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 ORIGINAL ARTICLE

Safety and Effectiveness of Hyaluronic Acid Fillers With Lidocaine for Full-Face Treatment in Asian Patients

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ABSTRACT

Background: There is a need for further evaluation of hyaluronic acid fillers for aesthetic use in Asia, where treatment goals may differ from western countries.

Objective: To evaluate 24-month safety and effectiveness of two hyaluronic acid fillers with lidocaine when used for full-face aesthetic treatment in Asian patients.

Methods: This was a 24-month, evaluator-blinded, non-comparative, multi-center study. Female subjects were injected with 3-5 mL Restylane® Lidocaine and/or Restylane Lyft Lidocaine, manufactured using the NASHA™ technology, in 2–4 pre-defined areas; upper cheeks, nasolabial folds, temples, nose, and chin. A second treatment was performed after 12 months. Assessments included aesthetic improvement, subject satisfaction, assessment scales for upper cheeks and nasolabial folds, and safety (adverse events and subject diaries).

Results: One hundred subjects were included; total mean volumes were 4.7 mL and 3.1 mL at first and second treatment, respectively. At least 82% of subjects were rated as aesthetically improved over 24 months by subjects themselves and by investigators. Most subjects (73-90%) were satisfied with the treatment throughout the study. Upper cheek improvement 12 months after treatment was significantly higher after second treatment (≥69% of subjects) than after first treatment (≥38%), $P<0.0001$, Fisher's exact test. A total of 29 treatment related adverse events were reported by 16% of subjects, all were mild (79%) or moderate (21%) in intensity. Most commonly reported were pain and bruising. Tenderness was the most common diary record in all treatment areas.

Conclusion: Full-face treatments with the study products resulted in long-term aesthetic improvement, perceived by both subjects and investigators. Subject satisfaction was high and maintained over 24 months with one re-treatment. Repeated treatment of several facial indications showed a satisfactory safety profile.

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INTRODUCTION

Effectiveness and safety of Restylane® Lidocaine (HA_R; Galderma, Uppsala, Sweden) and Restylane Lyft Lidocaine (HA_{RL}), manufactured using the NASHA™ technology, have been evaluated in clinical studies mostly performed in North America and Europe.[1-7] Market research has indicated different treatment needs from clinical practice in Asia (data on file), making it important to collect data on aesthetic treatments in Asian populations. Also, it is of interest to collect additional data on repeated full-face treatments and long-term follow-up. With these factors in mind, the objective of this study was to provide documentation of long-term safety and effectiveness of HA_R and HA_{RL} when used for repeated full-face treatment in Asian patients. The study products are approved for use in Taiwan, where the study was conducted.

METHODS

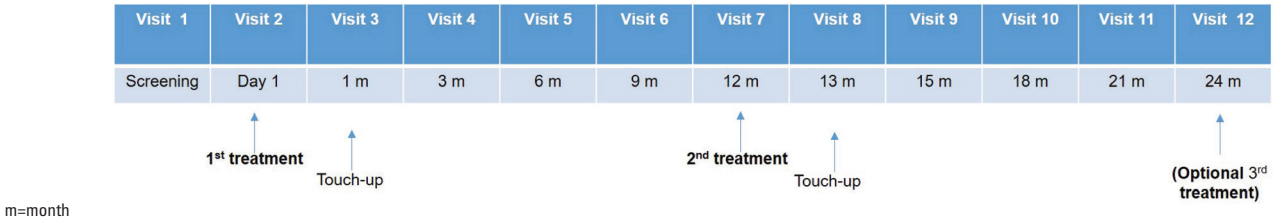
Study Design

This was a 24-month, evaluator-blinded, non-comparative, multi-center study (ClinicalTrial.gov ID: NCT02565784). The study was conducted at two hospitals in Taiwan, subjects were recruited from the clinics' patient records and through advertisement. The study protocol was approved by independent ethics committees and conformed to the Declaration of Helsinki.

Eligibility

Eligible subjects were females with Han Chinese facial appearance, aged 25 to 50 years, with the intention to undergo facial filler treatment for either contouring or to compensate for volume loss. Subjects would in the opinion of the investigator, require treatment in 2–4 of pre-defined areas; upper cheeks, nasolabial folds, temples, nose and chin, with 3–5 mL study product to achieve a clinically meaningful improvement in facial

FIGURE 1. Study timeline.



m=month

appearance. Subjects were required to sign informed consent for participation in the study.

Key exclusion criteria included previous facial surgery or permanent implant in area to be treated; permanent filler or fat injection in the facial area; treatment with non-HA fillers in the last 24 months; treatment with HA fillers in the facial area within 12 months before treatment; and revitalization treatment with neurotoxin, laser or light, mesotherapy, chemical peeling, or dermabrasion in the facial area within six months before treatment. Exclusion criteria also included hypersensitivity to any ingredient of the study product or to anesthesia, history of severe allergies, active skin disease, inflammation, or other related conditions in the treatment area.

Treatment Procedure

Subjects were treated with HA_R and/or HA_{RL} in 2–4 of predefined areas; upper cheeks, nasolabial folds, temples, nose, and chin, including at least one of the mandatory areas, upper cheeks and nasolabial folds. The aim of the treatment was to achieve a clinically meaningful improvement in facial appearance using 3–5 mL study products. The investigator could choose what study product(s) to use in different facial indications, in accordance with the Instructions for Use, and was free to use both products in one subject. However, only one study product and a maximum of 2 mL could be used in each treatment area. A second treatment was performed after 12 months in the same treatment areas and with the same product(s) as used at the first treatment (maximum volume 3 mL). Touch-up of 1 mL was allowed 1 month after both treatments. Subjects were followed for 24 months after initial treatment, including an optional third treatment at the end of the study (Figure 1).

Outcome Assessments

Photographs were taken at all study visits to the clinic to document treatment effect. Standardized 2D/3D photographs were taken at each visit from different angles with the LifeViz™ II camera system (QuantifiCare, France).

The primary objective of the study was to evaluate perceived improvement of facial aesthetic appearance 6 months after first treatment compared to baseline, as assessed by subjects themselves using the Global Aesthetic Improvement Scale (GAIS; rating Very much improved/Much improved/Improved/No change/Worse).

Secondary objectives included improvement of facial aesthetic appearance using GAIS, assessed by subjects (1, 3, 9, and 12 months after first treatment; 1, 3, 6, 9, and 12 months after second treatment), investigators (1, 3, 6, 9, and 12 months after first and second treatment), and three blinded evaluators with no information on study treatments (6 and 12 months after first and second treatment). GAIS ratings by subjects and investigators were performed by use of 2D-photographs, live assessment and mirror. Blinded evaluators performed the GAIS ratings retrospectively using 3D-photographs.

Subject satisfaction with facial appearance and treatment was evaluated using questionnaires at baseline, and 1, 3, 6, 9, and 12 months after first and second treatment.

A survey was completed by blinded evaluators to evaluate first impression of various measures of success (social skills, academic performance, attractiveness, dating success, occupational success, financial success, relationship success, and athletic success). Scoring from 1–10 was made for each measure and was based on retrospective review of photographs displayed on a computer screen, taken at baseline and 3 months after first and second treatment.

Upper cheek fullness and nasolabial fold wrinkle severity was assessed by investigators using validated aesthetic scales[8,9] at baseline, and 1, 3, 6, 9, and 12 months after first and second treatment, and by blinded evaluators (baseline, and 6 and 12 months after first and second treatment), both using 2D photographs.

Safety assessments included recording of pre-defined expected post-treatment symptoms (ie, bruising, redness, pain, tenderness, itching, and swelling) using a subject diary during 14 days after first and second treatment. Any symptom still ongoing at day 15 was reported as an adverse event. Evaluations of adverse events were made throughout the study.

Subjects who were treated in the chin according to protocol and who were photographed before and after treatment were

evaluated in a sub-study on aesthetic improvement of the chin. An independent evaluator assessed subject photographs using GAIS (2D, and 3D photographs), the validated Galderma Chin Retrusion Scale[10] (GCRS), and a Jawline Sagging Scale (JSS; improved/no change/worse) from timepoints 1, 6, and 12 months after both treatments. It should be noted that subjects were not treated specifically for chin retrusion or jawline sagging but for an overall clinically meaningful improvement. Main objective of the sub-study was aesthetic improvement of the chin 6 months after first treatment using GAIS (2D-photographs).

Statistical Analyses

The safety population included all subjects who were injected at least once in one area and the intention-to-treat (ITT) population included all subjects who were injected in at least two areas. The ITT population was the primary population for all effectiveness data. Assuming that 70% of the subjects were improved according to GAIS, assessed by the subject 6 months after initial treatment, 85 subjects would give 95% power to reject a proportion of 50% with 95% confidence. In order to account for drop-outs, 100 subjects were to be included.

GAIS assessment and proportion of improved subjects was presented with a two-sided 95% confidence interval. If the entire confidence interval was above 50%, the primary objective was met. The subject questionnaire was presented in frequency tables by question.

First impression survey assessments were presented descriptively and change from baseline was analyzed with Wilcoxon signed-rank test. Scale assessments for upper cheek fullness and nasolabial folds, as well as the proportion of improved cheeks/folds was presented with a 95% confidence interval. Safety variables including subject diary symptoms and adverse events were analyzed descriptively. All statistical analyses were performed using SAS® system version 9.4.

TABLE 1.

Number of Subjects Treated Per Area

Area	Number of subjects treated (N=100)			
	First treatment	Optional touch-up	Second treatment	Optional touch-up
Upper cheeks	100	70	89	52
Nasolabial folds	88	61	70	33
Chin	84	27	56	8
Nose	43	23	28	14
Temples	25	2	11	4

RESULTS

Subject Disposition, Demographic, Baseline and Injection Data

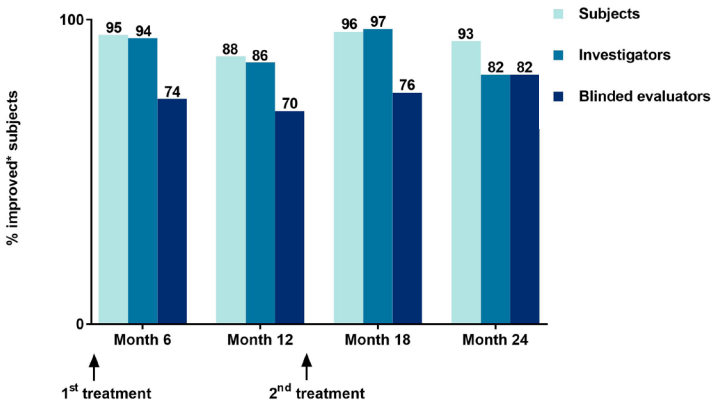
One hundred female subjects with Han Chinese facial appearance were included in the study. Mean age was 40 years (range, 27–49). Four subjects were withdrawn from the study during follow-up due to withdrawn consent (n=3) and adverse event (discomfort [mild]; n=1). The ITT and Safety population both comprised the 100 subjects enrolled in the study. The final per protocol population included 94 subjects; six subjects were excluded due to excess volume injected per treatment area at first treatment. At first treatment, 100 subjects were injected

TABLE 2.

Injection Details – Mean Volume Per Area and Product, First and Second Treatment Including Touch-Ups; ITT Population

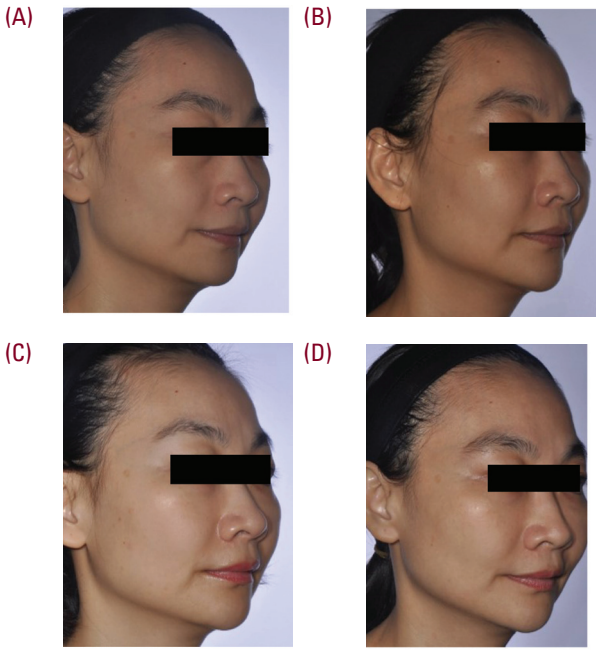
Area	Product	Volume (mL) injected					
		n	Mean	Standard deviation	Min	Median	Max
Upper cheeks	HA_R	54	3.2	1.2	0.6	3.2	5.6
	HA_{RL}	46	3.9	1.5	1.4	3.7	7.2
	Total	**100**	**3.5**	**1.4**	**0.6**	**3.4**	**7.2**
Nasolabial folds	HA_R	43	2.0	0.8	0.5	2.1	3.6
	HA_{RL}	45	2.0	1.1	0.5	1.9	4.0
	Total	**88**	**2.0**	**1.0**	**0.5**	**2.0**	**4.0**
Chin	HA_R	35	1.3	0.7	0.5	1.2	3.0
	HA_{RL}	49	1.9	0.9	0.4	1.9	3.9
	Total	**84**	**1.6**	**0.8**	**0.4**	**1.5**	**3.9**
Nose	HA_R	15	0.8	0.5	0.1	0.8	1.8
	HA_{RL}	28	1.2	0.7	0.1	1.3	2.4
	Total	**43**	**1.0**	**0.7**	**0.1**	**1.0**	**2.4**
Temples	HA_R	11	1.9	1.2	0.2	2.0	3.5
	HA_{RL}	14	1.9	1.0	0.3	1.8	3.5
	Total	**25**	**1.9**	**1.1**	**0.2**	**2.0**	**3.5**

FIGURE 2. GAIS–improved* subjects.



*Very much improved/Much improved/Improved

FIGURE 3. Subject photographs. Female subject aged 39: (A) Baseline, before 1st treatment (total volume 6 mL including touch-up); Upper cheeks, 2.0 mL HA_R, Nasolabial folds, 2.0 mL HA_{RL}, Chin, 2.00 mL HA_{RL} (B) Month 3. (C) Month 12, before 2nd treatment (total volume 4 mL); Upper cheeks, 2.4 mL HA_R, Nasolabial folds, 1.45 mL HA_{RL}, Chin, 0.15 mL HA_{RL} (D) Month 24.



with a mean volume of 4.7 mL study product, including touch-up (HA_R: 3.6 mL; HA_{RL}: 4.2 mL). At the second treatment, 94 subjects received a total mean volume of 3.1 mL study product, including touch-up (HA_R: 2.4 mL; HA_{RL}: 3.0 mL).

All subjects (100%) were injected in upper cheeks, and 88% and 84% received treatment in nasolabial folds and chin, respectively (Table 1). Injection details per indication are presented in Table 2.

Effectiveness

GAIS

Six months after first treatment, 95% (CI: 89%–98%) of subjects assessed themselves as improved (improved/much improved/very much improved; Figure 2). The primary endpoint of the study was thus met as the entire confidence interval was above 50%.

Twelve months after first and second treatment, 88% and 93% of subjects assessed themselves as improved, respectively (Figure 2). At least 94% of subjects were assessed as improved by the investigators up to six months after each treatment, and ≥82% of subjects were assessed as improved up to 12 months after both treatments (Figure 2). Photographs of a representative study subject are provided in Figure 3. At least 74% of subjects were assessed as improved by the blinded evaluators six month after both treatments, and ≥70% of subjects 12 months after both treatments (Figure 2).

Subject Satisfaction

Subject expectations prior to treatment mostly included that they wanted to improve their facial appearance (86%) and to look younger (75%). Subject satisfaction with facial appearance increased from 15% at baseline to 88% three months after first treatment. Most subjects (73–90%) were satisfied with the treatment results throughout the study; ≥80% were satisfied 12 months after both treatments. At least 96% of subjects would do the treatment again.

First Impression

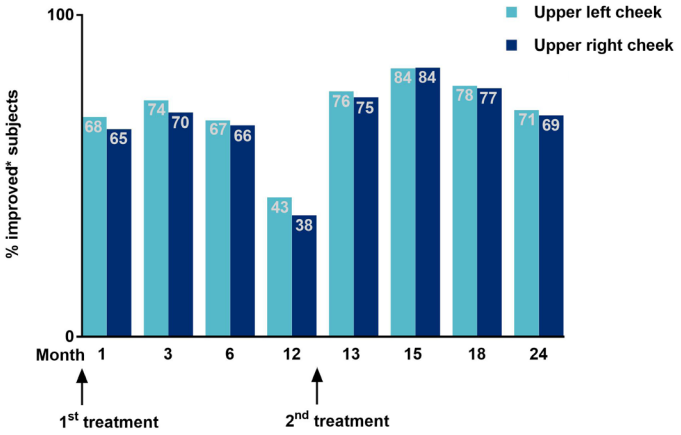
Overall first impression (ie, the sum of scores from all eight categories), assessed from photographs on a computer screen, was similar for the baseline and post-treatment assessments, with mean scores varying from 40.3 to 41.1. Correspondingly, no sub-scale measured separately showed any significant change from baseline.

Upper Cheek Fullness

Six months after first and second treatment, at least 66% and 67% of cheeks were assessed as improved (≥1-step improvement from baseline), respectively. Long-term improvement rate 12 months after treatment was significantly higher after second treatment (≥69%), compared to after first treatment (≥38%; *P*:<0.0001, Fisher's exact test; Figure 4).

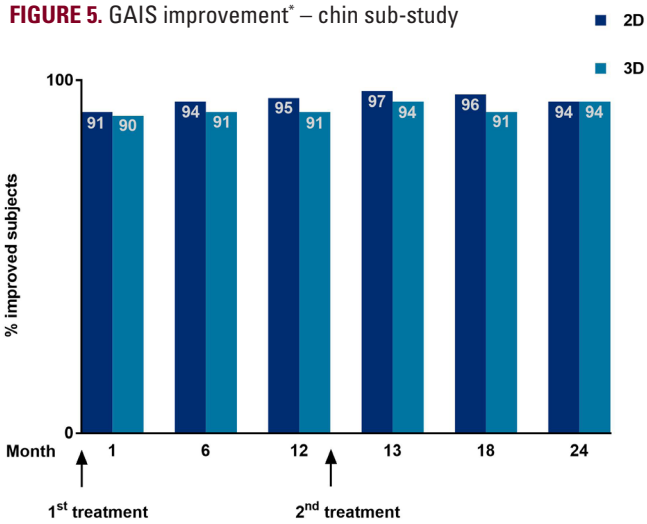
The blinded evaluators' retrospective assessment using photographs showed lower improvement rate compared to investigators, with 24%–29% improved cheeks on the right side, and 18%–33% on the left side, during the study.

FIGURE 4. Upper cheek improvement* – investigator assessment.



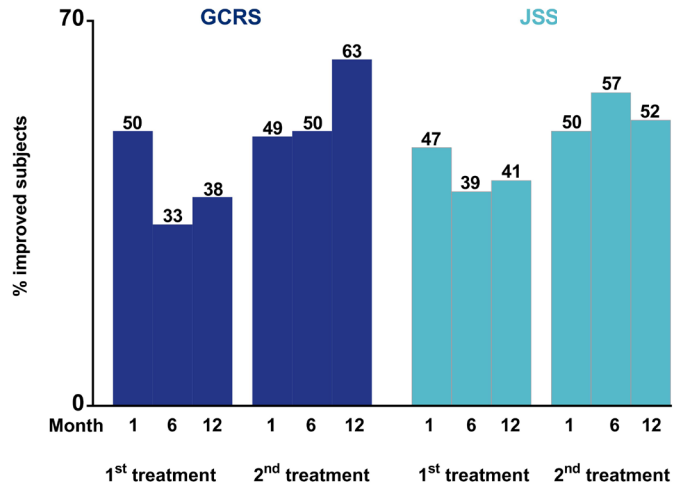
*At least 1-grade improvement from baseline

FIGURE 5. GAIS improvement* – chin sub-study



*Very much improved/Much improved/Improved. GAIS by independent reviewer using 2D, and 3D-photographs.

FIGURE 6. Improvement Galderma chin retrusion scale* and jawline sagging scale – chin sub-study.



*At least 1-grade improvement from baseline

Nasolabial Fold Wrinkle Severity

Considering both right and left nasolabial folds, the investigators rated ≥54% as improved (≥1-step improvement from baseline) at 6 months after first and second treatment. At least 46% and 54% were improved 12 months after the first and second treatment, respectively.

Blinded evaluators' retrospective evaluation using photographs, resulted in 28%–33% of right nasolabial folds, and 24%-38% of left nasolabial folds being assessed as improved during the study.

Sub-study on Chin Evaluation

Seventy-nine (79) female subjects with mean age 39.5 years (range, 28–49) were included in the sub-study. For these subjects, total mean volume injected in the chin, including both treatments with touch-up was 1.6 mL. Six months after first treatment, most chins (94%) were assessed as improved from 2D photographs (Figure 5). For subjects with chin retrusion at baseline (n=64), GCRS improvement rate was highest (63%) 12 months after second treatment (Figure 6). For JSS, improvement was also highest after the second treatment (57% at 6 months after treatment and 52% at 12 months after treatment; Figure 6).

Safety

The most common symptom reported through the subject diaries was tenderness in all treatment areas. Reporting of symptoms was generally declining 3 days after treatment, and with the exception of a few cases, symptoms were resolved after 14 days.

In total, 260 adverse events were reported by 64 subjects (64%), of which 5 events were serious. Twenty-nine (29) adverse events in 16 subjects (16%) were considered related to study product or treatment procedure, none of these were serious. Most commonly reported related adverse events were implant site pain with 13 events in 5 subjects (5%), and implant site bruising with 7 events in 6 subjects (6%). All related events were mild (79%) or moderate (21%). The frequency of reported adverse events decreased with the second treatment (9 events compared to 20 events after first treatment). Median duration of related events was 16 days; all events resolved with follow-up.

DISCUSSION

Modern treatment plans in clinical aesthetics require a full-facial assessment with attention to surface, volume and movement of all facial areas. The focus of treatment should preferably involve the whole face rather than certain areas, as treatment of one area will affect the overall balance and proportions of the face.[11] Treatment plans should also be based on patients' individual treatment goals within their own ethnic aesthetic boundaries. Due to an increasing number of treatments and partly different treatment needs in Asia compared to western

countries, treatment data from Asian patients, in particular from long-term follow-up is needed. This study evaluated safety and effectiveness of HA_R and HA_{RL}, when used for full-face treatment including upper cheeks, nasolabial folds, temples, chin, and nose in an Asian population. Assessments included well-defined outcome scales and blinded/independent evaluators, reducing the risk of bias.

The study provides further support to aesthetic improvement from using HA_R and HA_{RL}, as 95% of subjects were improved on the primary endpoint; subject-assessed GAIS 6 months after first treatment. This improvement was confirmed by investigators. The proportion of improved subjects remained high throughout the study (≥82%), as assessed both by subjects and investigators. Also, according to blinded evaluators, at least 70% of subjects were improved during the 24-month study period.

Subject expectations with treatment were met to a high degree, as satisfaction with facial appearance increased from 15% at baseline to 88% three months after first treatment. Comparably low mean injection volumes for a full-face treatment (4.7 and 3.1 mL including touch-up at first and second treatment, respectively), was still associated with high subject satisfaction, that remained throughout the 24-month study.

Although subjects were treated for an overall facial aesthetic improvement, there were indeed improvement reported for specific treatment areas. Upper cheek fullness, assessed by investigators, showed improvement for ≥66% of subjects up to 6 months after each treatment. Characteristic for upper cheeks was the significantly higher improvement rate observed 12 months after second treatment than 12 months after first treatment (≥69% vs 38% improved subjects). A previous study by Weiss et al[6] used a mean volume of 6.23 mL HA_{RL} for treating midface at the initial treatment, whereas in the current study, the total mean volume for both treatments was 3.5 mL for cheeks. This smaller volume still resulted in improvement for a majority of subjects at most timepoints. Nasolabial fold improvement was however lower than reported in other studies.[12,13] It should be noted though that the current study did not include subjects on the basis of nasolabial fold severity, which therefore could be less at baseline, potentially resulting in lower improvement rate. The blinded evaluators generally rated subjects as less improved compared to investigators on all effectiveness assessments. This can be explained by limitations associated with only using retrospective photographs for assessments. Also, 92–96% of subjects were assessed by the blinded evaluators as having full or only mildly sunken cheeks at baseline, leaving little room for improvement.

Both study products were used in comparable number of subjects and volume used for treating upper cheeks, nasolabial folds and temples. HA_{RL} was preferred over HA_R for treating nose and chin, all in line with the intended use for the firmer gel in areas requiring more support. The chin was a prioritized treatment area in this Asian population, being the most commonly injected area following the mandatory indications upper cheeks and nasolabial folds. From the sub-study on subjects treated in the chin, GAIS improvement rates were high at all timepoints (≥90%) both from 2D, and 3D-photograph evaluations. Although subjects were not treated specifically for chin retrusion or jawline sagging, long-term improvement 12 months after treatment increased with the second treatment for GCRS (63% vs 38% improved subjects) and to some extent for JSS (52% vs 41%).

Reporting of local tolerability symptoms from subject diaries was generally declining three days after both first and second treatment. Product/treatment related adverse events were predominantly mild and transient. The frequency of related adverse events decreased with the second treatment (9 events compared to 20 events after first treatment). Overall, pain (13 events in 5 subjects [5%]) and bruising (7 events in 6 subjects [6%]) were most commonly reported, both being known local site reactions after HA filler injections.[12,14] No new safety findings were reported in the study.

CONCLUSION

The study results indicate that HA_R and HA_{RL} is effective for full-face treatment in Asian patients, demonstrated by long-term aesthetic improvement and high subject satisfaction over 24 months with one re-treatment. Repeated treatment in several facial indications was well tolerated. These data may be used as support when establishing individual treatment plans in Asian patients.

DISCLOSURES

Dr Huang is a clinical trial investigator for Galderma; Dr Tsai is a clinical trial investigator for Galderma and Allergan.

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