

Two Randomized Controlled Trials of Hyaluronic Acid Fillers for the Correction of Nasolabial Folds

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Background: YVOIRE Classic s (YC) and Restylane (RES) have similar rheological properties, which suit mid-dermis injection, while the rheological properties of YVOIRE Volume s (YV) are comparable to those of Perlane (PER), which suit deep dermis injection to treat deep wrinkles. Two similarly designed studies aimed to evaluate the performance and safety of YC and YV injected into the nasolabial folds (NLFs).

Methods: These were split-face designed, evaluator-blind, noninferiority studies. Fifty-eight subjects with moderate-to-severe NLFs were enrolled in the first study and treated with YC and RES, and 57 subjects were enrolled in the second study and treated with YV and PER. The Wrinkle Severity Rating Scale ranged from 1 (no visible fold) to 5 (extremely deep and long folds), and subject satisfaction was evaluated.

Results: The least squares mean Wrinkle Severity Rating Scale scores (standard error) at week 26 were 2.56 (0.09) for both YC- and RES-treated NLFs and 2.89 (0.08) and 2.91 (0.08) for YV- and PER-treated NLFs, respectively. The difference between the groups was 0 and 0.02, and the lower limit of its 95% confidence interval was -0.0725 and -0.0125, which was greater than the predefined margin (-0.29), proving the noninferiority of YC and YV to RES and PER, respectively. The safety profiles and subject satisfaction of YC and YV were similar to those of RES and PER, respectively.

Conclusion: YC is comparable to RES and YV is comparable to PER in terms of performance and safety profiles, with NLF-correcting effects lasting for up to 26 weeks. (*Plast Reconstr Surg Glob Open* 2020;8:e2975; doi: [10.1097/GOX.0000000000002975](https://doi.org/10.1097/GOX.0000000000002975); Published online 23 July 2020.)

INTRODUCTION

Nasolabial folds (NLFs) appear to be one of the typical clinical manifestations of facial aging.^{1,2} The NLF is a distinct fusion plane separating the cheek from the upper lip,^{3,4} and it becomes more prominent with age, due to loss of moisture and volume.

In the past, surgical procedures have been performed for facial rejuvenation, but as interest in noninvasive procedures has increased, dermal fillers have become popular. Dermal fillers provide volume and skin structure that surgical procedures are not capable of⁵ and restore the youthful appearance of an aging face by filling out folds and by correcting wrinkles.⁶ Hyaluronic acid (HA)-based fillers are the most popular choice of dermal fillers.⁷⁻⁹ HA is a normal component of most tissues, including the dermis,¹⁰ and HA-based fillers provide structural properties similar to those of native tissue and have excellent biocompatibility and good tissue integration.¹¹ The facial artery branches in the region of the NLF, in most cases, are located in the subcutaneous layer on the surface of facial muscles; therefore, it is best to place the injection into the

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Both studies (HACL008 and HACL009) were conducted in accordance with the Korean Good Clinical Practice (KGCP), ISO GCP (ISO 14155), and the Declaration of Helsinki and were approved by the institutional review board of each study site.

Both studies were registered at ClinicalTrials.gov (identifier: NCT03738020 for HACL008 and NCT03738007 for HACL009).

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NLF in a more superficial plane, that is, dermal or immediately subdermal.¹² The ease of use and proven effectiveness and safety of HA dermal filler injection for the correction of facial wrinkles and folds account for the popularity of this minimally invasive cosmetic procedure.^{5,13,14}

A variety of HA products have been developed and are now commercially available, each with different rheological properties that allow for the treatment of problems ranging from superficial wrinkles to deep folds.^{6,9,15} The HA concentration, type and level of cross-linking, and particle size affect the properties of the final product.¹⁶ Increased HA concentration prolongs its longevity, but by itself is not the most important factor.¹⁰ The type and level of cross-linking have a greater effect on tissue persistence,¹⁰ and most market-leading HA dermal fillers are made by cross-linking HA polymers by conjugation with 1,4-butanediol diglycidyl ether (BDDE) to slow the degradation process.^{5,11} HA particle size and viscoelasticity influence the performance of HA dermal filler products and their suitability in different situations, with larger particle products best suited to fill deep facial folds and smaller particle products more suitable for more moderate folds.^{5,9} In addition, the elastic modulus G' , which is used to describe the hardness of a gel, also affects the performance of HA dermal fillers, and products with lower G' are suited in an area of thinner and softer skin,⁵ and products with a higher G' have a more volumizing effect and also require deeper placement.¹⁶ The deeper location of fillers allows for more gel injection with a larger bore needle and improves the effect of wrinkle correction,¹⁷ which also increases de novo collagen synthesis as a result of fibroblast stretching, replacing the HA, resulting in longer-lasting correction.¹⁰

YVOIRE Classic s (YC; LG Chem, Ltd., Seoul, Republic of Korea) and YVOIRE Volume s (YV; LG Chem, Ltd., Seoul, Republic of Korea) have high molecular weight (with an average molecular weight of 3 million Da), BDDE-cross-linked sodium HA dermal fillers produced using proprietary high concentration equalized cross-linking technology, increasing the probability of the molecules cross-linking with one another, resulting in higher mechanical properties.^{18,19} These complementary dermal fillers are used for the correction of moderate-to-severe facial wrinkles and folds, such as NLFs.^{18,20} The relatively large particles contained in YV and the accompanying increase in viscoelasticity make it an appropriate treatment choice for injection into the deep dermis to treat deep wrinkles and folds, whereas YC can be used for injection into the mid-dermis to treat more superficial wrinkles and folds.

Restylane (RES; Q-Med AB, Uppsala, Sweden) and Perlane (PER; Q-Med AB) are also biphasic (particle rather than gel type), BDDE-cross-linked, HA dermal fillers that are indicated for injection into the mid-to-deep dermis for the correction of moderate-to-severe facial wrinkles and folds.^{5,21,22} YC and RES have a similar viscoelasticity, while the rheological properties of YV are comparable to those of PER, which is a more viscoelastic version of RES.⁵ Here, we report the results of 2 pivotal randomized, split-face comparison designed studies evaluating the performance

and safety of YC versus RES and YV versus PER for the correction of NLFs.

METHODS

Subjects

Women aged 30–55 years with prominent NLFs with a Wrinkle Severity Rating Scale (WSRS) score of 3 or 4 on both sides were eligible for inclusion in this studies. Patients with active facial skin diseases were excluded from the study, as were subjects with a history of severe allergy, an autoimmune disorder, or hypersensitivity to HA or any of the excipients contained in the investigational devices. Neither study permitted enrollment of subjects who had used a local topical preparation (steroid and retinoid) within 4 weeks before the study, those who had undergone chemical peeling or a laser procedure, or those who had been injected with other biomaterials, including HA (see **table, Supplemental Digital Content 1**, which provides the complete list of inclusion and exclusion criteria in the HACL008 and HACL009 studies, <http://links.lww.com/PRSGO/B433>).

Study Design

Two similarly designed studies [HACL008 (clinicaltrials.gov identifier: NCT03738020) and HACL009 (clinicaltrials.gov identifier: NCT03738007)] were conducted at 2 and 3 study sites in the Republic of Korea from January to October 2009 and from March to December 2010, respectively. Written informed consent was obtained from all subjects. These studies were conducted in accordance with the Korean Good Clinical Practice, ISO GCP (ISO 14155), and the Declaration of Helsinki and were approved by the institutional review board of each study site.

An evaluator-blind split-face comparison study design was used in both studies, whereby the test device (YC or YV) was injected into one NLF on one side of the face and the active comparator (RES or PER) was administered into the NLF on the opposite side of the face. Study devices were assigned by the investigators according to a random sequence. The random sequence was generated by a statistician based on a block size of 4 using SAS (version 9.1; SAS Institute, Inc., Cary, N.C.), and sealed envelopes were used to implement the random sequence.

The 2 studies had identical treatment and follow-up schedules (**Fig. 1**). A touchup treatment could be performed 2 weeks after the initial injection at the treating investigator's discretion in cases that had no visible improvement of at least one grade on the 5-point WSRS or when the injection effect was not consistent in both NLFs. Subjects were followed up for 26 weeks after their final treatment.

Treatment

The HA concentration of YC and YV was 22 mg/mL and that of RES and PER was 20 mg/mL. The YC and RES prefilled syringes were equipped with a 30-gauge 12-mm needle, and the YV and PER syringes were equipped with a 27-gauge 12-mm needle. YC and RES injections were

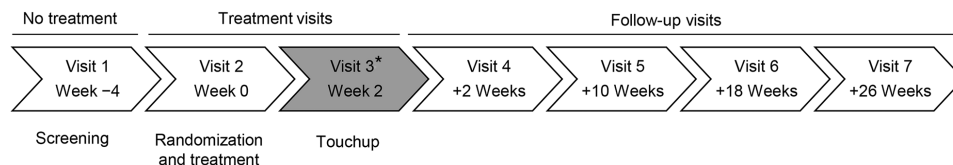


Fig. 1. Study flow for both HA CL008 and HA CL009. *Visit 3 is for touchup treatment if required and is not a mandatory visit.

administered into the mid-dermis, whereas YV and PER injections were administered into the deep dermis of the NLF. The injection volume was adjusted according to the length and depth of the wrinkles so that the maximal effect could be obtained for each subject, but the maximal injection volume for each side of the NLFs did not exceed 1.5 mL.

Assessments

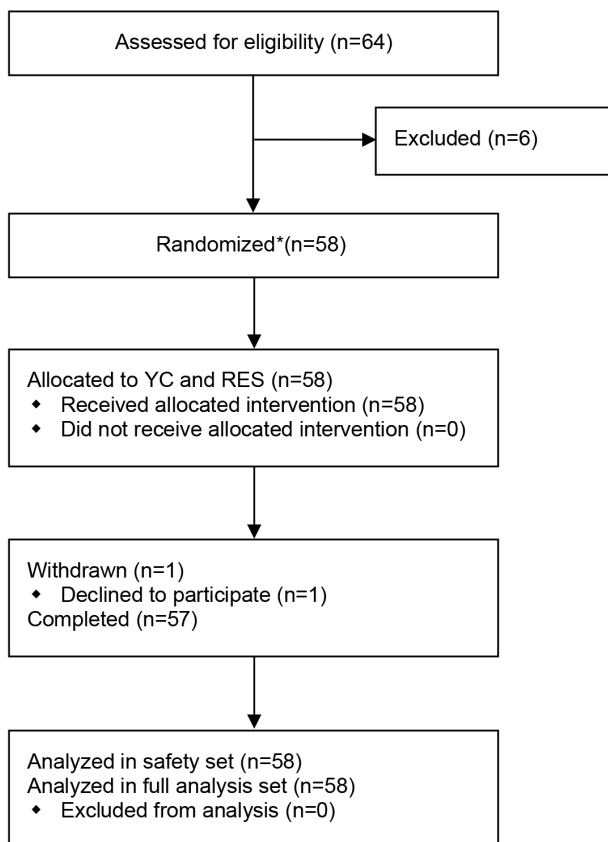
Performance was evaluated using the WSRS and Global Aesthetic Improvement Scale (GAIS). The WSRS score ranges from 1 (no visible fold) to 5 (extremely deep and long folds),²³ and the GAIS score ranges from 3 (very much improved) to -1 (worse).²⁴ At each visit, images of the NLFs were taken for the WSRS evaluation, and they were assessed by the evaluating and treating investigators separately, all of whom underwent training

in WSRS evaluation in advance to ensure the quality of evaluation.

For both the studies, the primary endpoint was the mean WSRS score assessed by the evaluating investigator at week 26 after the final treatment. Secondary endpoints included the mean WSRS score at weeks 2, 10, and 18 after the final treatment, treatment responder rates (improvement in WSRS scores of at least 1 grade from baseline), and subject-assessed GAIS score at each time point.

Safety endpoints included adverse events (AEs; occurring throughout the 26-week follow-up period), including immediate-onset reactions (occurring within 30 minutes after treatment) and local reactions (occurring within 14 days after treatment). Solicited local reactions (pain, tenderness, swelling, redness, bruising, itching, papules, and pigmentation) were evaluated through the subjects' diaries.

HA CL008



HA CL009

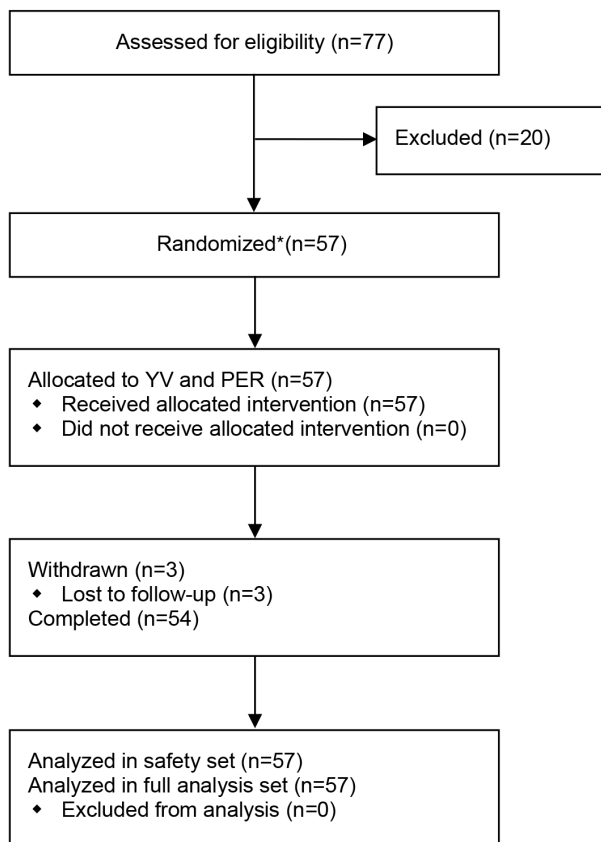


Fig. 2. Subject disposition. *Randomization was carried out to determine on which side of the face each treatment was administered.

Table 1. Demographic and Baseline Characteristics in the Full Analysis Set

	HACL008 (N = 58)		HACL009 (N = 57)	
	YC	RES	YV	PER
Age, y				
Mean (SD)	44.40 (5.82)		45.14 (6.63)	
Range		32–54		29–54
Weight, kg				
Mean (SD)	53.46 (5.80)		55.17 (6.46)	
Range		40–67		45–72
WSRS score*				
Mean (SD)	3.24 (0.43)	3.24 (0.43)	3.42 (0.50)	3.42 (0.50)
Range	3–4	3–4	3–4	3–4

*Assessed by the evaluating investigator.

Statistical Analyses

Accounting for a 20% dropout rate, it was calculated that, for each study, a sample size of 57 subjects was required to obtain 80% power at a significance level of 5% to demonstrate the non-inferiority of YC or YV relative to the respective comparator device for the mean WSRS score assessed by the evaluating investigator at week 26. Based on the results of a previous study of RES,^{22,25} a non-inferiority margin of -0.29 was chosen and a SD of 0.78 was assumed.

An intention-to-treat analysis was planned, and the main population for the performance analysis was the full analysis set, defined as subjects who received study treatment at least once and had at least 1 posttreatment WSRS assessment. For the primary performance variable, if the lower limit of the one-sided 95% confidence interval (CI) for the mean difference in WSRS scores at week 26 between the groups was >-0.29, the noninferiority of the test device (YC or YV) to the comparator (RES or PER) would be demonstrated. The CI for the least squares (LS) mean difference in WSRS scores at week 26 between the groups (comparator group versus test group) was estimated using the linear mixed model, with treatment as a fixed effect and subject as a random effect. For the secondary performance variables, descriptive statistics were summarized. The paired *t* test or Wilcoxon signed-rank test was used to compare the mean differences of continuous variables

between the groups, and McNemar’s test was performed to compare categorical variables.

Safety analyses were performed for the safety analysis set, defined as subjects who received study treatment at least once. Descriptive statistics were summarized, and McNemar’s test was used to analyze between-group differences in the incidence of local reactions.

RESULTS

Subject Disposition and Baseline Characteristics

A total of 58 and 57 subjects were enrolled and treated in HACL008 and in HACL009, respectively (Fig. 2). All subjects from both studies were evaluated for performance variables at least once and were therefore included in the full analysis set. In the HACL008 study, touchup treatment was performed on 37 subjects with YC and on 40 subjects with RES. In the HACL009 study, 26 subjects received both YV and PER touchup treatment. At baseline, the mean WSRS score was the same between the groups in both studies (Table 1).

WSRS Scores at Week 26

As determined by the evaluating investigator, the LS mean WSRS score (standard error) at week 26 was 2.56 (0.09) in both the YC and RES treatment groups in the HACL008 study (Fig. 3). In the HACL009 study, the LS mean WSRS score (standard error) at week 26 was 2.89 (0.08) in the YV group and 2.91 (0.08) in the PER group (Fig. 3). The lower limit of the one-sided 95% CI for the LS mean difference in the WSRS scores between the groups was -0.0725 in HACL008 and -0.0125 in HACL009, both of which were greater than the noninferiority margin of -0.29. YC was therefore noninferior to RES, and YV was noninferior to PER.

WSRS Scores over Time and Treatment Responder Rates

The mean WSRS scores assessed by the evaluating investigator showed a gradual increase from week 2 (2.40 in the YC group and 2.43 in the RES group; 2.68 in the

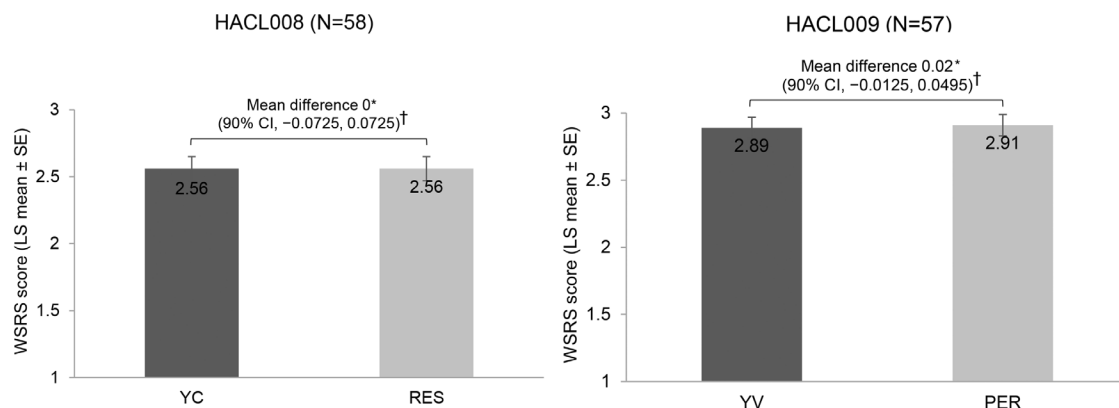


Fig. 3. Mean WSRS scores assessed by the evaluating investigator at week 26. *Mean difference = LS mean of comparator group – LS mean of test group. †Confidence interval for the difference in the LS mean WSRS scores between the groups was estimated using the linear mixed model to account for missing data. CI, confidence interval; LS mean, least squares mean; SE, standard error; WSRS, wrinkle severity rating scale.

YV group and 2.70 in the PER group) to week 26 (2.56 in both YC and RES groups; 2.89 in the YV group and 2.91 in the PER group) (Fig. 4A), and treatment responder rates gradually decreased from week 2 (81.03% in both YC and RES groups; 73.68% in the YV group and 71.93% in the PER group) to week 26 (56.14% in both YC and RES groups; 50.00% in the YV group and 48.15% in the PER group) (Fig. 4B). There were no significant differences between the groups at any of the time points in either study.

In addition, the mean WSRS scores assessed by the treating investigator also showed patterns similar to those assessed by the evaluating investigator (data not shown).

Subject-assessed GAIS

In both studies, the mean GAIS scores from week 2 to week 26 were >1 in both treatment groups (Fig. 4C), which revealed that the subjects considered NLFs to be improved compared with the NLFs pretreatment at all evaluation time points. There were no significant differences between the 2 groups at most time points, but at week 10 of the HACL009 study, the mean GAIS score of the YV group was significantly higher than that of the PER group (2.11 versus 1.85; $P = 0.0259$).

Safety

The overall incidence of AEs was 32.76% in the HACL008 study and 29.82% in the HACL009 study

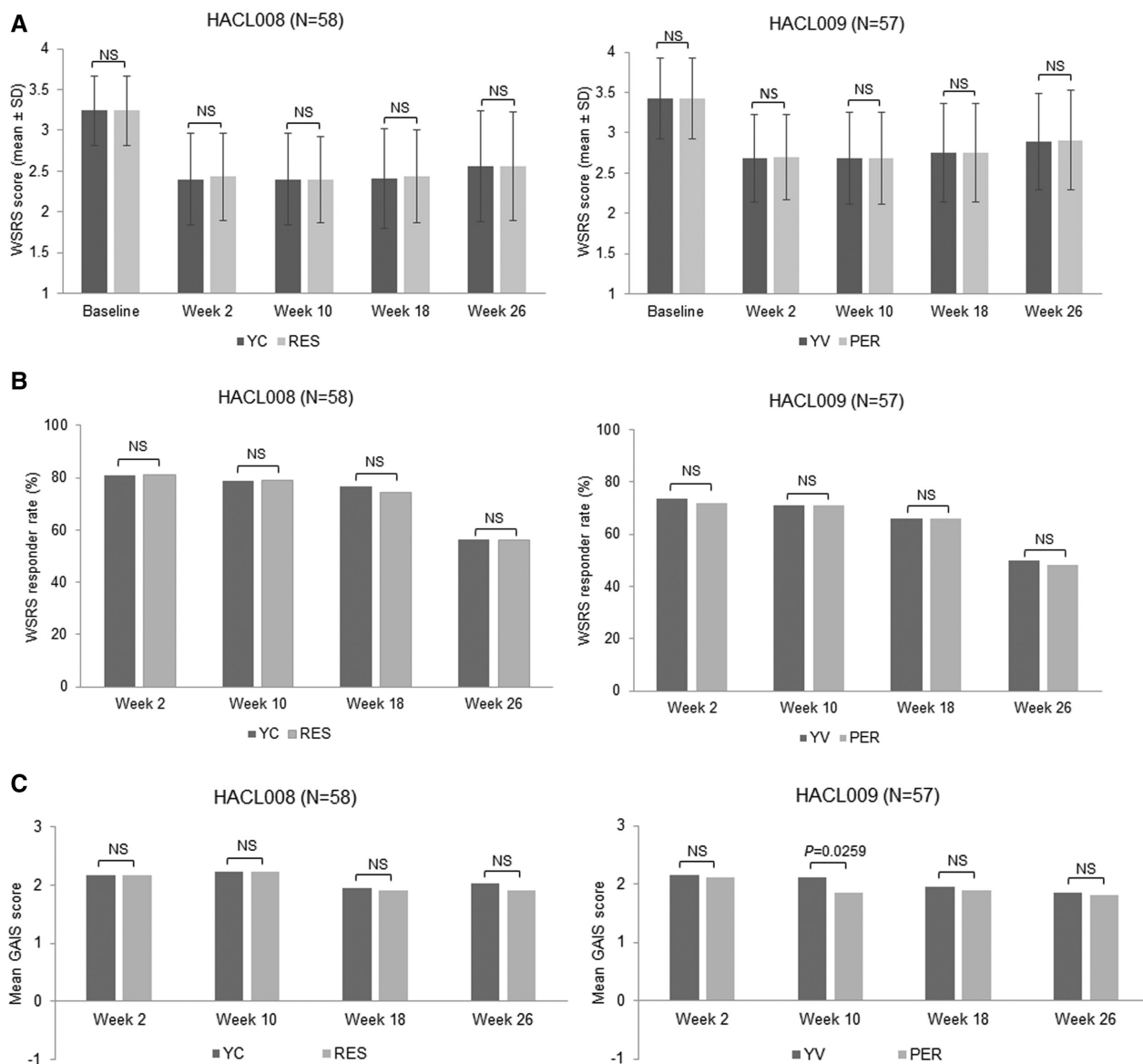


Fig. 4. Secondary performance results. A, Mean WSRS scores over time as assessed by the evaluating investigator. B, WSRS responder rates (improvement in WSRS scores by at least 1 grade from baseline) over time as assessed by the evaluating investigator. C, Mean GAIS scores over time as assessed by the subjects. The Wilcoxon signed-rank test was used to analyze between-group differences for mean WSRS scores and mean GAIS scores, and McNemar’s test was used for WSRS responder rates. GAIS, global aesthetic improvement scale; NS, not significant; WSRS, wrinkle severity rating scale.

Table 2. Incidences of Adverse Events in the Safety Set

	HACL008 (N = 58)		HACL009 (N = 57)	
	YC	RES	YV	PER
Overall adverse events	19 (32.76)		17 (29.82)	
Serious adverse events	0 (0.00)		1 (1.75)	
Treatment-related adverse events	3 (5.17)		0 (0.00)	
Local reactions*				
Pain	45 (77.59)	50 (86.21)	44 (78.57)	46 (82.14)
Tenderness	47 (81.03)	51 (87.93)	51 (91.07)	51 (91.07)
Swelling	46 (79.31)	46 (79.31)	41 (73.21)	43 (76.79)
Redness	42 (72.41)	43 (74.14)	31 (55.36)	36 (64.29)
Bruising	29 (50.00)	27 (46.55)	34 (60.71)	37 (66.07)
Itching	29 (50.00)	33 (56.90)	29 (51.79)	30 (53.57)
Papules	28 (48.28)	27 (46.55)	26 (46.43)	27 (48.21)
Pigmentation	30 (51.72)	29 (50.00)	27 (48.21)	30 (53.57)

Data are presented as the number of subjects (%) who experienced at least 1 adverse event.

*Local reactions that occurred within 14 days after the first injection are presented.

(Table 2). All reported AEs were of mild-to-moderate severity and resolved within the study period. Treatment-related AEs occurred in 3 subjects (5.17%) in the HACL008 study, all of which were local injection-site reactions (3 cases of erythema, 1 discoloration, and 1 nodule) that resolved without additional treatment. None of the AEs reported in the HACL009 study were considered to be related to the study treatment. One serious AE occurred in 1 subject (1.75%) only in the HACL009 study, which was reported as appendicitis and was not related to study treatment.

In both studies, the most frequently reported local reaction after the first injection was tenderness, followed by pain (Table 2). There were no significant differences between the groups for any incidence of local reactions in either study. Most local reactions were of mild-to-moderate severity and resolved within 14 days after treatment, and all other local reactions that did not recover during that period also recovered within the study period without additional treatment.

DISCUSSION

Our 2 randomized split-face comparison studies have shown that, in terms of WSRS score at week 26 after the final injection, the HA dermal fillers YC and YV are noninferior to RES and PER, respectively, for the correction of NLFs.

In addition, in both studies, there were no significant differences in the mean WSRS scores and treatment responder rates between the groups at each evaluation time point. Furthermore, the results of the subject-assessed GAIS scores indicated that subjects perceived NLF improvements throughout the 26-week follow-up period, regardless of the treatment (test or comparator device) received into the NLF, and remained satisfied with the NLF-correcting effect at week 26. The results of the primary and secondary endpoints showed similar patterns in each study, suggesting that the findings that YC and YV corrected the NLFs are reliable.

The performance of RES and PER for NLF correction is well established on the basis of extensive investigations in split-face designed, randomized controlled studies.^{26,27} In such studies, WSRS responder rates for the correction of NLFs at 6 months after treatment have ranged from approximately 70%–85% with RES and 63%–88% with PER,^{26–30} while those were comparatively low in our

studies, 56.14% with RES and 48.15% with PER. This difference between studies may be the result of differences in the timing of touchup treatment and/or the total volume injected into the NLFs. Consistent with the results of other studies, however, the WSRS responder rates in our studies reflected a gradual decline in performance over time, from week 2 to week 26, which was expected given the biodegradability of HA dermal fillers.²⁸

The AE profiles of YC and YV were similar to those of RES and PER in the HACL008 and HACL009 studies, respectively. Local injection-site reactions, which were commonly reported in our studies, are anticipated reactions to HA dermal filler injection.^{26,31–33} Tenderness was the most commonly reported local reaction in our studies, occurring in 91% of HACL009 study subjects with both YV and PER and in 81% of HACL008 study subjects with YC and 88% with RES. The incidence of local reactions of this magnitude is well within the range of those recently reported in RES/PER studies for the treatment of NLFs, in which injection-site reactions were reported in up to 50%–100% of subjects.^{27,29–31} AEs that were considered related to treatment occurred in a small proportion of subjects (5%) in the HACL008 study (all local injection-site reactions), and no treatment-related AEs were reported in the HACL009 study.

Different HA fillers are uniquely suited to specific indications and regions of the face.⁹ In addition to between-product differences in grades of BDDE cross-linking and HA raw materials, each HA dermal filler product has unique physical characteristics that influence rheology and can potentially affect performance and safety.^{5,9,34–36} As more HA dermal filler products are introduced into the global appearance medicine market, clinicians are encouraged to be familiar with the characteristics and appropriate uses of the different HA fillers.¹⁴ The 4 BDDE-cross-linked HA dermal fillers used in our 2 studies have comparable formulations, but the BDDE cross-linking technology used in the manufacture of YC and YV is different to that used in the manufacture of RES and PER.^{5,7,10,19,37} Compared with YC and RES, which are injected into the mid-dermis, YV and PER both contain relatively large particles resulting in greater viscoelasticity and are therefore better suited for injection into the deep dermis.^{5,7,10,16} Overall, the results of our studies showed that YC and YV are similarly effective and safe alternatives to RES and PER for the correction of moderate-to-severe NLFs.

Our findings are limited to NLFs and should not be generalized to other areas of the face. Although our studies were conducted in an Asian population, there have been no reported differences in the performance or safety of RES/PER used for NLF correction in Asian and non-Asian populations.^{27,29,30} We therefore expect that YC and YV will have similar risk–benefit profiles when used for NLF correction in Asian and non-Asian ethnic groups.

CONCLUSIONS

The HA dermal filler YC is comparable to RES and YV to PER in terms of performance and safety profiles when used to correct moderate-to-severe NLFs. The NLF-correcting effects of these products were maintained for up to 26 weeks after injection.

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