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 ORIGINAL ARTICLE

A Randomized, Comparator-Controlled Study of HA_{RC} for Cheek Augmentation and Correction of Midface Contour Deficiencies

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ABSTRACT

Background: HA_{RC} is a soft and flexible hyaluronic acid filler containing lidocaine, manufactured using XpresHAn® technology, restoring natural-looking volume and soft contours.

Objectives: To evaluate safety and effectiveness of HA_{RC} for cheek augmentation and correction of midface contour deficiencies compared to a control product HA_{JV} (hereafter referred to as Control). Primary objective was to demonstrate non-inferiority of HA_{RC} compared to the Control, by blinded evaluation of change from baseline in midface fullness 12 weeks after last injection, using a 4 grade midface volume scale (MMVS).

Materials and Methods: Subjects over the age of 21 with loss of fullness in the midface area (MMVS score 2, 3, or 4) were randomized 2:1 to treatment with HA_{RC} (n=142) or Control (n=68). Optional touch-up was allowed after 4 weeks. Study assessments included MMVS, aesthetic improvement, subject satisfaction, and safety. Subjects were followed for 48 weeks.

Results: Overall, most subjects were female (89%) and mean age was 53 years (range 24-80). Total mean volume injected was 4.3 mL for HA_{RC} and 4.9 mL for Control. Primary objective was met; mean change from baseline in MMVS score at week 12: -1.4 (HA_{RC}), -1.3 (Control), 95% CI: -0.22, 0.06. HA_{RC} effectiveness was supported by a high degree of aesthetic improvement and subject satisfaction throughout 48 weeks. Related adverse events were generally mild and transient.

Conclusions: HA_{RC} was well tolerated and non-inferior to Control for correction of midface fullness at 12 weeks after last injection. Aesthetic improvement and subject satisfaction were high and lasted through week 48.

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INTRODUCTION

Volume loss resulting in descent of midfacial soft tissues is a main factor for facial age-related changes. Dermal fillers are frequently used to address such losses by replenishing midface volume.[1,2] The Restylane® range of products are each designed to have optimal gel properties for their indication, by varying the degree of firmness (G') and flexibility (xStrain) for specific patient needs.[3] Restylane Contour (hereafter HA_{RC}) is a soft and flexible lidocaine-containing gel with high lifting capacity. It is manufactured using the XpresHAn® technology (OBT™ in the EU) that creates smooth gels with features that are characterized by varying degrees of cross-linking, which allows for volume and tissue integration, restoring natural expressions in dynamic areas and soft contours.[4-7]

HA_{RC} was first approved in the EU in 2009, where it is registered as Restylane Volyme. Depending on the area to be treated and the tissue support, HA_{RC} is designed for deep injections into the supraperiosteal zone or subcutis to augment the volume of facial tissues.[8] It is intended to be used for correction of facial volume and is an optimal gel for restoring a soft contour and natural looking volume. This gel has previously been investigated for full-face correction of volume loss in an open-label study with 18 months follow-up[9] and also in another open-label study to assess performance and tolerance of the product in patients with cheek volume loss.[10]

The purpose of this study was to evaluate effectiveness and safety of treatment with HA_{RC} for cheek augmentation and correction of midface contour deficiencies compared to a comparator product (Juvéderm Voluma XC), hereafter referred to as Control. Also, the choice of needle or cannula for midface injections depends on the physician's experience and preference, and in order to investigate both options, a second study group was included to assess HA_{RC} when used with a small blunt-tip cannula or a needle.

MATERIALS AND METHODS

Subjects and Treatment

This was a randomized, evaluator-blinded, parallel-group, comparator-controlled, multi-center study (NCT03700047). Group A subjects were randomized 2:1 to treatment with HA_{RC} or Control, with all treatments administered using the co-packed 27G needle. Group B subjects were treated with HA_{RC} using a randomized split-face design (1:1 right:left) where one cheek was treated using a small blunt tip cannula and the other cheek using the co-packed 27G needle. Eligible subjects were over the age of 21 and had mild to substantial loss of midface fullness (Medicis Midface Volume Scale [MMVS] score 2-4)[11] on each side of the face. Each cheek in a single subject could differ 1 grade on the MMVS. At least 15% of the subjects were to have a Fitzpatrick Skin Type (FST) IV–VI, with at least 10% having FST V–VI. Subjects provided a written informed consent for participation in the study. Main exclusion criteria included known or previous allergies/hypersensitivity to injectable hyaluronic acid (HA) gel, gram-positive bacterial proteins or lidocaine. Subjects were treated according to their randomization with a sufficient amount to achieve optimal correction of the midface defined as at least 1-grade improvement from baseline on the MMVS, and the best correction that could be achieved according to treating investigator and subject. Touch-up was allowed after 4 weeks if determined as necessary. The volume was recommended not to exceed 6 mL per treatment session (maximum total injection volume including touch-up: 12 mL). Study product was injected into the midface at the supraperiosteal to subcutaneous layer inferior to the maxillary prominence, superior to the plane of nasal alae, including the area from the lateral canthus to the medial canthus and lateral to the nose on the subject's right and left sides.

Study Assessments

Primary study objective was to demonstrate non-inferiority of HA_{RC} versus the Control in cheek augmentation. Blinded evaluators used the MMVS to compare change from baseline in midface fullness at 12 weeks after the last injection. Other assessments included 1) effectiveness of HA_{RC} in cheek augmentation, based on blinded evaluation of MMVS responder rate (at least 1-grade improvement on both sides of the face); 2) aesthetic improvement of overall appearance based on the Global Aesthetic Improvement Scale (GAIS) defined as at least improved, determined by subject and treating investigator separately; 3) subject satisfaction using the FACE-Q™ Satisfaction with Outcome and FACE-Q Satisfaction with Cheeks questionnaires, from which the overall Rasch transformed score was determined; 4) change from baseline in cheek volume using digital 3D photography and 5) improvement in cheek augmentation determined by an independent photographic reviewer using random, blinded pairings of baseline and post-treatment photographs. Safety assessments included adverse events collected throughout the study, and pre-defined symptoms including bruising, redness, tenderness, swelling, pain, and itching recorded in a subject diary for 4 weeks following each injection. Follow-up visits to the clinic were made 12, 24, 36, and 48 weeks since last injection.

Statistical Analyses

Statistical analyses were performed using the SAS® system version 9.4. All effectiveness variables were analyzed based on the Intention-to-Treat (ITT) population (all subjects who were randomized), and the basis for safety analyses was the safety population (all subjects who were injected at least once). For Group A, the primary effectiveness analysis of change from baseline in MMVS at week 12 was a test of non-inferiority of HAR_{RC} to Control. Difference (across sides) between treatments means (Control – HA_{RC}), and the corresponding 2-sided 95% confidence interval (CI) were calculated and used for assessing non-inferiority, which was demonstrated if the upper limit of the CI was below the pre-determined margin of 0.5. For Group B, the primary effectiveness analysis was a test of non-inferiority of HA_{RC} using cannula to needle. The change from baseline in MMVS for the treatment using cannula and needle was analyzed by calculating the two-sided 95% CI around the mean paired difference (cannula – needle) at week 12. Noninferiority was established if the upper limit of the CI was below the non-inferiority margin of 0.5 units. Robustness of the results of Group A and Group B primary endpoints was investigated across FST skin type. Other endpoints for effectiveness (MMVS responders, GAIS, subject satisfaction, independent photographic review, and cheek volume from 3D photography) were analyzed descriptively. Safety endpoints for Group A and Group B were analyzed descriptively and presented separately. Group B results were summarized separately for the needle and cannula sides of the face.

RESULTS

Demographics and Treatment

In Group A, 142 subjects were randomized to HA_{RC} and 68 to Control. A total of 60 subjects were included in Group B (split-face treatment with HA_{RC}). The FST enrollment goal of the study was met. Baseline demographics in Group A and Group B were similar; mean age was 53 and 52 years, respectively, and the majority of subjects were female (89% in Group A and 92% in Group B (Table 1). A majority of all subjects in Group A (57-61%) and Group B (52-57%) had MMVS score 3, ie moderate loss of midface fullness at baseline (Table 1). For Group A, total mean volume injected for initial and touch-up treatment was statistically less for HA_{RC} than Control (4.3 mL and 4.9 mL, respectively, P=0.0134, post-hoc calculation). Total mean volume HA_{RC} injected for Group B (initial and touch-up treatment) was 4.2 mL (2.10 mL for cannula and 2.07 mL for needle). Injection characteristics in terms of injection depth, method, and tool, are summarized in Table 2.

Effectiveness

The primary endpoint comprising non-inferiority of HA_{RC} to Control for cheek augmentation and correction of midface contour deficiencies was established based on MMVS change from baseline at week 12, as assessed by blinded evaluation

TABLE 1.

Baseline Characteristics				
	Group A: HA_{RC}	Group A: Control	Group A: Overall	Group B: HA_{RC}
Age (years)				
Mean (SD)	53 (13)	55 (12)	53 (12)	52 (10)
Min, Max	24, 79	24, 80	24, 80	28, 73
Gender (%)				
Female; Male	91; 9	85; 15	89; 11	92; 8
Race (%)				
White	88.0	83.8	86.7	73.3
Black or African American	5.6	10.3	7.1	21.7
Asian	1.4	1.5	1.4	5.0
American Indian or Alaska Native	1.4	0	1.0	0
Native Hawaiian or Other Pacific Islander	0.7	1.5	1.0	0
Other	2.8	2.9	2.9	0
Ethnicity (%)				
Hispanic or Latino	14.8	7.4	12.4	13.3
Not Hispanic or Latino	85.2	92.6	87.6	86.7
Fitzpatrick Skin Types (%)				
I	2.8	1.5	2.4	1.7
II	28.2	33.8	30.0	15.0
III	45.8	41.2	44.3	45.0
IV	12.0	13.2	12.4	13.3
V	5.6	4.4	5.2	5.0
VI	5.6	5.9	5.7	20
MMVS score* Left midface (%)				
2	33.8	26.5	31.4	31.7
3	59.2	63.2	60.5	56.7
4	7.0	10.3	8.1	11.7
MMVS score* Right midface (%)				
2	33.1	36.8	34.3	36.7
3	59.2	52.9	57.1	51.7
4	7.7	10.3	8.6	11.7

*Blinded evaluator assessment

TABLE 2.

Injection Characteristics			
	Group A: HA_{RC}	Group A: Control	Group B: HA_{RC} Needle vs cannula
Injection depth	Almost all injections were supraperiosteal (99%). Additionally, approximately half of the subjects received subcutaneous injections (53%)	Supraperiosteal: 97% Subcutaneous: 52%	Supraperiosteal was the most common injection depth for both needle (100%) and cannula (88%). In addition, subjects received subcutaneous injections with needle: (39%) and cannula: (68%)
Injection method	Depot was the most popular injection method (72%) followed by serial puncture (62%)	Depot: 70% Serial puncture: 62%	Cannula: Linear antegrade (100%), fan (73%) Needle: Depot (53%), serial puncture (53%)
Injection tool	The provided 27G ½" ultra-thin wall needle	--	The provided 27G ½" ultra-thin wall needle AND A 27G (71%), 1.5-inch (76%) cannula was most commonly used

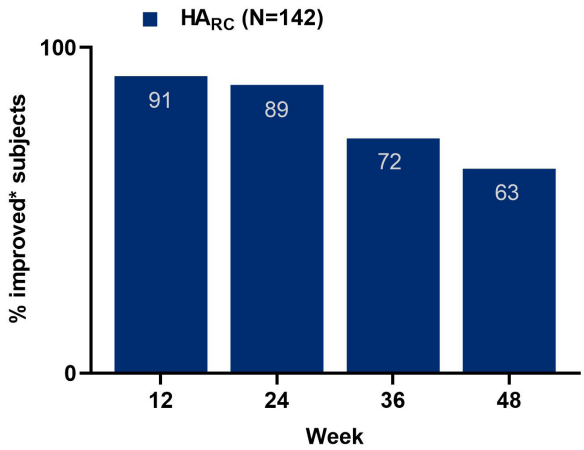
Note: Subjects may have experienced more than one injection depth and/or method.

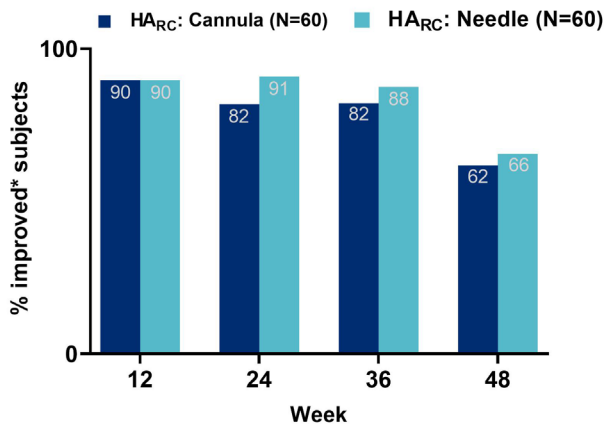
and the corresponding 2-sided 95% CI; mean difference HA_{RC}-Control: -0.1 (95% CI: -0.22, 0.06). Subgroup analyses by FST (I–III, IV, and V–VI), race and ethnicity confirmed the robustness of the primary analysis. In addition, midface fullness improvement was comparable with both needle and cannula devices; week 12 MMVS mean change from baseline: -1.3 (needle); -1.3 (cannula), 95% CI for the difference: -0.15, 0.05.

A majority of Group A HA_{RC} subjects were assessed as MMVS responders on both sides of the face throughout the study, ranging from 91% at week 12 to 63% at week 48 (Figure 1). Also, no notable difference was observed at any visit in MMVS response for Group B subjects injected using needle vs cannula (Figure 1). In order to show the versatility of the product, representative subject photographs of a male and female subject with different ethnicities, treated with HA_{RC} are presented in Figure 2 and Figure 3, respectively.

In Group A, subject assessment of aesthetic improvement in the midface using GAIS showed high levels of improvement that was maintained 48 weeks after treatment (95%-77%), and similar improvement was observed from assessments made by treating investigators (Figure 4). GAIS scores in Group B were similar for HA_{RC} injected by cannula (91–97%) and needle (89–97%) according to subject assessments, in line with treating investigators that scored 93–100% of subjects as improved during the study, with no differences between the injection tools (Figure 4).

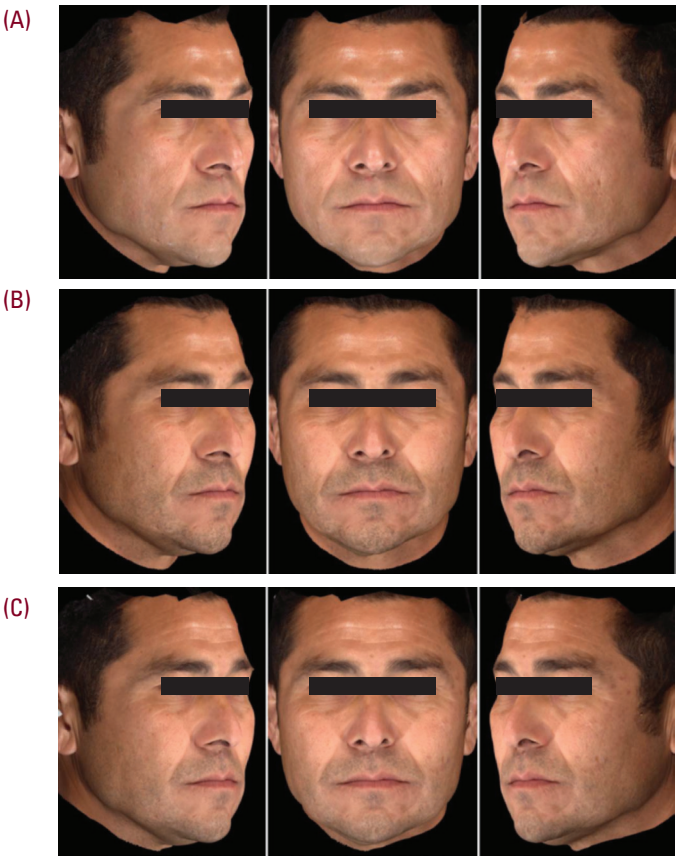
FIGURE 1. MMVS responder rate, ITT population, Group A (left) and Group B (right).





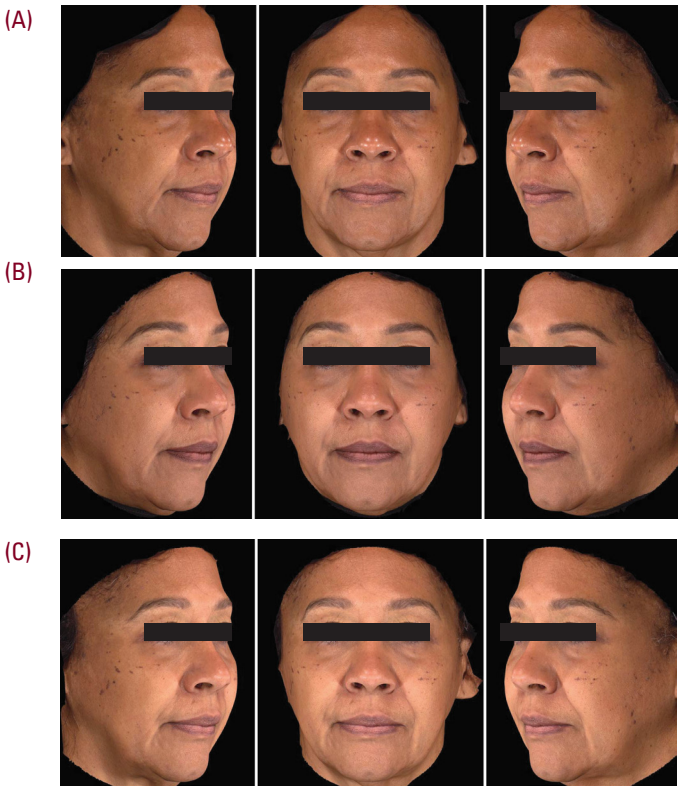
*Defined as a subject with at least 1-point improvement from baseline on both sides

FIGURE 2. Subject photographs (A) baseline; (B) week 12; (C) week 48.



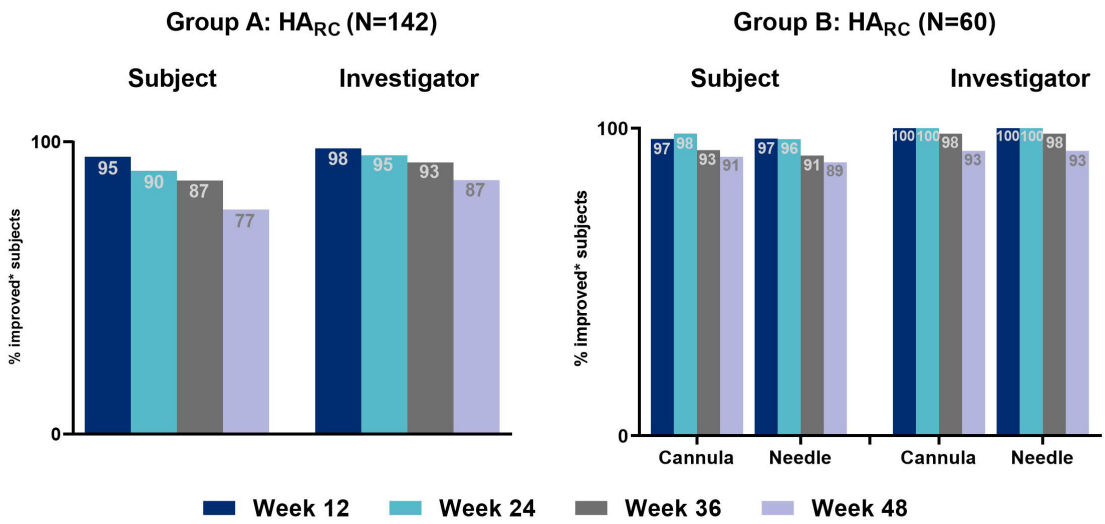
Male subject from Group A, age 51, FST V, at baseline and after treatment with 1.5 mL HA_{RC} on the right side of the face and 2.5 mL HA_{RC} on the left side at initial treatment. Touch-up was 0.5 mL on each side. The subject was rated as having moderate loss of midface fullness (MMVS: 3) at baseline, fairly full midface (MMVS: 1) at week 12 and mild loss of midface fullness (MMVS: 2) at week 48.

FIGURE 3. Subject photographs (A) baseline; (B) week 12; (C) week 48.



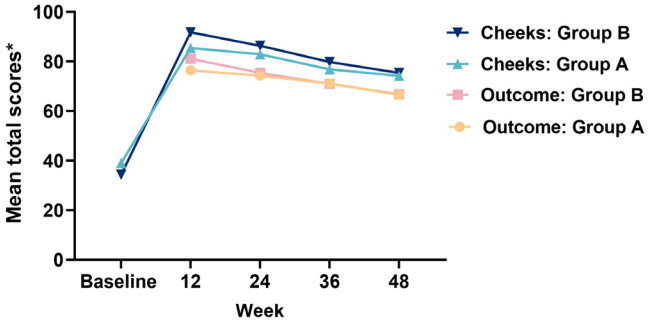
Female subject from Group B age 64, FST VI, at baseline and after treatment with 1.5 mL HA_{RC} on the right side of the face using needle and 1.5 mL HA_{RC} on the left side using cannula at initial treatment. Touch-up was 1.0 mL on each side. The subject was rated as having moderate loss of midface fullness (MMVS: 3) at baseline, and mild loss of midface fullness (MMVS: 2) at week 12 and week 48.

FIGURE 4. GAIS improvement, Group A HA_{RC} subjects, and Group B, ITT population.



*Defined as Improved/Much improved/Very much improved.

FIGURE 5. Subject-assessed FACE-Q satisfaction with cheeks and satisfaction with outcome: Group A HA_{RC} N=142; Group B HA_{RC} N=60, ITT population.



*Higher total scores reflect a better outcome ranging from 0 (worst) to 100 (best).

Subjects receiving HA_{RC} for cheek augmentation were satisfied with the outcome following treatment and remained so throughout the study, as per mean Rasch Transformed FACE-Q total scores (range, 0–100). Subject satisfaction with appearance of their cheeks, and satisfaction with treatment outcome ranged from 74–85 (baseline: 39) and 67–76, respectively for Group A HA_{RC} subjects. Group B subjects had similar level of satisfaction regardless of injection tool; 75–92 (baseline: 34) and 67–81, respectively (Figure 5).

By week 48, a majority of HA_{RC} subjects in Group A were assessed as having improvement in cheek augmentation by independent photographic review (left side: 66%; right side: 65%). For Group B, improvement was comparable between HA_{RC} injected by cannula and by needle.

For cheek volume calculated using digital 3D photography, the mean change from baseline in HA_{RC} subjects decreased over time and ranged from 3.3–2.7 mL for left side and 3.2-2.6 mL for right side of the face, across all timepoints. There was no notable difference in the volume increase between injection tools (needle vs cannula) at any visit.

Safety

As expected, most subjects in both group A (HA_{RC} and Control) and Group B (cannula and needle) reported pre-defined symptoms through subject diaries. The majority generally lasted 1–3 days.

Adverse events related to treatment or injection procedure included 21 (14.9%) HA_{RC} subjects and 13 (19.1%) Control subjects who experienced 57 and 79 related AEs, respectively (Table 3). No serious related adverse events were reported. In Group A, most related adverse events were classified as mild;

TABLE 3.

Related Adverse Events ≥3.0% in Either Treatment Group by Severity. Group A (Safety Population)

		HA_{RC} (N=141)		Control (N=68)	
		Subjects n (%)	Events	Subjects n (%)	Events
Subjects with any related adverse event	Total	21 (14.9)	57	13 (19.1)	79
	Mild	18 (12.8)	53	8 (11.8)	72
	Moderate	3 (2.1)	4	4 (5.9)	6
	Severe	0	0	1 (1.5)	1
Implant site pain	Total	6 (4.3)	16	9 (13.2)	36
	Mild	5 (3.5)	15	7 (10.3)	33
	Moderate	1 (0.7)	1	2 (2.9)	3
Implant site bruising	Total	5 (3.5)	5	1 (1.5)	1
	Mild	4 (2.8)	4	1 (1.5)	1
	Moderate	1 (0.7)	1	0	0
Implant site oedema	Total	3 (2.1)	6	5 (7.4)	15
	Mild	3 (2.1)	6	4 (5.9)	13
	Moderate	0	0	1 (1.5)	2
Implant site erythema	Total	2 (1.4)	6	5 (7.4)	11
	Mild	2 (1.4)	6	4 (5.9)	10
	Moderate	0	0	1 (1.5)	1
Implant site hemorrhage	Total	1 (0.7)	2	3 (4.4)	4
	Mild	1 (0.7)	2	3 (4.4)	4

HA_{RC}: 93%, Control: 91%. There was one event of severe implant site swelling in the Control group that resolved with no action taken, duration was 3 days. Median duration of related adverse events in Group A was 3 days for both HA_{RC} and Control. The most commonly reported related adverse events following treatment with HA_{RC} was pain (6 subjects [4.3%]) and bruising (5 subjects [3.5%]). The most reported related adverse events for both HA_{RC} and Control is displayed in Table 2.

In Group B, only 2 subjects (3.4%) experienced 1 related adverse event each (presyncope and catheter site erythema), both were mild.

DISCUSSION

This was a randomized, comparator-controlled, evaluator-blinded, multi-center study to evaluate the effectiveness and safety of HA_{RC} for cheek augmentation and correction of midface contour deficiencies (Group A); the study also evaluated HA_{RC} when injected by cannula vs. needle (Group B). This was the first HA_{RC} study conducted in the US, and subjects from all Fitzpatrick skin types were included. Subjects who were rated as MMVS grade 2–4 (mild to severe midface volume loss) at baseline were injected per their randomized allocation. In Group A, HA_{RC} subjects required less injected product than Control subjects to achieve optimal aesthetic results. Injection with needle and cannula in Group B required very similar volume of HA_{RC}.

The study met its primary objective demonstrating non-inferiority between HA_{RC} and Control, assessed by a blinded evaluator. In addition, a majority of subjects injected with HA_{RC}, both from Group A and B, achieved a 1-grade or greater MMVS improvement from baseline at all study timepoints until Week 48. The effectiveness of HA_{RC} was further supported by high levels of aesthetic improvement based on GAIS, as assessed by subjects themselves and by treating investigators, and many Group A and Group B subjects reported satisfaction with their cheeks and with treatment outcome from FACE-Q scores. It was also visible from blinded pairings of baseline and post-treatment photographs that most subjects had improvement in cheek augmentation by independent photographic review.

Quantification of cheek volume enhancement after HA_{RC} treatment was also confirmed by 3D photography; the largest change from baseline was 3.3 mL and decreased thereafter as the product degraded.

Treatment with HA_{RC} was well tolerated and fewer subjects reported related adverse events than in the Control group. Also, only 3% of Group B subjects reported related adverse events. HA_{RC} has previously been studied for full-face correction of volume loss in an open-label study with 18 months follow-up.[9] In that study, more than two thirds of subjects were improved from baseline at study end and the treatment was well tolerated with no significant safety concerns. HA_{RC} has also been investigated in another open-label study to assess performance and tolerance of the product in patients with cheek volume loss.[10] The results showed a majority of subjects with maintained cheek volume up to six months after treatment.

Injection technique is in many cases based on the injector's preference and experience, and the data from Group B in this study where subjects were injected using a split-face design with one cheek treated using cannula and the other cheek using needle, showed comparable effectiveness between injection tools and an overall good safety profile. Cannula injections have been reported to result in reduced bruising compared to needle,[12,13] this could not be confirmed in this study as no bruising was reported for either injection tool in Group B. Midface treatment using a small blunt-tip cannula with another filler from the Restylane range of products, Restylane Lyft, has previously been investigated and shown to be well tolerated for cheek augmentation and correction of age-related midface contour deficiency, and with visible aesthetic improvement.[14]

In conclusion, HA_{RC} was non-inferior to Control for correction of midface fullness at 12 weeks after last injection. This study also showed that midfacial treatment using HA_{RC} was well tolerated and effective, with high levels of aesthetic improvement and subject satisfaction for up to 48 weeks.

DISCLOSURES

Dr Jones is an investigator for Galderma, Allergan, Merz, and Revance; Dr Baumann is an investigator for Galderma; Dr Moradi is an investigator and consultant for Galderma; Dr Shridharani is an investigator and consultant for Allergan, Endo, Evolus, Galderma, and Prollenium; Dr Palm is an investigator, speaker, paid advisory board member, and consultant for Galderma; Dr Teller is an investigator for Galerma; Dr Taylor is an investigator for Galderma; Dr Kontis is an investigator for Galderma, Revance, and Allergan and a consultant for Revance; Dr Chapas is an investigator for Galderma and received research grant from Galderma R&D, LLC; Dr Kaminer is an investigator for Galderma and a consultant for L'Oreal, Revance, Allergan, Arctic Fox, and Soliton; Dr Bank is an investigator and speaker for Galderma, Allergan, Evolus, Johnson & Johnson, and Merz, and a consultant for Allergan, Johnson & Johnson, Croma Pharma, Merz, Galderma, and Evolus; Dr Beer is an investigator for Galderma; Dr Hooper is an investigator, speaker, paid advisory board member, and consultant for Galderma.

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