

# A Randomized, Controlled, Evaluator-Blinded, Multi-Center Study of Hyaluronic Acid Filler Effectiveness and Safety in Lip Fullness Augmentation

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**BACKGROUND** HA<sub>RK</sub> was recently approved in the US for lip augmentation and correction of upper perioral rhytids.

**OBJECTIVE** To demonstrate noninferiority of HA<sub>RK</sub> versus a control (HA<sub>JV</sub>) in lip fullness augmentation at Week 8 after last injection (blinded evaluation). Secondary objectives were to evaluate the effectiveness and safety of HA<sub>RK</sub> in lip fullness augmentation and correction of upper perioral rhytids.

**METHODS AND MATERIALS** Treatment with HA<sub>RK</sub> or control (randomized 2:1) was administered on Day 1 in this 48-week, evaluator-blinded study with optional touch-up at Week 4. Primary endpoint was change from baseline to Week 8 in lip fullness. Secondary endpoints included lip fullness, wrinkle severity, aesthetic improvement, subject satisfaction, adverse events, and local tolerability (subject diary entries).

**RESULTS** The primary objective was met; HA<sub>RK</sub> was noninferior to control in lip fullness augmentation at Week 8. Lip fullness and wrinkle severity improvement persisted at Week 48, and was accompanied by high aesthetic improvement and subject satisfaction scores. The mean volume of HA<sub>RK</sub> injected was approximately 20% lower than control. Treatment-related adverse events and local tolerability symptoms were predominantly mild and transient.

**CONCLUSION** HA<sub>RK</sub> was noninferior to control in lip fullness augmentation at Week 8, well-tolerated, and effective throughout this 48-week study.

Injectable hyaluronic acid (HA) gel fillers are commonly used for minimally invasive lip augmentation and correction of perioral rhytids.<sup>1–7</sup> Restylane Kysse (HA<sub>RK</sub>; Galderma, Sweden) is an HA gel filler produced with XPresHAN technology (also known as the Optimal Balance Technology). It was first approved in the EU in 2010 for restoration or augmentation of lip volume. Clinical data supporting its intended use are described in published

literature.<sup>6,8–10</sup> HA<sub>RK</sub> is also approved in many other countries worldwide, and was recently approved in the US for lip augmentation and correction of upper perioral rhytids.

Here, the authors present data from the first randomized, controlled, evaluator-blinded study performed with HA<sub>RK</sub> in the US to evaluate effectiveness and safety of HA<sub>RK</sub> versus a control (Juvéderm Volbella XC [HA<sub>JV</sub>], Allergan, CA) in lip fullness augmentation and correction of upper perioral rhytids.

## Materials and Methods

### Study Design

This was a randomized, controlled, evaluator-blinded 48-week pivotal study (NCT03320824) performed at 14 centers in the US to evaluate the effectiveness and safety of HA<sub>RK</sub> in lip fullness augmentation and correction of upper perioral rhytids. The primary objective was to demonstrate noninferiority of HA<sub>RK</sub> versus a control in lip fullness augmentation 8 weeks after last injection. Secondary objectives were to evaluate the effectiveness and safety of HA<sub>RK</sub> in lip fullness augmentation and correction of upper perioral rhytids. Follow-up was done at 72 hours and Weeks 2, 4, 8, 16, 24, 32, 40 and 48 after last injection (baseline or touch-up).

The study started after obtaining approval from the US FDA and Independent Review Board and was performed in accordance with the Declaration of Helsinki, Good Clinical

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Practice, and International Organization for Standardization (ISO) guidelines for clinical studies of medical devices in humans (ISO 14155:2011).

## Main Eligibility Criteria

Healthy subjects aged  $\geq 22$  years with “very thin” or “thin”<sup>11</sup> upper and lower lips, and who provided written informed consent were eligible to participate in this study. At least 42 subjects with Fitzpatrick skin Types IV–VI were to be included; of these, 21 subjects with skin Types V or VI were exempted from the requirement to have “very thin” or “thin” lips. For treatment of upper perioral rhytids, subjects had to have “moderately deep” to “very deep” wrinkles.<sup>12</sup>

Main exclusion criteria were allergy/hypersensitivity to any injectable HA gel, gram positive bacterial proteins, lidocaine, or other amide-type anesthetics; disease/lesions on or near the area to be treated (e.g., herpes labialis outbreak within 4 weeks before injection or  $\geq 4$  outbreaks within 12 months before baseline visit); facial treatment below the lower orbital rim (such as tissue augmentation with any HA- or collagen-based biodegradable product within 12 months before the baseline visit, or permanent or semi-permanent tissue augmentation, lifting threads, permanent implants or autologous fat); lip surgery, piercing or tattoo, or trauma to any area of the face; dental, oral or facial condition/treatment which could interfere with study injections/assessments; use of lip plumper within 10 days before any study visit; use of concomitant medication that potentially could prolong bleeding times (e.g., anticoagulants or inhibitors of platelet aggregation) within 14 days before injection.

## Treatment

HA<sub>RK</sub> or control (HA<sub>JV</sub>), randomized 2:1, was injected into lips and upper perioral rhytids at baseline to achieve optimal correction. Injection into upper perioral rhytids, vermilion, vermilion border, philtral columns, cupid’s bow, and/or oral commissures was optional. For lips, optimal correction was typically  $\geq 1$ -grade improvement on the Medicis Lip Fullness Scale (MLFS). Treatment was stratified by Fitzpatrick skin type (I–III, IV or V–VI) and center (only for skin Type I–III). It was recommended to not inject more than 3 mL in lips (i.e., 1.5 mL per lip, including vermilion, vermilion border and cupid’s bow) and not more than 3 mL in the perioral area (upper perioral rhytids, philtral columns and/or oral commissures) per treatment. Optional touch-up was offered at Week 4 after baseline if optimal correction was not achieved after baseline injection. Optional retreatment with HA<sub>RK</sub> was offered at Week 48 after last injection.

HA<sub>RK</sub> was to be injected in the submucosal layer of the lips, or in the mid-dermis to subcutaneous layer of upper perioral rhytids, using the co-packed needles and an aseptic injection technique. Investigators were recommended to use linear antegrade/retrograde threading, serial puncture, fanning or fern pattern for lip injections, and linear retrograde threading, fanning or fern pattern for upper

perioral rhytids. HA<sub>JV</sub> was injected in line with manufacturer recommendations.

The treated area could be gently massaged to correct slight irregularities, and ice packs could be applied to minimize post-treatment swelling.

## Effectiveness Assessments

Assessments were done at baseline and Weeks 8, 16, 24, 32, 40, and 48 after last injection, unless otherwise stated.

### By Blinded Evaluator

#### Lip Fullness

Lip fullness was evaluated using live scoring against the validated MLFS,<sup>11</sup> ranging from 1 (very thin) to 5 (very full). The primary endpoint was change from baseline in MLFS score, assessed at Week 8 (separately for the upper and lower lip).

#### Wrinkle Severity of Upper Perioral Rhytids/Oral Commissures

Wrinkle severity was evaluated using live scoring against the validated Wrinkle Assessment Scale,<sup>12</sup> ranging from 0 (no wrinkles) to 5 (very deep wrinkle/redundant fold).

#### Independent Photographic Reviewer Assessment

A central independent photographic reviewer assessed improvement in lip fullness by comparison of random, blinded pairings of subjects’ baseline and post-treatment photos (Weeks 8, 24, 40 and 48).

### By Treating Investigator or Subjects

#### Aesthetic Improvement of Lips

Aesthetic improvement was evaluated using live scoring against the Global Aesthetic Improvement Scale, ranging from 3 (very much improved) to  $-3$  (very much worse), by comparison to the subjects’ baseline photo.

#### Subject Satisfaction

Satisfaction with lips and appraisal of lip lines was evaluated using FACE-Q questionnaires.<sup>13</sup>

## Safety Assessments

Safety assessments included adverse events, entries of predefined local tolerability symptoms in 30-day subject diaries, and lip assessments (palpation, texture, symmetry, movement, function, and sensation).

## Statistics

### Sample Size

Approximately 280 subjects were to be included to ensure 234 evaluable subjects, with an overall power of 85% to test upper and lower lips separately using a noninferiority margin of 0.5% and 95% 2-sided confidence intervals (CIs).

The safety population included all subjects who received HA<sub>RK</sub> or control, based on the as-treated principle. The intention-to-treat (ITT) population was used for all effectiveness analyses and included all randomized subjects who had a baseline upper and lower lip MLFS score <5, based on the as-randomized principle. The per protocol population was used for the primary effectiveness analysis and included all subjects in the ITT population who completed the Week 8 visit without any deviations considered to substantially affect the primary effectiveness outcome.

Analyses

Analyses were done using SAS version 9.4. Formal statistical testing was done at a significance level of 5% (2-sided). No correction for multiplicity was done. For the primary effectiveness analysis, noninferiority was only demonstrated if the CIs for both the upper and lower lip were entirely below the predetermined noninferiority margin of 0.5 in both the ITT and PP populations. Difference between treatments means (control—HA<sub>RK</sub>), and the corresponding 2-sided 95% CI, were calculated for both the upper and lower lip using the Student’s *t*-statistic. Difference in injection volume between treatment groups was analyzed using a post-hoc 2-sample *t*-test. Other data were presented descriptively. For the primary endpoint, missing data were primarily handled using the hot deck imputation method. Missing values were not imputed for other effectiveness endpoints.

Results

Subject Disposition and Demographics

The first subject was enrolled November 13, 2017; the last subject completed the study April 23, 2019. Subject disposition is shown in Supplemental Digital Content 1, Figure, <http://links.lww.com/DSS/A607>; demographics are shown in Supplemental Digital Content 2, Table, <http://links.lww.com/DSS/A608>.

Injection Details

In all treatment areas, the volume of HA<sub>RK</sub> injected was approximately 20% lower than control (Figure 1). The mean volume injected in lips was 1.82 mL (HA<sub>RK</sub>) and 2.24 mL (control); *p* < .001. Overall, the mean total volume injected in all treatment areas was 2.65 mL (HA<sub>RK</sub>) and 3.33 mL (control); *p* < .001.

Effectiveness

Blinded Evaluator Assessments

Lip fullness

The primary objective was met. As CIs for both ITT and PP populations were below the predetermined noninferiority margin of 0.5 for both upper and lower lips, HA<sub>RK</sub> was noninferior to control in lip fullness augmentation at 8 weeks after last injection (Table 1).

HA<sub>RK</sub> responder rates (≥1-point improvement from baseline in MLFS score for both upper and lower lips) over time ranged between 88% (Week 8) and 60% (Week 48; Figure 2).

Wrinkle severity

HA<sub>RK</sub> responder rates (≥1-point improvement from baseline in Wrinkle Assessment Scale score) for upper perioral rhytids ranged between 94% (Week 8) and 83% (Week 48; Figure 2).

HA<sub>RK</sub> responder rates (≥1-point improvement from baseline in Wrinkle Assessment Scale score) for left and right oral commissures were 74% at Week 8 and 58% at Week 48 (Figure 2).

Independent Photographic Reviewer assessment

According to the independent photographic reviewer, upper and lower lip fullness improved from baseline with HA<sub>RK</sub> treatment (See Figure, Supplemental Digital Content 3, <http://links.lww.com/DSS/A609>). At Week 8, ≥95% of subjects were improved. Lip fullness improvement remained high (≥88%) at Week 48.

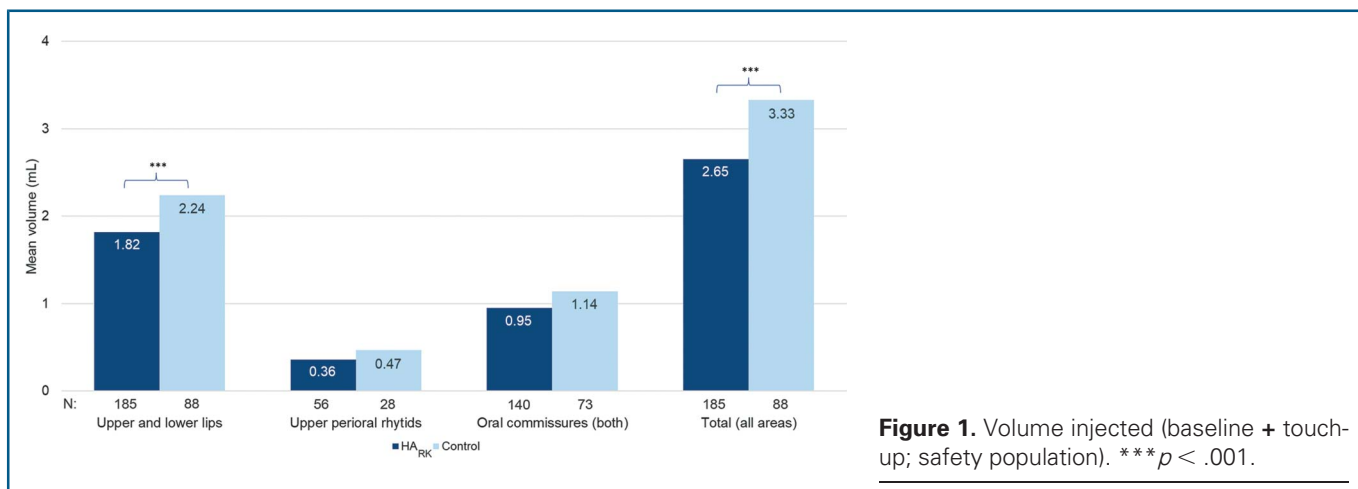


Figure 1. Volume injected (baseline + touch-up; safety population). \*\*\**p* < .001.

**TABLE 1. Change From Baseline in Lip Fullness\* at 8 Weeks After Last Injection**

	HA <sub>RK</sub> (N = 183†/176‡)	Control (N = 87†/85‡)
Upper lip Mean (SD)	1.8 (0.98)†	1.7 (0.90)†
95% CI mean of (control—HA <sub>RK</sub> )	1.8 (0.96)‡ (−0.31, 0.18)†	1.7 (0.91)‡
	(−0.32, 0.17)‡	
Lower lip Mean (SD)	1.8 (0.98)†	1.8 (0.85)†
95% CI mean of (control—HA <sub>RK</sub> )	1.8 (0.98)‡ (−0.32, 0.16)†	1.8 (0.86)‡
	(−0.30, 0.19)‡	

\* Blinded Evaluator live assessment of upper and lower lip MLFS score.

† ITT.

‡ PP.

CI, confidence interval; ITT, intention-to-treat population; MLFS, medicis lip fullness scale; PP, per protocol population.

### Treating Investigator or Subjects' Assessments

#### Aesthetic improvement of lips

Treating investigators and subjects assessed that HA<sub>RK</sub> responder rates ranged between 96% and 98% (Week 8) and 67% and 78% (Week 48; See Figure, **Supplemental Digital Content 4**, <http://links.lww.com/DSS/A610>).

Figure 3 and Figure 4 illustrate aesthetic improvement of lips after HA<sub>RK</sub> injection. For the subject in Figure 3, blinded evaluator-assigned MLFS scores for both lips were 1 (Baseline), 4 (Week 8), and 3 (Week 48). For the subject in Figure 4, blinded evaluator-assigned MLFS scores for upper/lower lips were 2/2 (Baseline), 4/3 (Week 8), and 3/3 (Week 48).

#### Subject satisfaction

The sum of the subjects' FACE-Q scores were converted to Rasch-transformed total scores according the FACE-Q manual; higher total scores indicated greater subject satisfaction.

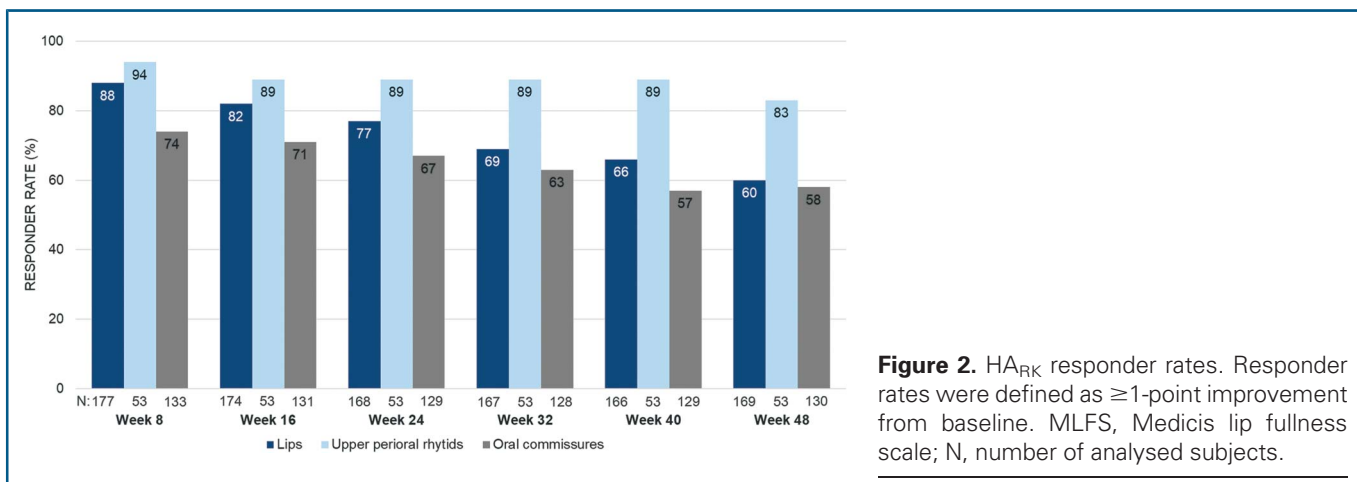
After treatment with HA<sub>RK</sub>, subjects' satisfaction with their lips increased and subjects' appraisal of their lip lines indicated that the lines were less bothersome, as assessed by FACE-Q Rasch mean total scores, which peaked at Week 8 after treatment with HA<sub>RK</sub> and remained higher than the baseline score through Week 48.

Satisfaction with specific FACE-Q questionnaire items is shown in **Supplemental Digital Content 5**, Figure, <http://links.lww.com/DSS/A611> and **Supplemental Digital Content 6**, Figure, <http://links.lww.com/DSS/A612>.

## Safety

### Adverse Events

No treatment-emergent adverse events (TEAEs) were reported for most subjects in either group (HA<sub>RK</sub>: 61%, control: 65%) throughout Week 48. Treatment-related TEAEs were predominantly mild (HA<sub>RK</sub>: 96%, control: 91%), none were severe, and most resolved spontaneously (median duration approx. 2 weeks).



**Figure 2.** HA<sub>RK</sub> responder rates. Responder rates were defined as  $\geq 1$ -point improvement from baseline. MLFS, Medicis lip fullness scale; N, number of analysed subjects.





**Figure 3.** Subject photographs. Lip appearance of a 31-year-old woman at (A) baseline, and at (B) Week 8 and (C) Week 48 after injection of HA<sub>RK</sub> (total volume: 1.0 mL in upper lip; 1.5 mL in lower lip).

The most commonly reported treatment-related TEAEs (occurring in  $\geq 5\%$  of subjects) were injection-site mass (HA<sub>RK</sub>: 10%; control: 11%), injection-site bruising (HA<sub>RK</sub>: 8%; control: 10%), and injection-site nodule (HA<sub>RK</sub>: 5%; control: 7%). All of the most commonly reported treatment-related TEAEs were mild, except one event of moderate injection-site bruising.

The reporting frequency of late-onset events (occurring  $\geq 21$  days after treatment) was similar between groups (HA<sub>RK</sub>: 5%; control: 6%). All late-onset events were mild (HA<sub>RK</sub>) or mild-to-moderate (control), and all resolved or were assessed as stable.

#### *Subject Diary Entries of Pre-defined Local Tolerability Symptoms*

Events typically lasted  $\leq 7$  days; most ( $\geq 67\%$  in both groups) were rated as “tolerable.” The most commonly reported events in lips and oral commissures were tenderness, swelling and lumps/bumps. The most commonly reported events in upper perioral rhytids were tenderness and swelling, and for HA<sub>RK</sub> also redness.

#### *Lip Assessments*

None of the lip assessments were remarkable or presented any safety concerns.

## Discussion

This was the first study with HA<sub>RK</sub> conducted in the US. Subjects with all Fitzpatrick skin types were included, although most had light skin types. The primary objective was met; HA<sub>RK</sub> was noninferior to control in lip fullness augmentation at 8 weeks after last injection as assessed by blinded evaluation of change from baseline in MLFS score.

The total mean volume of HA<sub>RK</sub> used in this study was approximately 20% lower than control, and was significantly lower than control for lips and all treatment areas, which supports previous findings.<sup>6</sup> Effectiveness in terms of improvement of lip fullness, upper perioral rhytids, and oral commissures was maintained at Week 48 in most subjects

injected with HA<sub>RK</sub> as assessed by a blinded evaluator. HA<sub>RK</sub> effectiveness was also corroborated by an independent photographic reviewer, who assessed that lip fullness improvement was maintained in most subjects at Week 48. Thus, at study end, most subjects still had a clinically relevant result that was visible in photographs. Treatment with HA<sub>RK</sub> was also associated with a high degree of aesthetic improvement and subject satisfaction, which is in line with previous findings for HA<sub>RK</sub>.<sup>6</sup>

The postmarket safety experience collected during the first 5 years of commercial use of XPresHAn fillers (including HA<sub>RK</sub>) worldwide indicated that the frequency of potentially related AEs is low and stable, and did not identify any new, unexpected AEs compared with what has been reported for other HA filler products on the market.<sup>14</sup> In our study, HA<sub>RK</sub> was well-tolerated, with treatment-related TEAEs and subject diary entries of local tolerability reactions predominantly being mild and transient. Most commonly reported treatment-related TEAEs were injection-site reactions, which is in line with previous findings.<sup>6</sup> The reporting frequency of late-onset events was similar between treatment groups, and all such events were mild or moderate and resolved or were assessed as stable.

In summary, these data show that HA<sub>RK</sub> is well suited for lip fullness augmentation and correction of upper perioral rhytids.

## Conclusion

HA<sub>RK</sub> was noninferior to the control in lip fullness augmentation at 8 weeks after last injection. Also, HA<sub>RK</sub> was well-tolerated and achieved lip fullness improvement and correction of upper perioral rhytids that persisted in  $\geq 60\%$  of subjects at Week 48 after the last injection. HA<sub>RK</sub> effectiveness was supported by a high degree of aesthetic improvement and subject satisfaction.

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**Figure 4.** Subject photographs. Lip appearance of a 29-year old woman at (A) baseline, and at (B) Week 8 and (C) Week 48 after injection of HA<sub>RK</sub> (total volume: 0.85 mL in upper lip; 0.6 mL in lower lip).

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