A RANDOMIZED, CONTROLLED, EVALUATOR-BLINDED, MULTI-CENTER STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF HAKYS VERSUS A CONTROL IN THE AUGMENTATION OF SOFT TISSUE FULLNESS OF THE LIP

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INTRODUCTION

- HA_{RK} is an injectable hyaluronic acid gel filler designed with technology that allows for natural, flexible movement in dynamic areas,[1] and is approved outside of the US for restoration or augmentation of lip volume.
- Among the injectable hyaluronic acid gel fillers that are available for lip augmentation and correction of perioral rhytids in the US, HA_{JV} was selected as the control as it was most recently approved at the time of the study.

Table 1. Outline of study details

• Study design	• Randomized, controlled, evaluator-blinded multi-center study (NCT03320824) • 14 centers (273 subjects) in the US
• Assessments	• Lip fullness: MLFS[2] • Wrinkle severity: Wrinkle Assessment Scale (WAS)[3] • Aesthetic improvement of lips: Global Aesthetic Improvement Scale • Subject satisfaction with lips and appraisal of lip lines: FACE-Q scales[4] • Adverse events • Subject diary entries of local tolerability symptoms: 30-day diary
• Treatment	• HA_{RK} or control (randomized 2:1) on Day 1 • Optional: - Touch-up Week 4 after initial injection - Re-treatment with HA_{RK} Week 48 after last injection
• Assessment schedule	• Assessments were done at screening/baseline, and at 72 hours and Weeks 2, 4, 8, 16, 24, 32, 40 and 48 after last injection - Also at 72 hours and at Weeks 2 and 4 after optional re-treatment

Table 3. Change from baseline in lip fullness[a] at 8 weeks after last injection

Intention-to-treat population	HA_{RK} (N=183)	Control (N=87)
Upper lip		
Mean (standard deviation)	1.8 (0.98)	1.7 (0.90)
95% confidence interval mean of (Control – HA_{RK})	(-0.31, 0.18)	
Lower lip		
Mean (standard deviation)	1.8 (0.98)	1.8 (0.85)
95% confidence interval mean of (Control – HA_{RK})	(-0.32, 0.16)	
Per protocol population	**HA_{RK} (N=176)**	**Control (N=85)**
Upper lip		
Mean (standard deviation)	1.8 (0.96)	1.7 (0.91)
95% confidence interval mean of (Control – HA_{RK})	(-0.32, 0.17)	
Lower lip		
Mean (standard deviation)	1.8 (0.98)	1.8 (0.86)
95% confidence interval mean of (Control – HA_{RK})	(-0.30, 0.19)	

[a]Blinded Evaluator assessment of upper and lower lip MLFS score

OBJECTIVES

PRIMARY OBJECTIVES:

- To demonstrate non-inferiority of HA_{RK} versus a control in lip fullness augmentation at Week 8 after last injection (blinded evaluation).
  - Determined by change from baseline in Medicis Lip Fullness Scale (MLFS) score, assessed by blinded evaluation of the upper and lower lip separately.
  - Non-inferiority was established if the confidence interval was entirely below 0.5 for the upper and lower lip separately in both study populations.

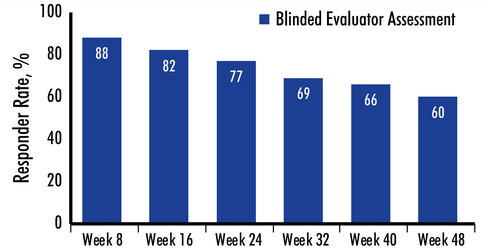
SECONDARY OBJECTIVE:

- To evaluate the effectiveness and safety of HA_{RK} in lip fullness augmentation and correction of upper perioral rhytids.

METHODS

- Subjects aged ≥22 years with 'very thin' or 'thin'[2] upper and lower lips were eligible for this 48-week Phase III study (Table 1).
- ≥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 wrinkles' to 'very deep wrinkles'.[3]

Figure 1. Lip Fullness Responder Rates[a]



[a]Percent subjects with ≥1-point improvement from baseline in upper and lower lip MLFS score.

Table 2. Total (initial and touch-up) mean volumes

	Lips (upper and lower)		Upper perioral rhytids	
	n	Mean volume	n	Mean volume
HA_{RK}	185	1.82 mL	56	0.36 mL
Control	88	2.24 mL	28	0.47 mL

REFERENCES

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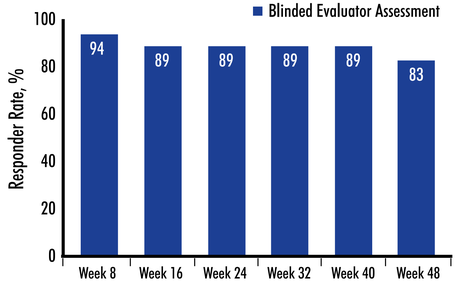
RESULTS

EFFECTIVENESS

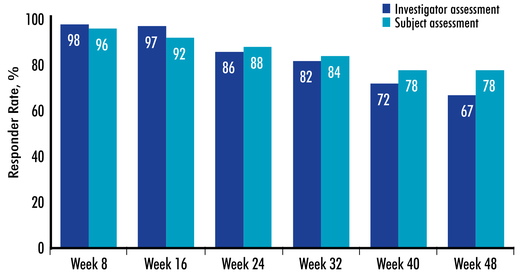
- Lip fullness
  - Primary objective was met: HA_{RK} was non-inferior to control in lip fullness augmentation at 8 weeks after last injection (Table 3).
    - Confidence intervals for both study populations were below the pre-determined non-inferiority margin of 0.5.
  - HA_{RK} responder rates are shown in Figure 1.
- Wrinkle improvement – upper perioral rhytids
  - HA_{RK} responder rates are shown in Figure 2.
- Aesthetic improvement of lips (Figure 3)
  - HA_{RK} responder rates were 96% and 98% (Week 8) and 67% and 78% (Week 48; Figure 4).
- Subject satisfaction (FACE-Q Rasch mean total scores)
  - Lips
    - Satisfaction increased from baseline (28.1) to Week 8 (83.3) after treatment with HA_{RK} and remained higher than baseline through Week 48 (66.3).
  - Appraisal of lip lines
    - Lines were less bothersome after treatment with HA_{RK}; satisfaction increased from baseline (41.8) to Week 8 (76.0) after treatment with HA_{RK} and remained higher than baseline through Week 48 (65.8).

Figure 2. Wrinkle Improvement Responder Rates[a]



[a]Percent subjects with ≥1-point improvement from baseline in upper perioral rhytids WAS score

Figure 4. Aesthetic Improvement Responder Rates[a]



[a]Percent subjects with a GAIS score of 'improved', 'much improved' or 'very much improved' for both upper and lower lips.

SAFETY RESULTS

- Treatment-emergent adverse events (TEAEs)
  - None reported for most subjects in either group (HA_{RK}: 61%, control: 65%) throughout Week 48.
  - Most commonly reported treatment-related TEAEs:
    - Injection-site mass (HA_{RK}: 10%; control: 11%)
    - Injection-site bruising (HA_{RK}: 8%; control: 10%)
    - Injection-site nodule (HA_{RK}: 5%; control: 7%)

  All of these were mild, except one event of moderate injection-site bruising.
- Subject diary entries of local tolerability symptoms
  - Symptoms typically lasted ≤7 days; most (≥67% in both groups) were rated as tolerable.
  - Most commonly reported: tenderness, swelling and lumps/bumps

Figure 3. Subject Photographs

Lip appearance of a 31-year old woman at Baseline, and at Weeks 8 and 48 after injection of HA_{RK} (total volume injected: 1.0 mL in upper lip, 1.5 mL in lower lip).

SUMMARY

- HA_{RK} was non-inferior to the control in lip fullness augmentation at 8 weeks after last injection
- HA_{RK} effectiveness in terms of lip fullness improvement and correction of upper perioral rhytids persisted in ≥60% of subjects at Week 48 after the last injection
- HA_{RK} effectiveness was supported by a high degree of aesthetic improvement and subject satisfaction
- HA_{RK} was well-tolerated
- Considering both effectiveness and safety data, HA_{RK} was well-suited for lip fullness augmentation and correction of upper perioral rhytids

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