Juvéderm Injectable Gel: A Multicenter, Double-Blind, Randomized Study of Safety and Effectiveness

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BACKGROUND: A high concentration of crosslinked hyaluronic acid (HA) in a smooth, malleable formulation is the hallmark of the new Juvéderm dermal fillers.

OBJECTIVE: To determine the long-term effectiveness and safety of Juvéderm Ultra and Ultra Plus injectable gel.

METHODS: In the multicenter study approved by the Food and Drug Administration, subjects were randomized to treatment with Juvéderm Ultra or Ultra Plus in one nasolabial fold (NLF) and Zyplast collagen in the other. After optimal correction was achieved (treatment plus up to 2 touch-ups at 2-week intervals), effectiveness was assessed on a 5-point scale through the 6-month study period. An additional poststudy visit provided long-term effectiveness data. Safety was evaluated through subjects’ daily diaries for 14 days after treatment.

RESULTS: A total of 292 subjects were randomized and treated, 146 in each cohort. A total of 280 subjects completed the 6-month study, and 227 attended the poststudy visit. Clinically significant mean wrinkle correction (≥ 1 point improvement) was still in evidence at >9 months for both Juvéderm formulations but not for the Zyplast control. At >9 months, 75% of Juvéderm Ultra– and 81% of Juvéderm Ultra Plus–treated NLFs maintained a clinically significant correction. Moreover, 78% of NLFs treated with Juvéderm Ultra Plus still had a clinically significant improvement beyond 1 year. Local treatment site reactions were comparable for Juvéderm and Zyplast.

CONCLUSIONS: These next-generation HA dermal fillers can be reliably expected to provide long-term correction, with Juvéderm Ultra lasting more than 9 months and Juvéderm Ultra Plus lasting for a year or more.


Dermal fillers have steadily grown in use over the years, despite limitations of products that were available. Longevity without permanence and the absence of animal proteins have been desired attributes in fillers. Some hyaluronic acids (HA), including the Juvéderm family of dermal fillers (Allergan, Santa Barbara, CA), have these desired characteristics that have been lacking in other available fillers. These next-generation HA fillers are derived from Streptococcus equi bacteria and thus contain no animal proteins. In addition, they use a high concentration of crosslinked HA to provide long-lasting, but not permanent, correction.

Juvéderm dermal fillers are manufactured differently from other HA fillers and have a smooth consistency attributable to a proprietary process known as Hylacross technology. The smooth consistency of the Juvéderm dermal fillers is in contrast to the granular consistency of other HA fillers such as Restylane and Perlane (Medicis, Scottsdale, AZ), which can be seen under magnification. Reportedly, the Juvéderm gels flow easily during injection and are malleable and appear smooth after injection. Three different formulations of Juvéderm were compared with Zyplast bovine collagen (Allergan, Santa Barbara, CA) for the correction of nasolabial folds (NLFs) in a double-blind, randomized multicenter clinical trial. The results of that study formed the basis for approval by the Food and Drug Administration of the products in June 2006 and have previously been published. Presented here are longer-term follow-up data for a subset of pivotal study subjects randomized to treatment with Juvéderm Ultra or Juvéderm Ultra Plus, the 2 formulations currently available in the United States.

METHODS

Subjects were randomly assigned to treatment with either Juvéderm Ultra or Juvéderm Ultra Plus in one NLF and Zyplast bovine collagen in the other NLF. Subjects were blinded to treatment assignment and served as their own control subjects because of the split-face nature of the study. The study was carried out at 11
Subject demographics at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Juvéderm Ultra/Zyplast group who received repeat treatment (n = 116)</th>
<th>Juvéderm Ultra Plus/Zyplast group who received repeat treatment (n = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range)</td>
<td>50 years (31-75 years)</td>
<td>48 years (30-74 years)</td>
</tr>
<tr>
<td>Gender</td>
<td>94% female</td>
<td>92% female</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>72% Caucasian</td>
<td>76% Caucasian</td>
</tr>
<tr>
<td></td>
<td>12% Hispanic</td>
<td>14% Hispanic</td>
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<tr>
<td></td>
<td>10% African American</td>
<td>9% African American</td>
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<tr>
<td></td>
<td>5% Asian</td>
<td>0% Asian</td>
</tr>
<tr>
<td></td>
<td>0% other</td>
<td>2% other</td>
</tr>
<tr>
<td>Fitzpatrick skin type</td>
<td>3% Type I</td>
<td>5% Type I</td>
</tr>
<tr>
<td></td>
<td>23% Type II</td>
<td>23% Type II</td>
</tr>
<tr>
<td></td>
<td>39% Type III</td>
<td>36% Type III</td>
</tr>
<tr>
<td></td>
<td>19% Type IV</td>
<td>21% Type IV</td>
</tr>
<tr>
<td></td>
<td>12% Type V</td>
<td>14% Type V</td>
</tr>
<tr>
<td></td>
<td>4% Type VI</td>
<td>1% Type VI</td>
</tr>
</tbody>
</table>

Centers across the United States, with 2 investigators at each site, all of whom were dermatologists or plastic surgeons experienced in the use of dermal fillers. The treating investigator at each site could not be blinded because of the difference in appearance of Juvéderm and Zyplast, so an evaluating investigator who was blinded to treatment identity provided additional effectiveness assessments.

The main inclusion criteria for subjects were fully visible bilateral NLFs that were approximately symmetrical and of equal severity with a rating of moderate or severe (assessed at the deepest part) on a scale of none, mild, moderate, severe, and extreme. The main exclusion criteria were hypersensitivity to bovine collagen or HA; history of atopy, anaphylaxis, multiple severe allergies, or allergy to meat or lidocaine; current immune therapy or history of autoimmune disease; tendency to development of hypertrophic scarring; use of oral retinoids or, in the NLF area, over-the-counter or prescription anti-wrinkle treatments, microdermabrasion, or chemical peels in the 4 weeks before randomization; and any cosmetic procedure or tissue augmentation at the NLF injection site in the 6 months before trial entry. All subjects provided written informed consent, and the study was approved by institutional review boards governing each investigational site. Enrollment took place August to November 2004.

The study protocol specified that each NLF should be filled to full correction but not overcorrected, and a maximum of 3 treatments were allowed to achieve optimal correction (initial treatment plus up to 2 touch-ups at 2-week intervals). After each treatment session, subjects recorded treatment site reactions in daily diaries for 2 weeks. Any additional adverse events reported by the subject or observed by the investigators were also recorded. Effectiveness was assessed on a 5-point scale by the subject and both investigators at least every 4 weeks for 24 weeks after last treatment.

After completing the 6-month pivotal trial, subjects could return for a complimentary follow-up treatment with their preferred product, at which time an additional effectiveness assessment was performed by the subject and treating investigator before treatment. Because effectiveness was assessed by the treating investigator but not the evaluating investigator at the post-trial visit, all data presented in this study use the ratings supplied by the treating investigator. It should be noted that the assessments for the 6-month study period demonstrated negligible differences between the scores of the treating and evaluating investigators.

Numerous factors affected the timing of posttrial treatment visits, including investigator and subject schedules, the closing of one investigational site for several months because of Hurricane Katrina and subjects’ desire to correct asymmetry caused by NLFs treated with Zyplast returning to baseline wrinkle severity whereas NLFs treated with Juvéderm maintained correction. Because the repeat treatment visits occurred at a variety of timepoints, they were grouped for analysis into time period brackets (eg, ≤ 9 months and >9 months) to ascertain overall trends in product duration.

For effectiveness and injection volume data, statistical analyses were performed on the intent-to-treat population who returned to receive repeat treatment after the end of the 6-month trial. For safety data, analyses were performed on the entire “as-treated” study population. Injection volume was analyzed with a paired t test, mean improvement with a signed rank test, and clinically significant improvement percentage with a McNemar test. A P value < .05 was considered statistically significant for all analyses.

RESULTS

Subjects
Of 292 subjects randomized and treated with Juvéderm Ultra or Juvéderm Ultra Plus, 280 (96%) completed the 6-month pivotal trial. No subjects discontinued because of lack of effectiveness or adverse events. Among these 280 subjects, 227 (81%) received a follow-up treatment after the end of the pivotal trial (116 with Juvéderm Ultra and 111 with Juvéderm Ultra Plus). Figure 1 shows the flow of subjects through the study.

Demographic details were similar in both treatment groups (Table 1), with the vast majority of subjects being female and a mean age of 50 years (Ultra) or 48 years (Ultra Plus). The full range of Fitzpatrick skin phototypes was represented, with approximately one quarter...
of subjects being non-Caucasian and one third having Fitzpatrick skin phototypes IV through VI.

To ensure that the results for subjects attending a poststudy follow-up visit can be generalized to the entire study population, statistical analyses were conducted that established there were no significant differences in the NLF severity score at baseline, the NLF severity score at the 6-month follow-up visit, or the total injection volume used for initial treatment in the returning subjects relative to the overall study population. Furthermore, additional analyses showed that there were no significant differences in these 3 key variables for subjects who returned at an earlier timepoint (up to 9 months after treatment for Ultra and up to 1 year for Ultra Plus) versus those who returned later (greater than 9 months after treatment for Ultra and greater than 1 year for Ultra Plus). This demonstrates that the long-term effectiveness results can be generalized to the study subjects overall.

**Effectiveness**

At baseline, before any treatment, the mean investigator assessment of NLF severity was 2.6 (moderate to severe) on the 5-point scale for both treatment groups. After treatment, the mean NLF severity was reduced by approximately 2 points to the none-to-mild range. At the end of the 6-month pivotal trial, the mean level of improvement remained clinically significant (≥1-point improvement from baseline) for the NLFs treated with Juvéderm Ultra or Juvéderm Ultra Plus but not for NLFs treated with Zyplast (Figure 2).

At the posttrial follow-up visits, the mean level of improvement was still clinically significant for subjects who returned either up to 9 months or more than 9 months after Juvéderm treatment (Figure 3). The proportion of NLFs still showing clinically significant improvement beyond 9 months after last treatment (Figure 4) was 75% with Juvéderm Ultra and 81% with Juvéderm Ultra Plus. Moreover, 68% of NLFs (13 of 19) treated with Juvéderm Ultra and 78% of NLFs (18 of 23) treated with Juvéderm Ultra Plus still had clinically significant improvement beyond 1 year. Effectiveness is further documented by serial subject photographs showing that Juvéderm Ultra (Figure 5) and Juvéderm Ultra Plus
Figure 5. A, Pretreatment views of left and right nasolabial folds in a 66-year-old Asian woman. B, Posttreatment views following Zyplast injection in the left nasolabial fold (reader’s left) and Juvederm Ultra injections in the right, 2 weeks after the last treatment. C, Posttreatment views 1 year following the last treatment.
Figure 6. **A**, Pretreatment views of a 49-year-old Hispanic woman. **B**, Posttreatment views following Juvederm Ultra Plus injection in the left nasolabial fold (reader's left) and Zyplast injections in the right, 2 weeks after the last treatment. **C**, Posttreatment views 9 months after the last treatment.
TABLE 2. Total volume (mL) injected (repeat treatment population)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Initial treatment</th>
<th>Repeat treatment</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvéderm Ultra</td>
<td>N 116</td>
<td>116</td>
<td>116</td>
</tr>
<tr>
<td>Median</td>
<td>1.45</td>
<td>0.73</td>
<td>.80</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; .0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvéderm Ultra Plus</td>
<td>N 109</td>
<td>109</td>
<td>109</td>
</tr>
<tr>
<td>Median</td>
<td>1.50</td>
<td>0.70</td>
<td>.80</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; .0001</td>
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</tr>
</tbody>
</table>

(Figure 6) provide a smooth natural look after treatment, as well as longer-lasting improvement than Zyplast.

Injection Volume
Subjects were treated with an average of 2 syringes of Juvéderm dermal filler at the beginning of the 6 month pivotal trial. At the poststudy repeat treatment visit, on average, only 1 syringe was required for each NLF to achieve optimal correction at a mean of 9 months after last treatment. Median injection volumes were 1.5 mL for initial treatment (achieved with 2 syringes, because each syringe contains 0.8 mL) and 0.7 mL for repeat treatment (achieved with 1 syringe; Table 2).

Safety and Tolerability
The frequency and severity of treatment site reactions was similar for all of the fillers (both of the Juvéderm formulations and Zyplast). Most individual treatment site reactions lasted 7 days or less, and there were no treatment-related adverse events other than those localized to the area of injection. For both treatment groups, most treatment site reactions (eg, erythema, induration, pain, edema, nodule formation, bruising, pruritus, and discoloration) were mild or moderate in severity and did not require intervention. No serious treatment-related adverse events were reported with any of the fillers.

DISCUSSION
The significance of these clinical study findings emerges from the search for a dermal filler that is clinically proven to be safe and to last beyond 6 months without being permanent. Of all resorbable fillers currently approved in the United States, only those with high concentrations of crosslinked HA could be expected to have a duration of more than 6 months. This includes Juvéderm Ultra and Ultra Plus (24 mg/mL), Restylane and Perlane (20 mg/mL), and the recently approved Elevess (formerly CTA; Anika Therapeutics, Woburn, MA) at 28 mg/mL.4

Examining the pivotal studies for Juvéderm Ultra and Ultra Plus (n = 146 each),5,6 Restylane (n = 138),7 and Elevess (n = 191)4 yields an interesting contrast in results despite the similarity in study designs. Each of the studies had a split-face design, and injectable collagen was used as a control in the contralateral NLF (human collagen in the Elevess study and bovine collagen in the other studies). In all of the studies, touch-up treatments were allowed at 2-week intervals after initial treatment to achieve optimal correction. Primary effectiveness was assessed via 5-point scales for all but the Elevess study, which used a 6-point scale (although still defined a 1-point improvement as clinically significant).

At 6 months after last treatment, the mean improvement in wrinkle severity on the basis of investigator assessments remained clinically significant for Juvéderm Ultra and Ultra Plus (1.3 and 1.5 points, respectively)2 but not for Restylane (0.9 points)7 or Elevess (0.8 points).4 Furthermore, 30% of wrinkles treated with Restylane had returned to baseline severity at 6 months compared with only 12% for Juvéderm Ultra and 10% for Juvéderm Ultra Plus. Juvéderm is the first HA product to prove effectiveness with clinical data at the later timepoints (9 to 12 months).5,6

Although 2 randomized clinical trials of Perlane have been published, and 2 more are described on the product package insert, mean improvement in wrinkle severity is not provided for any of the studies. All 4 of these studies used the same 5-point wrinkle assessment scale and allowed touch-up treatments to achieve optimal correction. One U.S. study involved 141 subjects receiving Perlane and 142 receiving Restylane and found that at 6 months after treatment, 37% of Perlane NLFs and 26% of Restylane NLFs had returned to baseline severity. The second U.S. study included 150 subjects, primarily African American women treated with Perlane in one NLF and Restylane in the other NLF. Results showed that 29% of Perlane NLFs and 27% of Restylane NLFs had returned to baseline severity at 6 months.8

A split-face Canadian study in which 150 subjects received Perlane and Hylaform found that 25% of the Perlane-treated NLFs had returned to baseline at 6 months.9 The fourth Perlane study was conducted at 2 Scandinavian centers and involved 68 subjects treated with Perlane in one NLF and Zyplast on the contralateral side. The 6-month results showed that 41% of wrinkles treated with Perlane had lost their correction.10

Interestingly, long-term effectiveness data are hard to come by for all of these dermal fillers. For the Restylane and Elevess studies, subjects were followed up through 1 year, but only safety data were collected beyond 6 months. The only Perlane study beyond 6 months was the one conducted in Scandinavia, which obtained 1-year safety data but effectiveness data through just 9 months, and stated only in relation to Zyplast, with Perlane superior to Zyplast at 49%, Perlane equivalent to Zyplast at 37% and Zyplast superior to Perlane at 15%.10

CONCLUSION
Advances in HA technology have culminated in the development of the Juvéderm family of next-generation
HA dermal fillers, which offer additional treatment options for facial aesthetic therapy. Juvéderm Ultra and Ultra Plus are the only HA fillers proven to last beyond 6 months while maintaining a safety profile consistent with injectable collagen.

Juvéderm Ultra provides long-lasting clinical improvement for more than 9 months after treatment, and Juvéderm Ultra Plus provides correction for a year or more. Therefore individuals treated with these Juvéderm dermal fillers will require repeat treatments less frequently than those treated with fillers that do not provide the same duration of correction. Furthermore, only 1 syringe of Juvéderm dermal filler was needed to achieve optimal correction at repeat treatment (an average of 9 months after last treatment), thus indicating persistence of the product in the skin. This extended duration, combined with the safety of HA technology, position Juvéderm Ultra and Ultra Plus as an optimal choice in facial aesthetics.

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DISCLOSURES

Dr. Pinsky is an investigator for this device and owns Allergan stock. Ms. Thomas and Ms. Murphy are Allergan employees and stockholders. Dr. Walker is an Allergan stockholder and a former employee. Financial support provided by Allergan.

REFERENCES