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Juvéderm Volbella with Lidocaine for Lip and Perioral Enhancement: A Prospective, Randomized, Controlled Trial

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Background: Juvéderm Volbella with Lidocaine is a new hyaluronic acid dermal filler.
Methods: In this prospective, randomized, multicenter study, 280 subjects desiring lip volume enhancement were treated with Juvéderm Volbella with Lidocaine or Restylane-L. Investigators rated treatment outcomes on Allergan's Lip Fullness Scale, Perioral Lines Scale, and Oral Commissures Severity Scale. A blinded independent central reviewer (ICR) assessed 3-dimensional digital photographs using these scales. Subjects evaluated outcomes using the FACE-Q Recovery Early Life Impact and Recovery Early Symptoms modules. The primary endpoint was noninferiority of Juvéderm Volbella with Lidocaine to Restylane-L based on responder rate (percentage of subjects with ≥1-point Lip Fullness Scale improvement at month 3 ICR assessment vs baseline).
Results: Juvéderm Volbella with Lidocaine was noninferior to Restylane-L. Although responder rates based on ICR assessments of lip fullness, perioral lines, and oral commissures did not differ between treatments, investigator assessments showed significant improvements in perioral lines and oral commissures with Juvéderm Volbella with Lidocaine vs Restylane-L ($P \leq 0.029$). Subjects treated with Juvéderm Volbella with Lidocaine had higher mean FACE-Q scores on day 1 ($P \leq 0.001$), indicating less disruption of daily activities. Mean change in lip volume from baseline to day 1 was smaller in the Juvéderm Volbella with Lidocaine group (but similar between treatments on day 14), indicating less acute swelling. Severe injection site responses occurred less frequently with Juvéderm Volbella with Lidocaine.
Conclusions: Juvéderm Volbella with Lidocaine is effective for lip enhancement, improves perioral lines and oral commissures, and results in less short-term swelling and disruption in daily activities than Restylane-L. *(Plast Reconstr Surg Glob Open 2015;3:e321; doi: 10.1097/GOX.0000000000000266; Published online 9 March 2015)*

Lip fullness and definition are key facial aesthetic features associated with attractiveness and youth. However, lips are prone to multiple factors that can dramatically change their shape over time, resulting in a narrower, pale, and flat appearance.[1–3] Temporary dermal fillers containing hyal-

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uronic acid are commonly used to enhance overall lip fullness and the vermilion border, minimize perioral lines, and provide lip definition.[4–7] Juvéderm Volbella with Lidocaine (Allergan, Santa Barbara, Calif.) is a moldable filler that uses the Vycross (Allergan, Irvine, Calif.) technology platform, which combines low- and high-molecular-weight hyaluronic acid with a novel cross-linking process.[7] These properties increase cross-linking efficiency, resulting in a tightly cross-linked hyaluronic acid network, which increases product duration of action and produces a higher-viscosity gel with greater lift capacity.[7] A small quantity of non–cross-linked hyaluronic acid is included to reduce extrusion force and allow injection through a 30-gauge, half-inch needle.

The present study evaluated the safety and effectiveness of Juvéderm Volbella with Lidocaine for lip volume enhancement versus Restylane-L (Medicis Aesthetics, Scottsdale, Ariz.), another lidocaine-containing hyaluronic acid dermal filler approved for lip augmentation. The FACE-Q—a new subject-reported outcome questionnaire[8]—was used to assess treatment outcomes.

METHODS

Study Design

This ongoing, prospective, randomized, 2-arm, active-controlled study is being conducted at 12 sites in the United Kingdom and France. Subjects were enrolled and treated in 2012; this report covers data collected through 3 months. The study (NCT01579305) was approved by independent ethics committees, and all subjects provided written informed consent.

Subjects were randomized (1:1) to receive Juvéderm Volbella with Lidocaine or Restylane-L based on a central randomization schedule. An automated interactive voice and Web response system was used to manage the randomization and treatment assignment. Sites dispensed treatment according to the instructions provided by the automated system. Investigators at each site determined the appropriate treatment injection volume based on clinical experience and subject lip treatment goals. The primary treatment site was the vermilion body and vermilion border; additional perioral sites could also be treated, including perioral lines, Cupid's bow, philtral columns, and oral commissures. An optional top-up treatment could be performed 2 weeks after initial treatment if the investigator and subject agreed that optimal lip fullness had not been achieved. The maximum allowable treatment volume was 4.0 mL (4 syringes) for initial and top-up treatments combined. Subjects, independent central reviewers (ICRs) from Canfield Scientific (Fairfield, N.J.), and all investigational site staff, except for the investigator and study coordinator, were blinded to treatment assignment.

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Subjects

Adults aged 18 years old or older desiring lip enhancement were eligible if they had a score of 1 (minimal) or 2 (mild) on the validated 5-point Allergan Lip Fullness Scale[9] (LFS: minimal, mild, moderate, marked, and very marked) and had established a realistic treatment goal deemed achievable by the investigator. Subjects who had undergone cosmetic facial, lip, or perioral procedures or had received botulinum toxin therapy in the lower face within the previous 6 months were excluded. Other exclusion criteria were as follows: semi-permanent fillers or permanent implants in the lips; history of multiple severe allergies, autoimmune disease, or skin cancer; and allergy to lidocaine, hyaluronic acid, or streptococcal proteins.

Effectiveness Assessments

Follow-up visits occurred at 1 and 14 days after each treatment and at 1 and 3 months after the last treatment. Additional visits are planned at 6, 9, and 12 months. Facial 3-dimensional (3D) images were taken at all visits for ICR use. Subjects completed the 23-item Recovery Early Life Impact and 17-item Recovery Early Symptoms modules of the FACE-Q on days 1 and 14 after each treatment.[10] The Recovery Early Life Impact module evaluated the effect of treatment on daily activities and feelings; the Recovery Early Symptoms module assessed whether various symptoms had been bothersome. Subjects also completed the 22-item Satisfaction with Lips and 10-item Satisfaction with Outcome modules of the FACE-Q through month 3 after treatment.

Investigators and subjects assessed lip fullness using the LFS. Investigators assessed the severity of perioral lines and oral commissures using Allergan's validated Perioral Lines Severity Scale (POL) and Oral Commissures Severity Scale (OCS),[11] respectively (Table 1), and overall satisfaction with the aesthetic features of the lips and mouth in repose and in animation using an 11-point scale ranging from 0 (not at all) to 10 (very much).

Table 1. Grades and Descriptions of the Allergan Lip Fullness Scale, Perioral Lines Severity Scale, and Oral Commissures Severity Scale

Scale	Grade	Description
LFS	Very marked	Very significant red lip show, lower lip pout, and upper lip pout
	Marked	Significant red lip show and lower lip pout
	Moderate	Moderate red lip show and slight lower lip pout
	Mild	Some red lip show; no lower lip pout
	Minimal	Flat or nearly flat contour, minimal red lip show
POL	Severe	Many, deep lines or crevices
	Moderate	Some, moderate lines
	Mild	Few, shallow lines
	None	No lines
OCS	Severe	Very deep and/or long wrinkle or crease; frown at rest
	Moderate	Moderately deep and/or long wrinkle or crease; downturned corners
	Mild	Shallow, just perceptible wrinkle or crease; horizontal or slightly downturned corners
	None	No wrinkle or fold; slight upturned corners

Safety Assessments

Adverse events (AEs) were monitored throughout the study, and injection site responses (ISRs) were assessed by subjects in a diary kept for 30 days after each treatment. At visits through month 1, lip sensation was evaluated by 2-point discrimination and by light touch tests at 4 lip sites; lip function was evaluated by an independent speech and language professional based on the subject's ability to pronounce specific words and phrases.

Effectiveness Measures

The primary measure was lip fullness assessed from 3D images by the ICR using the LFS. Responders were defined as the percentage of subjects with a ≥1-point improvement on LFS at month 3 compared with baseline. The primary endpoint was a noninferiority comparison of responders to Juvéderm Volbella with Lidocaine versus Restylane-L.

Secondary measures included the FACE-Q Recovery Early Life Impact and Recovery Early Symptoms modules and objective measurement of lip volume and surface area from analysis of the 3D images. Additional measures included investigator and subject (live) assessment of lip fullness using the LFS; ICR (3D images) and investigator (live) assessments of the severity of perioral lines and oral commissures using the POL and OCS, respectively; FACE-Q Satisfaction with Lips and Satisfaction with Outcome modules; individual items from the FACE-Q modules; and investigator's overall satisfaction with treatment results. Investigators were asked to assess ease of injection on a scale of 0 (very easy) to 10 (very difficult) and to describe their experience with massage/molding (gentle, moderate, or vigorous).

Statistical Analyses

For the primary endpoint, a 1-sided 97.5% Wald confidence interval (CI) was constructed for the difference in responder rate between groups. Noninferiority was concluded if the lower confidence limit was >−15%. Secondary analyses included between-group comparisons in Recovery Early Life Impact and Recovery Early Symptoms scores on day 1 posttreatment and changes in lip volume from baseline to month 3; each was assessed using an independent *t* test. Between-group comparisons of individual items on FACE-Q modules were assessed at day 1 or month 3 as applicable using the Wilcoxon rank-sum test. Between-group comparisons in Satisfaction with Lips and Satisfaction with Outcome scores were assessed at month 3 using an independent *t* test. Responder rates in investigator and subject assessments using LFS, POL, and OCS were compared between treatments using Fisher's exact test. Statistical analyses were performed using SAS (SAS Institute, Cary, N.C.) version 9.1 or higher.

RESULTS

Subject Disposition and Characteristics

A total of 281 subjects were randomized to treatment: 139 to Juvéderm Volbella with Lidocaine and 142 to Restylane-L. One subject in the Restylane-L group discontinued before receiving treatment. Most subjects remained in the study at month 3, including 133 (95.7%) in the Juvéderm Volbella with Lidocaine group and 132 (93.6%) in the Restylane-L group.

Treatment groups were well balanced with respect to demographic and baseline characteristics (Table 2). Although lip fullness ratings at baseline did not differ significantly between groups, lip fullness was categorized as mild by investigators in ≈70% of subjects based on live assessment and as moderate by the ICR in ≈50% of subjects based on 3D photographs (Table 2). The total volume injected and the volume injected at the upper lip, lower lip, and

Table 2. Demographic and Baseline Characteristics

Characteristic*	Juvéderm Volbella with Lidocaine (*n* = 139)	Restylane-L (*n* = 141)
Age, years	48 (18–76)	49 (18–75)
Female	135 (97.1)	139 (98.6)
Fitzpatrick skin type		
I	14 (10.1)	15 (10.6)
II	49 (35.3)	54 (38.3)
III	50 (36.0)	46 (32.6)
IV	23 (16.5)	25 (17.7)
V	3 (2.2)	1 (0.7)
VI	0 (0)	0 (0)
Primary reason for treatment		
Lip enhancement	107 (77.0)	120 (85.1)
Lip definition	10 (7.2)	5 (3.5)
Wrinkle treatment	14 (10.1)	11 (7.8)
Other	8 (5.8)	5 (3.5)
Lip fullness (by investigator)		
Minimal (1)	36 (25.9)	41 (29.1)
Mild (2)	101 (72.7)	97 (68.8)
Moderate (3)	2 (1.4)	3 (2.1)
Marked (4)	0 (0)	0 (0)
Very marked (5)	0 (0)	0 (0)
Lip fullness (by ICR)		
Minimal (1)	11 (8.0)	16 (11.3)
Mild (2)	47 (34.3)	44 (31.2)
Moderate (3)	71 (51.8)	73 (51.8)
Marked (4)	8 (5.8)	8 (5.7)
Very marked (5)	0 (0)	0 (0)

Numbers in parentheses under lip fullness represent the score for each LFS grade.
*Age expressed as median (range); all other characteristics expressed as *n* (%).

Table 3. Treatment Characteristics

Characteristic	Juvéderm Volbella with Lidocaine (*n* = 139)	Restylane-L (*n* = 141)
Treatment sites,* *n* (%)		
Upper lip	139 (100)	141 (100)
Lower lip	134 (96.4)	136 (96.5)
Perioral lines	88 (63.3)	83 (58.9)
Oral commissures	126 (90.6)	124 (87.9)
Top-up treatment, *n* (%)	17 (12.2)	13 (9.2)
Anesthesia administered at initial treatment, *n* (%)		
Any	79 (56.8)	84 (59.6)
Topical	54 (38.8)	56 (39.7)
Local	8 (5.8)	10 (7.1)
Nerve block	17 (12.2)	18 (12.8)
Anesthesia administered at top-up treatment, *n* (%)		
Any	9 (52.9)	7 (58.3)
Topical	5 (29.4)	4 (33.3)
Local	4 (23.5)	3 (25.0)
Nerve block	0 (0)	0 (0)
Treatment volume,* mean mL (SD)		
Total	1.97 (0.773)	1.86 (0.737)
Upper lip	0.65 (0.332)	0.63 (0.316)
Lower lip	0.56 (0.288)	0.54 (0.295)
Perioral lines	0.38 (0.270)†	0.29 (0.213)
Oral commissures	0.59 (0.333)	0.61 (0.360)

*Initial and top-up treatment combined.
†$P = 0.015$ for independent *t* test comparison with Restylane-L.

oral commissures did not differ significantly between groups; the volume injected at the perioral lines was significantly greater ($P = 0.015$) in the Juvéderm Volbella with Lidocaine group than in the Restylane-L group (Table 3). Injections were administered mainly into the intradermal (81.8%) and subdermal (77.9%) planes of the upper and lower lips. Although tunneling was the primary injection technique, serial puncture and fanning were often used for perioral lines and oral commissures, respectively. Investigators indicated that Juvéderm Volbella with Lidocaine was easier to inject than Restylane-L (mean scores, 0.9 vs 2.3). Investigators also indicated that gentle (vs moderate or vigorous) molding/massage after injection was more common for subjects in the Juvéderm Volbella with Lidocaine group (91.4%; 127/139) versus the Restylane-L group (58.9%; 83/141).

Effectiveness

For the primary measure (overall lip fullness), the responder rate at month 3, based on ICR assessment, was 34.1% (42/123) in the Juvéderm Volbella with Lidocaine group versus 29.3% (36/123) in the Restylane-L group. The between-group difference in responder rate was 4.9%, and the lower limit of the 97.5% CI was –6.7% (greater than the noninferiority limit of –15.0%), supporting a conclusion of noninferiority for the primary endpoint. Lip enhancement improvement with Juvéderm Volbella with Lidocaine is illustrated in Figure 1. Lip fullness responder rates for the Volbella group, based on the ICR assessment, remained consistent from day 14 through month 3, whereas the responder rates for the Restylane group declined. Responder rates varied between assessors, with the highest rates reported by investigators, followed by subjects and ICRs (Fig. 2). Lip fullness responder rates, based on subject assessments, were significantly greater with Juvéderm Volbella with Lidocaine versus Restylane-L (month 3, 73.8% vs 59.8%; $P = 0.010$). Responder rates based on ICR assessment were generally consistent across age, sex, and skin type groups, although higher responder rates were achieved with Juvéderm Volbella with Lidocaine versus Restylane-L in subjects who received a total injection volume ≤2.0 mL (42.1% vs 26.2%).

Both treatments reduced the severity of perioral lines and oral commissures at month 3. Consistent with the LFS data, the percentage of subjects with ≥1-point improvement on the POL and OCS scales was greater based on the investigator assessment versus the ICR assessment (Figs. 3, 4). In the investigator assessment, the percentage of subjects with improvement in perioral lines was significantly greater with Juvéderm Volbella with Lidocaine versus Restylane-L (77.3% vs 61.3%; $P = 0.0292$). The mean change from baseline in POL scores also favored Juvéderm

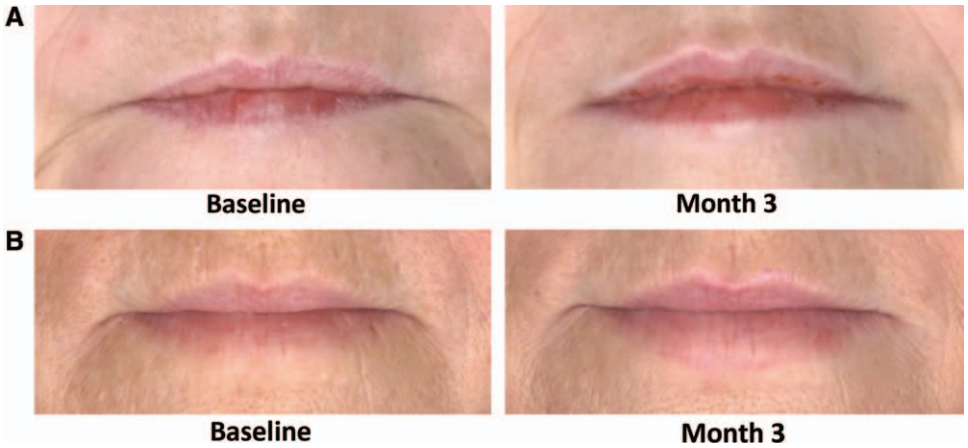

Fig. 1. Representative examples of improvement in overall lip fullness following Juvéderm Volbella with Lidocaine treatment. A, This 41-year-old white woman was injected with 0.5 mL in the upper lip, 0.45 mL in the lower lip, 1.0 mL in the oral commissures, and 0.05 mL in the perioral lines. Baseline lip fullness was rated as minimal by the investigator and mild by the ICR; at month 3, lip fullness was rated as moderate by both the investigator and the ICR. B, This 66-year-old white woman was injected with 0.5 mL each in the upper and lower lips, 0.3 mL in the oral commissures, and 0.2 mL in the perioral lines. Baseline lip fullness was rated as mild by the investigator and moderate by the ICR; at month 3, lip fullness was rated as moderate by both the investigator and the ICR. Photographs courtesy of Allergan.

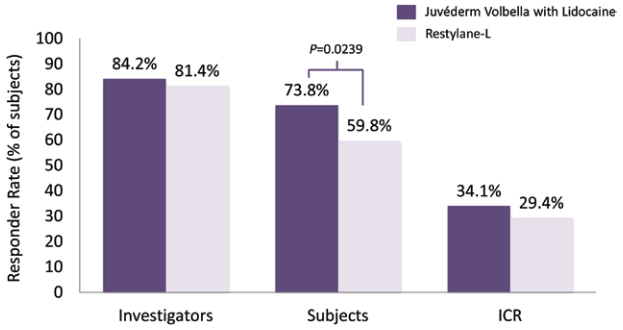

Fig. 2. Overall lip fullness responder rate at month 3 as assessed by investigators, subjects, and the ICR.

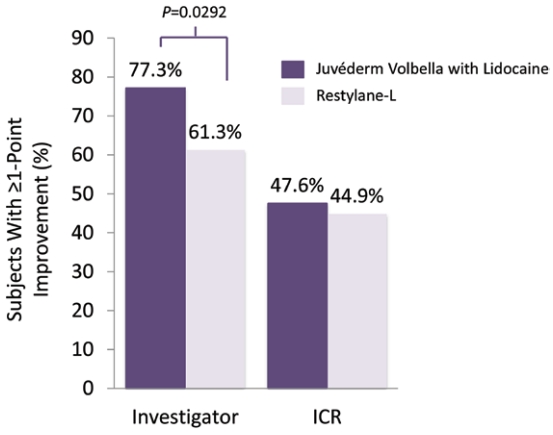

Fig. 3. Percentage of subjects with ≥1-point improvement from baseline to month 3 in perioral lines as assessed on the Allergan Perioral Lines Severity Scale.

Volbella with Lidocaine (1.0, 95% CI: 0.88–1.21 vs 0.7, 95% CI: 0.57–0.86). Improvement in oral commissures and changes from baseline in mean OCS scores did not differ significantly between treatment groups, as assessed by the ICR. However, investigator assessment showed that the percentage of subjects with improvement in oral commissures was significantly greater with Juvéderm Volbella with Lidocaine versus Restylane-L (69.9% vs 58.7%; $P = 0.0126$).

Juvéderm Volbella with Lidocaine was less disruptive to daily activities versus Restylane-L based on the subject-reported FACE-Q Recovery Early Life Impact and Recovery Early Symptoms modules assessed on day 1. On the Recovery Early Life Impact module, the mean score was significantly higher with Juvéderm Volbella with Lidocaine versus Restylane-L (77.5 vs 69.6; between-group 95% CI, 3.6–12.1; $P < 0.001$) (Fig. 5). Similarly, on the Recovery Early Symptoms module, mean score was significantly higher for Juvéderm Volbella with Lidocaine (85.5 vs 73.4; between-group 95% CI, 8.4–16.0; $P < 0.001$). Subjects in the Juvéderm Volbella with Lidocaine group were significantly less bothered by discomfort, pain, swelling, tenderness, feeling sore, numbness, throbbing, and tingling versus the Restylane-L group ($P < 0.001$) on day 1 as assessed on individual items of the Recovery Early Symptoms module.

Subjects in the Juvéderm Volbella with Lidocaine group were significantly more satisfied with their lips and the outcomes of treatment at month 3 than subjects in the Restylane-L group ($P = 0.015$ and $P = 0.031$, respectively) based on the Satisfaction with Lips and Satisfaction with Outcome modules of the FACE-Q. Individual items of the Satisfaction with

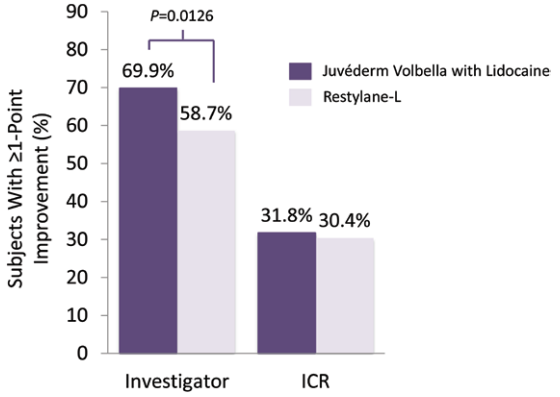

Fig. 4. Percentage of subjects with ≥1-point improvement from baseline to month 3 in oral commissures as assessed on the Allergan Oral Commissures Severity Scale.

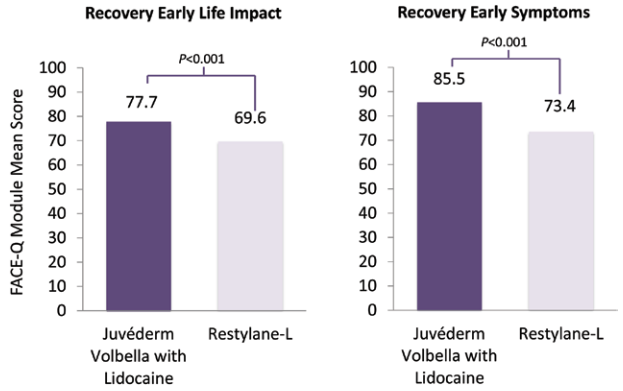

Fig. 5. FACE-Q module scores on the day after treatment with Juvéderm Volbella with Lidocaine or Restylane-L.

Lips module at month 3 showed that Juvéderm Volbella with Lidocaine subjects were significantly more satisfied than Restylane-L subjects with lip fullness ($P = 0.010$), natural look of lips ($P = 0.023$), softness of lips ($P = 0.001$), attractiveness of lips ($P = 0.026$), and overall look of lips ($P = 0.038$).

Mean changes in lip volume (0.68 mL vs 0.93 mL) and lip surface area (31% vs 38%) on day 1 were smaller with Juvéderm Volbella with Lidocaine versus Restylane-L. By day 14, mean change from baseline did not differ between treatments, likely reflecting less short-term swelling following treatment with Juvéderm Volbella with Lidocaine. At month 3, mean lip surface area had increased by 19% with Juvéderm Volbella with Lidocaine versus 13% with Restylane-L. Based on self-assessments, the percentage of subjects achieving treatment goal was similar between groups at month 1 but was numerically higher with Juvéderm Volbella with Lidocaine at month 3 (73.3% vs 62.2%; $P = 0.0629$) (Fig. 6).

Investigators assessed their overall satisfaction with the aesthetic features of the subject's lips and mouth in repose and in animation. At month 3, investigators indicated that they were "very satisfied" with the

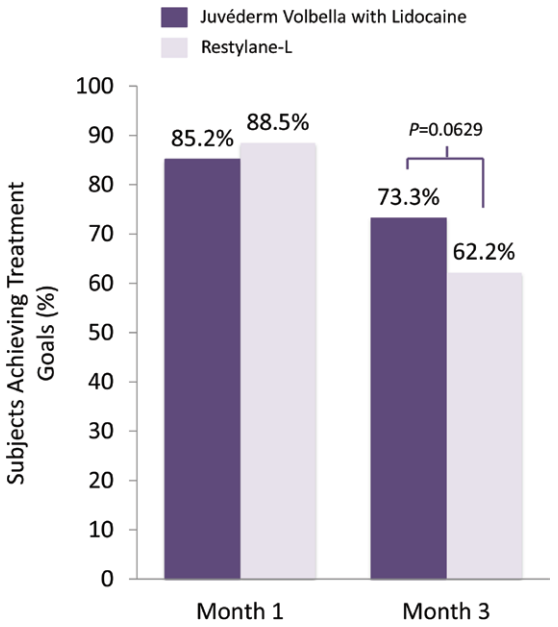

Fig. 6. Percentage of subjects who achieved their treatment goals.

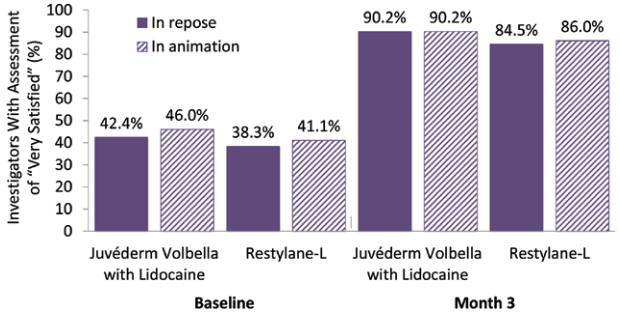

Fig. 7. Investigator assessment of overall satisfaction with lips and mouth at baseline and month 3 in repose and in animation. Scores of 7–10 on the 0–10 scale were grouped to create a "very satisfied" category.

aesthetic features in most subjects at repose (90.2% with Juvéderm Volbella with Lidocaine, 84.5% with Restylane-L; scores of 7–10 on the 0–10 scale were grouped to create a "very satisfied" category) (Fig. 7).

Safety

Most subjects reported ≥1 ISR, with swelling, tenderness, and firmness being the most frequently reported in both treatment groups (Table 4). Several ISR categories were reported significantly less frequently with Juvéderm Volbella with Lidocaine versus Restylane-L, including lumps/bumps, firmness, pain, itching, and discoloration. Moreover, subjects receiving Juvéderm Volbella with Lidocaine were less likely to report severe ISRs (32.0% vs 60.2%). More than twice as many subjects reported severe swelling after treatment with Restylane-L (49.2%) than with

Table 4. Incidence of ISRs Based on Subject Entries in a 30-day Diary

ISRs*	Juvéderm Volbella with Lidocaine (n = 134)	Restylane-L (n = 134)
Subjects with any ISR, n (%)	128 (95.5)	133 (99.3)
Severity, n (% of ISRs)		
Mild	23 (18.0)	5 (3.8)
Moderate	64 (50.0)	48 (36.1)
Severe	41 (32.0)†	80 (60.2)
Type, n (% of subjects)		
Swelling	122 (91.0)	132 (98.5)
Tenderness	118 (88.1)	128 (95.5)
Firmness	111 (82.8)†	128 (95.5)
Bruising	104 (77.6)	119 (88.8)
Lumps/bumps	103 (76.9)†	121 (90.3)
Redness	102 (76.1)	118 (88.1)
Pain	92 (68.7)†	119 (88.8)
Itching	29 (21.6)†	71 (53.0)
Discoloration	24 (17.9)†	58 (43.3)

*ISRs for initial and top-up treatments combined for subjects who completed 30-day diaries.
†Significant difference between treatment groups based on nonoverlapping 95% confidence intervals.

Juvéderm Volbella with Lidocaine (22.1%). Most ISRs lasted ≤14 days; 23.4% of subjects receiving Juvéderm Volbella with Lidocaine and 25.6% receiving Restylane-L had ISRs lasting for 15–30 days, most commonly lumps/bumps (22.3% vs 23.1%) and firmness (10.8% vs 10.9%). Swelling lasting 15–30 days was reported by 1 subject (0.8%) receiving Juvéderm Volbella with Lidocaine and 6 subjects (4.5%) receiving Restylane-L.

Device-related AEs were reported in 14 subjects (10.1%) receiving Juvéderm Volbella with Lidocaine versus 19 subjects (13.5%) receiving Restylane-L; all occurred at the injection site. The Juvéderm Volbella with Lidocaine group had 22 device-related AEs, all mild or moderate in severity, with the most frequent being lumps/bumps (n = 11) and firmness (n = 4). In comparison, the Restylane-L group had 55 device-related AEs, including 18 that were severe. The most frequent events were injection site pain (n = 17), lumps/bumps (n = 12), paresthesia (n = 9), and firmness (n = 5). For both treatment groups, lip sensitivity and speech pronunciation were not affected by treatment.

DISCUSSION

This study met its primary endpoint: the effectiveness of Juvéderm Volbella with Lidocaine for lip enhancement was noninferior to treatment with Restylane-L. The analysis was based on a subjective assessment by the ICR of overall lip fullness from 3D images using the LFS. Results were supported by subjective assessments made by investigators and subjects and by objective measurements of lip volume and surface area from analysis of the 3D images. Besides improving overall lip fullness, Juvéderm Volbella with Lidocaine was at least as effective as Restylane-L for improving perioral lines and oral commissures, including fine lines and wrinkles in the perioral region. In the investigator assessment, a significantly greater percentage of subjects receiving Juvéderm Volbella with Lidocaine achieved improvements in perioral lines and oral commissures at month 3 versus Restylane-L. These results agree with studies using other injectable gels from the Juvéderm family, including Juvéderm Volbella (without lidocaine) and Juvéderm Ultra, which were effective in augmenting lip fullness and reducing perioral lines and oral commissures.[7,12] Juvéderm Volbella with Lidocaine was also shown to be effective in the correction of tear troughs and sunken eyes in the periocular area.[13]

Subjects receiving Juvéderm Volbella with Lidocaine reported better outcomes on day 1 than those receiving Restylane-L. This was evidenced by higher scores on the FACE-Q Recovery Early Life Impact and Recovery Early Symptoms modules, indicative of less disruption of normal daily activities. Lip volume measurements on day 1 support these findings. Subjects receiving Juvéderm Volbella with Lidocaine had a smaller mean change from baseline in lip volume on day 1 compared with those receiving Restylane-L, suggesting less acute, short-term swelling. At month 3, subjects reported greater satisfaction with Juvéderm Volbella with Lidocaine versus Restylane-L on the FACE-Q. Although investigators evaluated satisfaction based on the aesthetic features at 3 months after treatment, subjects evaluated satisfaction based on aesthetic features and other factors, indicating that patient satisfaction is a multidimensional concept.

The responder rate for overall lip fullness in both treatment groups, based on ICR assessment, was surprisingly low, particularly compared with a recent lip augmentation study conducted in the United States with a Restylane formulation without lidocaine.[14] However, the injection volume for upper and lower lips was >2-fold higher in the Restylane study, possibly reflecting cultural differences between European and American ideals of lip enhancement. In the present study, investigators enrolled subjects who had minimal or mild baseline LFS scores, and the primary endpoint was based on LFS assessments made by the ICR from 3D images. The ICR and investigator assessments of LFS at baseline differed considerably; the ICR assessment found a higher mean LFS score and rated >50% of the subjects as having moderate or marked lip fullness at baseline. Accordingly, these subjects had little room to show the 1-point improvement in overall lip fullness necessary for classification as a responder. Differences were also observed between assessors for oral commissures and perioral lines. Together, these data suggest that photographs may present less detail and

therefore are less sensitive for measuring observable changes compared with in-person assessment. In the Restylane study, responder rates were notably lower when based on assessments from photographs compared with live evaluations.[14] In the present study, the month 3 responder rates based on the investigator assessments (84.2% with Juvéderm Volbella with Lidocaine and 81.4% with Restylane-L) suggest a much better outcome compared with the ICR assessments.

The overall incidence of subject-reported ISRs and device-related AEs was similar between treatment groups and consistent with expectations for hyaluronic acid dermal fillers. However, ISR severity was generally lower with Juvéderm Volbella with Lidocaine, and several types of ISRs, including lumps/bumps and firmness, were reported less frequently with Juvéderm Volbella with Lidocaine.

Two study limitations are notable. First, subjects were enrolled based on in-person assessment of lip fullness by investigators, whereas the primary analysis of treatment effectiveness depended on ICR assessment of 3D images. This contributed to differences in responder rate depending on the assessor. Regardless of the assessor, Juvéderm Volbella with Lidocaine was at least as effective as Restylane-L. Second, investigators were not blinded to the treatment assignment; consequently, they may have been biased in their assessments. However, qualitatively similar findings were obtained by the ICR and subjects themselves, who were blinded to treatment assignment.

CONCLUSIONS

This study demonstrates that Juvéderm Volbella with Lidocaine is safe and effective for aesthetic lip augmentation and improvement in perioral lines and oral commissures. Juvéderm Volbella with Lidocaine displayed a favorable risk-benefit profile for volumizing the lips and perioral area, including less early life impact and early symptoms compared with Restylane-L. Most ISRs and device-related AEs were mild or moderate in severity, and lidocaine effectively managed injection pain.

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REFERENCES

1. Coleman SR, Grover R. The anatomy of the aging face: volume loss and changes in 3-dimensional topography. *Aesthet Surg J.* 2006;26(1S):S4–S9.
2. Brandt FS, Cazzaniga A. Hyaluronic acid gel fillers in the management of facial aging. *Clin Interv Aging* 2008;3:153–159.
3. Belhaouari L. How to enhance lips with hyaluronic acid. *Prime* 2011;March:14–21.
4. Bogdan Allemann I, Baumann L. Hyaluronic acid gel (Juvéderm) preparations in the treatment of facial wrinkles and folds. *Clin Interv Aging* 2008;3:629–634.
5. Sarnoff DS, Saini R, Gotkin RH. Comparison of filling agents for lip augmentation. *Aesthet Surg J.* 2008;28:556–563.
6. Beasley KL, Weiss MA, Weiss RA. Hyaluronic acid fillers: a comprehensive review. *Facial Plast Surg.* 2009;25:86–94.
7. Eccleston D, Murphy DK. Juvéderm® Volbella™ in the perioral area: a 12-month prospective, multicenter, open-label study. *Clin Cosmet Investig Dermatol.* 2012;5:167–172.
8. Pusic AL, Klassen AF, Scott AM, et al. Development and psychometric evaluation of the FACE-Q satisfaction with appearance scale: a new patient-reported outcome instrument for facial aesthetics patients. *Clin Plast Surg.* 2013;40:249–260.
9. Werschler WP, Fagien S, Thomas J, et al. Development and validation of a photographic scale for assessment of lip fullness. *Aesthet Surg J.* 2015; in press.
10. Klassen AF, Cano SJ, Scott A, et al. Measuring patient-reported outcomes in facial aesthetic patients: development of the FACE-Q. *Facial Plast Surg.* 2010;26:303–309.
11. Cohen JL, Thomas J, Paradkar D, et al. An interrater and intrarater reliability study of 3 photographic scales for the classification of perioral aesthetic features. *Dermatol Surg.* 2014;40:663–670.
12. Fagien S, Maas C, Murphy DK, et al; Juvéderm Lips Study Group. Juvederm ultra for lip enhancement: an open-label, multicenter study. *Aesthet Surg J.* 2013;33:414–420.
13. Raspaldo H. Injection of a new hyaluronic acid (HA) in the peri-ocular area to reduce tear trough deformities and sunken eyes: retrospective study based on 120 cases [Poster]. *Presented at: Anti-Aging Medicine World Congress,* April 3–5, 2014, Monte Carlo, Monaco.
14. Glogau RG, Bank D, Brandt F, et al. A randomized, evaluator-blinded, controlled study of the effectiveness and safety of small gel particle hyaluronic acid for lip augmentation. *Dermatol Surg.* 2012;38(7, Part 2):1180–1192.