than those treated with Restylane. The median initial treatment volume was 0.8 mL (range, 0.3–1.5 mL) for Juvéderm Ultra Plus and 1.0 mL (range, 0.3–1.5 mL) for Restylane (Table 3). Median touch-up volumes were smaller than initial volumes. Touch-up treatment was administered to 27 of 124 NLFs (21.8%) initially treated with Juvéderm Ultra Plus and 29 of 124 NLFs (23.4%) initially treated with Restylane.

Treating investigators rated 65.3% (81/124) of initial treatments with Juvéderm Ultra Plus injections very easy to handle and rated 33.1% (41/124) of initial Restylane injections very easy to handle. Of the remaining injections, 46.5% (20/43) of Juvéderm Ultra Plus and 55.4% (46/83) of Restylane injections were rated moderately easy to handle. Touch-up treatments with Juvéderm Ultra Plus and Restylane were rated as very easy to handle by 70.4% (19/27) and 37.9% (11/29) of treating investigators, respectively. There were no device/needle problems or malfunctions with Juvéderm Ultra Plus and 1 device/needle problem or malfunction (0.8%) with Restylane that did not harm the subject.

Primary Endpoint: Evaluating Investigator-assessed Responder Rates at 6 Months

The primary effectiveness endpoint was met for Juvéderm Ultra Plus. The NLF responder rates as assessed by the evaluating investigator at 6 months in the per-protocol population were 90.4% for Juvéderm Ultra Plus and 89.6% for Restylane, resulting in a difference (Restylane – Juvéderm Ultra Plus) of –0.9% and an upper CI of 3.5%, establishing noninferiority of Juvéderm Ultra Plus to Restylane. Noninferiority was also established in the ITT population: the responder rate for Juvéderm Ultra Plus was 90.8% and the responder rate for Restylane was 89.9%, resulting in a difference (Restylane – Juvéderm Ultra Plus) of –0.8% and an upper CI of 3.4%.

Secondary Effectiveness Measures: Subject-assessed Responder Rates and Product Preference at 6 Months

Subject-assessed responder rates at 6 months were 87.3% (95% CI, 81–93) for NLFs treated with Juvéderm Ultra Plus and 83.9% (95% CI, 77–91) for NLFs treated with Restylane. The responder rates based on subject assessments were similar to those based on evaluating investigator assessments. Fifty-eight of the 124 subjects (47%) expressed a preference for 1 NLF over the other at 6 months. Of those subjects who expressed a preference, 62.1% preferred the NLF injected with Juvéderm Ultra Plus compared with 37.9% of subjects who preferred the NLF injected with Restylane (P = 0.087).

Additional Effectiveness Measures: Evaluating Investigator and Subject Assessments of NLF Severity Over Time

The ITT responder rates based on evaluating investigator NLFSS scores for Juvéderm Ultra Plus were slightly higher than the responder rates for Restylane at all timepoints (Fig. 2). The mean (SD) NLFSS score at baseline was 3.0 (0) for both products by evaluating investigator assessment and decreased to 1.2 (0.70) at 1 month for Juvéderm Ultra Plus and to 1.3 (0.72) for Restylane, resulting in a mean improvement from baseline of 1.8 (0.70) for Juvéderm Ultra Plus and 1.7 (0.72) for Restylane. Mean improvement decreased to 1.2 (0) at 1 month for Juvéderm Ultra Plus and to 1.3 (0.72) for Restylane. Noninferiority of Juvéderm Ultra Plus compared with Restylane was established at 6 months as indicated by a mean evaluating investigator assessment and decreased to 1.2 (0.70) at 1 month for Juvéderm Ultra Plus and to 1.3 (0.72) for Restylane, resulting in a mean improvement from baseline of 1.8 (0.70) for Juvéderm Ultra Plus and 1.7 (0.72) for Restylane. Mean improvement from baseline at 3 months was 1.6 (0.60) for Juvéderm Ultra Plus and 1.4 (0.61) for Restylane. The improvement was maintained at 6 months as indicated by a mean evaluating investigator NLFSS score of 1.5 (0.75) for Juvéderm Ultra Plus and 1.4 (0.73) for Restylane. Figure 3 shows representative before and after photographs of NLFSS responders over time. The ITT responder rates based on subject NLFSS scores for Juvéderm Ultra Plus were slightly higher than the responder rates for Restylane at all timepoints (Fig. 4).
Fig. 2. Five-point photonumeric Allergan Nasolabial Fold Severity Scale responder rates by visit as assessed by the evaluating investigator: intent-to-treat population.

Fig. 3. Representative pre- and posttreatment photographs of subjects (A: 45 y old, 1-point improvement, each side; B: 44 y old, 2-point improvement, each side; C: 40 y old; 3-point improvement, Juvéderm Ultra Plus; 2-point improvement, Restylane) on the 5-point photonumeric Allergan Nasolabial Fold Severity Scale by evaluating investigator assessment.

Fig. 4. Five-point photonumeric Allergan Nasolabial Fold Severity Scale responder rates by visit as assessed by subjects: intent-to-treat population.
The mean (SD) NLFSS score at baseline was 2.7 (0.48) for Juvéderm Ultra Plus and 2.7 (0.47) for Restylane by subject assessment and decreased at 1 month to 1.2 (0.74) for Juvéderm Ultra Plus and 1.2 (0.83) for Restylane, resulting in a mean improvement from baseline of 1.5 for both products (1.5 [0.71] for Juvéderm Ultra Plus and 1.5 [0.80] for Restylane). At 3 months, the mean improvement from baseline in the NLFSS score was 1.5 (0.69) for Juvéderm Ultra Plus and 1.5 (0.76) for Restylane. The improvement was maintained at 6 months, as indicated by mean subject NLFSS scores of 1.4 (0.79) and 1.5 (0.78) for Juvéderm Ultra Plus and Restylane, respectively.

Safety

Of the 122 Juvéderm Ultra Plus subjects who completed safety diaries, 118 (96.7%) reported at least 1 treatment site response to Juvéderm Ultra Plus and 117 (95.9%) reported at least 1 treatment site response to Restylane (Table 4). The 3 most commonly reported injection responses to Juvéderm Ultra Plus were swelling, tenderness, and firmness. The 3 most commonly reported responses to Restylane were swelling, tenderness, and lumps.

The incidence rates of each treatment site response (except bruising and color change) were lower for Juvéderm Ultra Plus than for Restylane. After initial treatment, 63.2% of treatment site responses in NLFs treated with Juvéderm Ultra Plus and 73.3% of treatment site responses in NLFs treated with Restylane lasted 2 weeks or less. Most treatment site responses were mild or moderate: after initial treatment, 70.1% (82/117 NLFs) of treatment site responses to Juvéderm Ultra Plus were mild or moderate and 56.9% (66/116 NLFs) of treatment site responses to Restylane were mild or moderate. Juvéderm Ultra Plus treatment resulted in fewer severe treatment site responses than Restylane (29.9% [35/117 NLFs] vs 43.1% [50/116 NLFs], respectively).

A large percentage of treatment site responses were mild or moderate after touch-up treatment: 90.9% (20/22 NLFs) for Juvéderm Ultra Plus and 84.0% (21/25 NLFs) for Restylane. After touch-up treatment, treatment site responses lasted 2 weeks or less in 68.2% of NLFs (15/22) treated with Juvéderm Ultra Plus and 76.0% (19/25 NLFs) treated with Restylane. All treatment site responses resolved without intervention. These safety results are consistent with those of the current study: at months 1 and 6, respectively, 98.8% and 90.0% of NLFs had improved greater than or equal to 1 point on the NLFSS compared with 99.1% and 90.8% in the current study based on evaluating investigator assessment. Juvéderm Ultra Plus also demonstrated long-term maintenance of clinically significant correction at 12 months in the study by Goodman et al.16

Treatment site response rates were similar between products although Juvéderm Ultra Plus treatment resulted in fewer severe treatment site responses than Restylane. Juvéderm Ultra Plus was well tolerated, and treatment site responses were generally mild or moderate in severity and resolved without intervention. These safety results are consistent with other studies reporting on NLF correction with Juvéderm Ultra Plus.6,9,10,16 Treatment site responses with Juvéderm Ultra Plus tended to last longer than Restylane, which may have been a result of the larger needle size used with Juvéderm Ultra Plus.

One plausible limitation of this study is that treating investigators may have been influenced in their assessments of product characteristics or the way they treated each NLF because they were not blinded. However, evaluating investigators were blinded to treatment.

In conclusion, this study demonstrates that Juvéderm Ultra Plus is safe and effective for correcting severe NLFs.

Table 4. Incidence of Treatment Site Responses

| Treatment Site Responses* | Juvéderm Ultra Plus | Restylane |
|--------------------------|---------------------|----------|
| Subjects with any treatment site response, n (%) | 118 (96.7) | 117 (95.9) |
| Type, no. of subjects, n (%) | | |
| Swelling | 104 (85.2) | 111 (91.0) |
| Tenderness | 102 (83.6) | 109 (89.3) |
| Firmness | 98 (80.3) | 102 (83.6) |
| Lumps | 97 (79.5) | 104 (85.2) |
| Pain | 94 (77.0) | 103 (84.4) |
| Redness | 80 (65.6) | 90 (73.8) |
| Bruising | 83 (68.0) | 79 (64.8) |
| Itching | 63 (53.3) | 67 (54.9) |
| Discoloration | 39 (32.0) | 37 (30.3) |
| Other | 18 (14.8) | 20 (16.4) |

*Subjects with diary recordings (n = 122).

DISCUSSION

This study met its primary effectiveness endpoint: Juvéderm Ultra Plus treatment was noninferior to Restylane treatment for correction of severe NLFs in Chinese subjects. Evaluating investigator and subject NLFSS responder rates were similar and remained high at all timepoints through the 6-month period of effectiveness assessments. Of the 47% of subjects who expressed a preference, a greater number preferred Juvéderm Ultra Plus over Restylane, and treating investigators indicated that Juvéderm Ultra Plus injections were easier to handle than Restylane injections in this trial. Ease of handling could have contributed to the overall treatment experience of subjects resulting in greater preference for Juvéderm Ultra Plus. Furthermore, because facial aesthetic injections require technical precision to achieve optimal treatment outcomes,25 a filler that is very easy to handle provides an advantage in facilitating the achievement of both physician and patient treatment goals.

The superior effectiveness of Juvéderm Ultra Plus compared with a bovine collagen filler in correcting severe NLFs was demonstrated in a 6-month U.S. study conducted primarily in white subjects with moderate or severe NLFs by Baumann et al.6 Analysis of a subset of subjects with severe NLFs from the same study by Lupo et al19 showed findings consistent with the current study for subjects treated with Juvéderm Ultra Plus, with a mean NLFSS score at 6 months of 1.3 compared with 1.5 in the current study; that study also showed clinically significant improvement beyond year 1 in 81% of severe NLFs treated with Juvéderm Ultra Plus. A prospective randomized study by Goodman et al16 investigated the effectiveness of a single administration of Juvéderm Ultra Plus versus Perlane (Medicis Aesthetics Inc., Scottsdale, Ariz.), a 20 mg/mL HA particulate gel, in correcting severe NLFs. Results were consistent with those of the current study: at months 1 and 6, respectively, 98.8% and 90.0% of NLFs had improved greater than or equal to 1 point on the NLFSS compared with 99.1% and 90.8% in the current study based on evaluating investigator assessment. Juvéderm Ultra Plus also demonstrated long-term maintenance of clinically significant correction at 12 months in the study by Goodman et al.16

Treatment site response rates were similar between products although Juvéderm Ultra Plus treatment resulted in fewer severe treatment site responses than Restylane. Juvéderm Ultra Plus was well tolerated, and treatment site responses were generally mild or moderate in severity and resolved without intervention. These safety results are consistent with other studies reporting on NLF correction with Juvéderm Ultra Plus.6,9,10,16 Treatment site responses with Juvéderm Ultra Plus tended to last longer than Restylane, which may have been a result of the larger needle size used with Juvéderm Ultra Plus.
in Chinese subjects and served as the basis for approval of Juvéderm Ultra Plus in China. Safety and effectiveness profiles were similar compared with studies enrolling mainly non-Asian subjects.

Qingfeng Li, MD, PhD
Department of Plastic and Reconstructive Surgery
Shanghai 9th People’s Hospital School of Medicine
Shanghai Jiao Tong University
639 Zhizaoju Road
Shanghai, China, 200011
E-mail: dr.liqingfeng@yahoo.com

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