Efficacy and Safety of a Hyaluronic Acid Filler to Correct Aesthetically Detracting or Deficient Features of the Asian Nose: A Prospective, Open-Label, Long-Term Study

Steven Liew, MD, FRACS; Terrence Scamp, MD; Mauricio de Maio, MD; Michael Halstead, MS; Nicole Johnston; Michael Silberberg, MD, MBA; and John D. Rogers, MD, MPH

Aesthetic Surgery Journal
2016, Vol 36(7) 760–772

DOI: 10.1093/asj/sjw079
www.aestheticsurgeryjournal.com
OXFORD UNIVERSITY PRESS

Abstract

Background: There is increasing interest among patients and plastic surgeons for alternatives to rhinoplasty, a common surgical procedure performed in Asia.

Objectives: To evaluate the safety, efficacy, and longevity of a hyaluronic acid filler in the correction of aesthetically detracting or deficient features of the Asian nose.

Methods: Twenty-nine carefully screened Asian patients had their noses corrected with the study filler (Juvéderm VOLUMA [Allergan plc, Dublin, Ireland] with lidocaine injectable gel), reflecting individualized treatment goals and utilizing a standardized injection procedure, and were followed for over 12 months.

Results: A clinically meaningful correction (≥1 grade improvement on the Assessment of Aesthetic Improvement Scale) was achieved in 27 (93.1%) patients at the first follow-up visit. This was maintained in 28 (96.6%) patients at the final visit, based on the independent assessments of a central non-injecting physician and the patients. At this final visit, 23 (79.3%) patients were satisfied or very satisfied with the study filler and 25 (86.2%) would recommend it to others. In this small series of patients, there were no serious adverse events (AEs), with all treatment-related AEs being mild to moderate, transient injection site reactions, unrelated to the study filler.

Conclusions: Using specific eligibility criteria, individualized treatment goals, and a standardized injection procedure, the study filler corrected aesthetically detracting or deficient features of the Asian nose, with the therapeutic effects lasting for over 12 months, consistent with a high degree of patient satisfaction. This study supports the safety and efficacy of this HA filler for specific nose augmentation procedures in selected Asian patients.

Level of Evidence: 3

Accepted for publication March 29, 2016.

Dr Liew is a plastic surgeon in private practice in Sydney, NSW, Australia. Dr Scamp is a plastic surgeon in private practice in Main Beach, Queensland, Australia. Dr de Maio is a plastic surgeon in private practice in São Paulo, Brazil. Mr Halstead is Associate Director and Ms Johnston is Study Manager, Scientific & Medical Affairs, plc Australia, Gordon, NSW, Australia. Dr Silberberg is Medical Director, Aesthetics International, Allergan plc, Marlow, United Kingdom. Dr Rogers is Therapeutic Area Medical Director, Scientific & Medical Affairs, Allergan plc, Singapore, Singapore.

Corresponding Author:
Dr Steven Liew, Shape Clinic & MediSpa, Suite 109, 19A Boundary Street, Darlinghurst, NSW 2010, Australia.
E-mail: steven@shapeclinic.com.au

Rhinoplasty is one of the most common surgical procedures performed by plastic surgeons worldwide.[1] In Asia, it ranks second only to blepharoplasty.[2] This is consistent with Asian patients seeking advice and treatment for features of their nose which they consider aesthetically detracting or otherwise deficient. This includes a flat bridge, an indistinct dorsal aesthetic line, an under-projected and broad nasal tip, a wide alar base, and/or a retracted columella.[2-9] It is not surprising, therefore, that medical and surgical treatment goals for Asians would focus on the correction of one or more of these features, rather than a reduction procedure more commonly performed in Caucasians due to a prominent dorsum or nasal tip.[6,10] Furthermore, the corrective procedures conducted on the nose are performed with consideration of the facial morphology commonly encountered in the Asian patient, including a recessed position of the orbit, a flat or concave shape of the forehead, and a recessed projection of the midface and the chin.[4,11-12] For Asian patients, there is often a concern over unpredictable adverse outcomes and potential need for revision surgery. They are made aware of risks associated with surgical rhinoplasty, including rare adverse reactions to anesthesia and procedural complications such as numbness, asymmetries, infection, extrusion of prosthetic implants, and morbidity associated with autologous cartilage harvesting. Even in the absence of these adverse events (AEs), prolonged downtime associated with post-surgical bruising or swelling is not accepted by patients.[6,10-15] Thus, a non-surgical approach which could achieve the same treatment goals without these potential complications would be a compelling alternative.

The use of fillers as a primary non-surgical procedure to correct deficient or aesthetically detracting facial features is well described in the literature. Historically, these fillers consisted of autologous fat, silicone, poly-tetrafluoroethylene, poly-methylmethacralate, calcium hydroxyapatite, polylactic acid, or hydrogel.

Over the last decade, hyaluronic acid (HA) fillers have become the mainstay treatment for nasolabial folds, the mid-face, the chin, the lips, and the perioral region.[16-22] This is principally due to the ease of administration, the limited downtime for the patient, the product's malleability and durability, and the low potential for immunogenicity. Importantly, full reversibility of the treatment is achievable with the administration of hyaluronidase. With the availability of HA fillers providing structure and support, related to properties of high gel hardness and cohesivity, their applicability for correcting features of the nose is clear.[23-25] In the literature, however, there are only a few prospective studies focused on the efficacy, safety, and longevity of HA fillers to support their utility as a non-surgical alternative to augmentation rhinoplasty in Asians.[8-9,15,26-28]

In the present study, our objective was to evaluate the safety and efficacy of the study filler for correcting the nose of Asian patients, with consideration of both immediate and long-term (> 12 months) outcomes. This was conducted within the context of a rigorous eligibility criteria and a well-defined injection procedure focused principally on the safe administration of the study product. The use of fillers may also be associated with severe AEs such as vascular compromise or inadvertent injection into the vasculature. (This issue is thoroughly explored in the discussion section.)

A new evaluation tool was developed for this study to classify the structural features of the nose as a means to document the aesthetic and structural deficiencies present in each patient. Furthermore, our protocol facilitated alignment of patient expectations with the injecting physician's assessment to create an individualized treatment plan. All of the above procedures reflected a consensus approach developed by the authors.

METHODS

Clinical Study Design and Ethics

Healthy Asian patients, aged 20 years or older, dissatisfied with their facial appearance due to aesthetically detracting or deficient features of their nose, and who, in the opinion of the injecting physician, could achieve a clinically meaningful aesthetic correction with the study filler (Juvéderm VOLUMA [Allergan plc, Dublin, Ireland] with lidocaine injectable gel), were eligible for the study after fulfilling strict screening requirements.

Key exclusion criteria included the following:

- Patients requiring filler treatment in the nasal tip, alar recess, and/or glabellar areas to achieve a good aesthetic outcome.
- Patients with a small, shallow nose ("micronose") requiring a filler volume in excess of the ability of the skin and soft tissue to expand to accommodate (thereby associated with a high risk of lateral displacement of the implant causing an unesthetic dorsal width).
- Patients with history of prior nose surgery, including cartilage grafts and/or prior biomaterial implants, including fillers.
- Patients with a history of sinusitis or rhinitis.
- Patients requiring dental or oral surgery, including dental implants, during the study period.
- Patients with any pre-existing condition that might affect the evaluation of outcome and/or patient safety, including visible scars, active inflammation, infection, and cancerous or precancerous lesions.
- Patients with a known hypersensitivity to lidocaine, hyaluronic acid, and/or Gram positive bacteria proteins.
- Patients with a history of connective tissue disease or bleeding disorders; use of aspirin and/or concomitant antithrombotic therapy during the week preceding the study treatment.

Women of childbearing potential were required to have a negative urine pregnancy test prior to the administration of the study filler and to use adequate contraception while participating in the study. The study was approved by a central Institutional Review Board (Bellberry Limited, Eastwood, SA, Australia) and was conducted at 2 Australian private plastic surgery clinics, in accordance with the applicable Good Clinical Practice (GCP) regulations and International Council on Harmonisation (ICH) guidelines. All patients were required to provide written informed consent, which included a photography release form, prior to any study-related procedure. This study was conducted over 66 weeks, between April 2013 and August 2014 and is listed on the ClinicalTrials.gov Registry (NCT01846039).

Systematic Nasal Analysis and Treatment Goal Setting

Prior to the study treatment (baseline visit) the nose of each study patient was formally evaluated with a focus on 4 key structural features: (I) the nasofrontal angle; (II) the radix breakpoint and dorsum; (III) the alar base and nostril shape; and (IV) the nasal tip, columella, and nasolabial angle. The injecting physicians documented each feature as "normal/acceptable/ideal," or otherwise catalogued them as aesthetically detracting or deficient by identifying the most relevant descriptive term from a protocol-specific instrument; the Nose Treatment Goal Attainment Scale (NTGAS; Table 1). Upon reviewing the completed NTGAS, the injecting physicians determined one primary and one secondary treatment goal, in consultation with the patient. The evaluation and goal setting process not only prioritized and aligned the patient's and the injecting physician's interests, but it also informed the injecting physicians as to the appropriate injection sites and the sequence of these injections. A blank copy of the NTGAS is available as Supplementary Material at www.aestheticsurgeryjournal.com.

Injection Procedure

A needle was used for all injection procedures. The injecting physicians administered the study filler at Day 0 (maximum of 2.0 mL) and then 4 weeks later (maximum of 1.0 mL), if required. Due to the common features of a recessed mid-face, poor tip projection and/or weak columella structural support, the injection sequence was standardized, as detailed below. This injection procedure was designed to minimize the risk of vascular complications due to either an intravascular deposition of the study filler or the external compression of a vessel. As such, injecting the study filler in the glabellar area, the alar rim, the alar recess, or directly into the nose tip was prohibited. Further, all injections were in the supra-periosteum and perichondrium; dermal and sub-cutaneous injections were not permitted. The slow injection of the study product and the limitation on volume which could be administrated helped to ensure integrity of the skin envelope.

Table 1. Nose Treatment Goal Attainment Scale (NTGAS): Determining the Primary and Secondary Treatment Goals in the Correction of Deficient or Detracting Features of the Subject's Nose (*Injecting Physicians and Central Evaluating Physician*)

Goal A: Improvement in Nasofrontal Angle	Goal C: Alar Base Narrowing and Altering Nostril Shape
Define nasofrontal angle (profile view) — Normal/acceptable/ideal — Increased/open — Decreased/closed	**Define alar base width** — Normal/acceptable/ideal — Wide — Narrow
	Define nostril show in frontal and lateral views — Normal/acceptable/ideal — Excessive — Reduced
	Define nostril aperture shape and orientation in basal view — Normal/acceptable/ideal — Too vertical — Too horizontal
Goal B: Improvement of Radix Break Point Position and Dorsum Width/Height and Surface Contour (profile view)	**Goal D: Improvement of Nasal Tip, Columella, and Nasolabial Angle**
Define radix break-point in horizontal plane — Normal/acceptable/ideal — Too anterior/absent — Shallow — Deep	**Define tip projection** — Normal/acceptable/ideal — Under-projected — Slightly over-projected — Over-projected
Define height profile of dorsum — Normal/acceptable/ideal — Under-projected — Over-projected	**Define tip rotation** — Normal/acceptable/ideal — Rotated downward — Rotated upward
Define the nasal dorsum width at level of radix — Normal/acceptable/ideal — Too wide — Too narrow	**Define the columella-labial angle** — Normal/acceptable/ideal — Increased — Decreased
Define profile over dorsum (both bony and cartilaginous) — Straight — Slightly concave — Slightly convex — Hump — Saddle	**Define the columella length** — Normal/acceptable/ideal — Long — Short — Retruded

Adapted from: Meneghini F, Biondi P. Nasal Analysis; In: *Clinical Facial Analysis. Elements, Principals & Techniques.* 2nd ed. New York, NY: Springer; 2012:71-94.

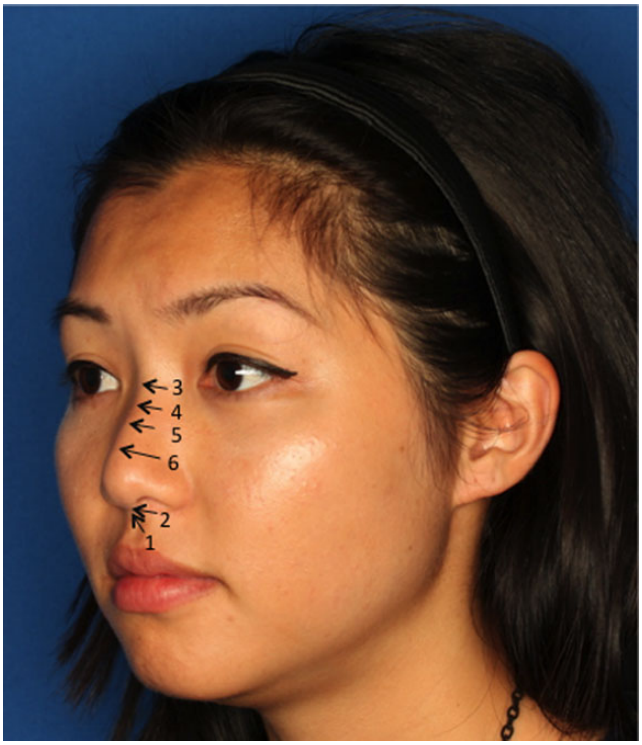

Figure 1. Injection sequence protocol (as required, in accordance with the pre-specified treatment goals) demonstrated on a pre-treatment image of a 32-year-old woman enrolled in the study: (1) Entry point into subnasale with deposition on surface of anterior nasal spine (*correcting nasolabial angle*); (2) Entry point into columella just superficial to caudal septum and medial crura (*creating columella support and tip projection*); (3) Entry point (*correcting nasofrontal angle, position and height of radix*); and (4-6) Entry points into dorsum (*correcting nasofrontal angle; dorsal height and width, and contour features including supra-tip*).

The following injection sequence was adhered to, based on the patient's clinical presentation and aforementioned treatment goals, while utilizing a full aseptic technique (Figure 1):

- To correct the nasolabial angle, the study filler was first injected towards the subnasale with deposition on the surface of the anterior nasal spine (1 to 2 entry points).
- To promote columella support and tip projection, the study filler was then injected into the columella at an entry point just superficial to the caudal septum and medial crura.
- To correct the nasofrontal angle, the position and height of radix, the study filler was injected at 1 entry point.
- To correct the width, height, and contour features of the dorsum, including the supra-tip area, the study filler was subsequently injected in the dorsum (2 to 3 entry points).

Prior to the injection procedure, the injecting physicians estimated the volume required by assessing the distensibility of tissue at the level of the radix, the dorsum, and the columella. Using a marker to identify the midline from the glabella to the dorsum and the subnasale, a 2 to 3 mm wide rectangle (corresponding to the width of the individual dorsal aesthetic line) was drawn from the radix break point to the supra-tip as a guide for the placement of the study filler. The non-injecting hand was used to guide the needle and to avoid inadvertent implantation of the study filler beyond its intended location. When injecting the columella, the injecting physicians were advised not to widen the medial crura and when injecting the dorsum, they were instructed to place their thumb and second finger on both lateral walls of the dorsum to ensure precision and to reduce risk of filler displacement. The study filler was administered at multiple entry points to create the desired dorsal shape and contour. The injecting physicians were advised to avoid overcorrection (suggested by excessive force required to depress the syringe plunger) and to aspirate prior to injection. The protocol also instructed the injecting physicians to mold the implanted product into place using a saline-soaked gauze pad or a cotton tip.

The study filler was administered slowly with constant minuscule movements of the needle tip anteriorly as an additional safeguard against intravascular deposition. During and for a few minutes after the injection procedure, the injecting physicians were instructed to monitor for signs of skin blanching or discoloration and to ask the patients to report pain at or distal to the injection site. If an ischemic event was suspected, the injecting physicians were instructed to discontinue the injection procedure immediately and to administer hyaluronidase as per the manufacturers' recommendations. In addition, any patient report of visual disturbance or a change in visual acuity would necessitate the same procedure and an immediate consultation with an ophthalmologist.

Post-Injection Management

At each post-injection clinic visit, the skin of the patients was closely inspected for bleeding, edema, and evidence of discoloration. In addition, on the injection day, the patients were given an information sheet highlighting the importance of immediately reporting swelling, pain, discomfort, tingling, change in sensation, and/or visual disturbance, particularly during the first 12 to 72 hours post-treatment. The patients were also instructed to avoid unnecessary external compression of the nose which could cause filler displacement, indentation, or depression of the dorsal surface. To this end, they were advised not to sleep face down and to avoid wearing goggles and sun or reading glasses for 1 week. During this period, they were also informed not to have a facial massage, enter a sauna, receive excess sun

Table 2. Physician's Nose Profile Assessment Scale (NPAS): Number of Deficient or Aesthetically Detracting Features of the Subject's Nose (*Injecting Physicians and Central Evaluating Physician*)

	Number of the Following Features of the Nose Which Are Deficit or Aesthetically Detracting				
a. Nasofrontal angle b. Position of radix break point; dorsal width, height, and surface contour c. Alar base width and nostril shape d. Nasal tip, columella, and nasolabial angle	None[a]	One Feature	Two Features	Three Features	Four Features
Score	0	−1	−2	−3	−4

[a]No correction required.

exposure, or to swim. No phototherapy or laser treatment could be performed for 3 months post-injection.

Assessment Scales

All eligible patients were evaluated prior to study filler administration (baseline) and at 3 post-treatment clinic visits. Patients also completed a series of qualitative self-assessment scales (*see below*) while viewing themselves in the mirror and by referencing 2D images (frontal, lateral, and oblique) of their face captured at the clinic visits. They were required to complete these scales on patient-specific case report forms, with the individual patient's initials and study ID number entered into the header of each form, to ensure document control while maintaining patient confidentiality. All patient self-assessments occurred prior to the injecting physician's evaluations, to minimize the impact on the patient's subjectivity. The study coordinators could only reaffirm the written instructions on each scale and to ensure that the patient successfully completed scales at each scheduled visit prior to leaving the clinic. The injecting physicians made "live" assessments of the patients at the scheduled visits, while an independent, non-injecting central evaluating physician scored all the study patients at a single session by viewing the baseline and the 3 post-treatment 2D images of each patient. All images were captured using the Canfield IntelliStudio (Canfield Scientific, Inc., Fairfield, NJ), designed to achieve reproducible patient positioning and imaging. The central evaluating physician was unaware of which physician had injected a particular patient, the site of the injections, the total volume injected, and the number of injection sessions.

Physician and Patient-Reported Outcomes

The co-primary efficacy measure was the proportion of patients who achieved a ≥1 grade improvement from baseline at the first post-treatment follow-up visit, based on the Assessment of Aesthetic Improvement Scale (AAIS), as independently evaluated by the patient and the central evaluating physician. The AAIS is a 5-grade Likert Scale, ranging from +2 (much improved) to −2 (much worse). It is very similar to the Global Aesthetic Improvement Scale (GAIS), albeit the patients were asked to specifically evaluate their nose. The AAIS was also scored at the 2 subsequent post-treatment clinic visits as secondary outcome parameters. Further, at these 3 post-treatment clinic visits, the patients were asked to evaluate the degree of satisfaction with their nose appearance (Nose Satisfaction Scale [NSS]), as well as level of satisfaction with the study filler (Treatment Satisfaction Scale [TSS]). Both instruments also employed 5-grade Likert Scales, ranging from +2 (very satisfied) to −2 (very unsatisfied). Lastly, the patients were required to indicate whether they would recommend the study filler treatment to others, with this evaluation also documented at the 3 post-treatment clinic visits.

An additional qualitative assessment tool, the Nose Profile Assessment Scale (NPAS; Table 2), was used to assess patient outcome. This assessment was performed independently by the injecting physicians and the central evaluating physician for the baseline and the 3 post-treatment clinic visits. This 5-grade scale evaluated the impact of the study filler on the 4 specific features of the nose, based on a change of 1 grade or more from the patient's baseline score to a less negative score. This was consistent with reduction in the same key deficit or aesthetically detracting features identified on the NTGAS (Table 1). Finally, the injecting physicians and the central evaluating physician independently assessed whether the primary and secondary treatment goals, determined by the injecting physicians at baseline, had been achieved at the first post-treatment visit.

Blank copies of the AAIS, NSS, TSS, and NPAS are available as Supplementary Material at www.aestheticsurgeryjournal.com.

Safety and Tolerability Assessment

The evaluation of the safety and tolerability of the study treatment was based on AEs spontaneously reported by the study patients, or in response to a general question on the patient's health at the scheduled clinic visits and during telephone calls at 24 and 72 hours after the administration of the study filler. The injecting physicians were also required to confirm or exclude the presence of bruising, swelling, or

erythema and the severity thereof on the injection days, as well as document all other AEs independently observed by them at any clinic visit.

Statistical Analysis

All patients receiving the study treatment were included in the efficacy and safety analyses. All primary, secondary, and exploratory analyses were conducted using the intent-to-treat population. Missing data were imputed using the last observation carried forward (LOCF) methodology. All statistical analyses were performed with version 9.2 of the SAS System (SAS Institute, Inc., Cary, NC). Data were summarized with descriptive statistics, frequency tables, and by data listings. Categorical variables were analyzed using binomial tests with 80% probability of success. Continuous variables were analyzed using 2-sided t tests. Results were expressed as the proportion of patients achieving each event and the 95% confidence interval (95% CI) at each time point. P values of $\leq .05$ were considered statistically significant. Treatment responders were defined as a $\geq$1 grade improvement on the AAIS at the first post-treatment follow-up visit, as determined independently by the patient and the central evaluating physician.

In the statistical analysis plan, cut-off dates were determined for the 3 scheduled post-treatment clinic visits for the purposes of the data analysis by the independent statisticians for the study, with a LOCF methodology applied, as required. These cut-off dates were Study Days 113, 239, and 421. Adopting these analysis windows resulted in 27 of 29 patients having valid measurements at the first analysis time point (Day 113), with the remaining 2 patients attending the clinic after Day 113 having their neutral/negative assessments carried forward.

RESULTS

Patients

A total of 29 eligible patients were enrolled in this study, each receiving treatment with the study filler, and were followed for a mean of 378 days (range, 204-434 days). All patients were Asian with a mean age of 40.2 years (range, 20-61 years), the majority of whom were female (26/29; 89.7%). No patient had received prior aesthetic treatment or procedures to their nose. A total of 27 (93.1%) patients completed the study. One patient withdrew her consent following the second post-treatment follow-up visit, while another was withdrawn by the investigator after the same visit due to a positive pregnancy test. The pregnancy went to term with no complications.

Prior to administration of the study filler, the majority of the patients (n = 27; 96.6%) presented with 2 or more of the 4 possible key nasal features which the injecting physicians considered aesthetically detracting or deficient, based on the NPAS (Table 2). The position of the radix breakpoint, dorsal width/height, and/or surface contour was an issue in most (23; 79.3%). Consistent with this finding, 15 (51.7%) patients presented with a nasofrontal angle requiring correction. The injecting physicians also determined that a further 18 (62.1%) and 11 (37.9%) patients, respectively, had an aesthetically detracting or deficient nasal tip/columella/nasolabial angle and/or alar base width/nostril shape.

Dosing

All 29 eligible patients received the study filler at baseline (Day 0) at each of the 3 possible treatment areas: the anterior nasal spine, the columella, and the dorsum. Four weeks later, a total of 14/29 patients had supplementary treatment with the study filler at one or more of the treatment sites: anterior nasal spine (n = 6); columella (7); and/or dorsum (13). At these 2 clinic visits, the mean injection volume of the study filler was 1.36 mL (SD, 0.41) and 0.37 mL (SD, 0.23), respectively.

Efficacy

Patients with ≥1 Grade Improvement on AAIS (independent central evaluating physician and patient assessment)

The proportion of patients who achieved a 1 grade or better improvement in their pretreatment appearance (AAIS responders) at each clinic visit is presented in Figure 2

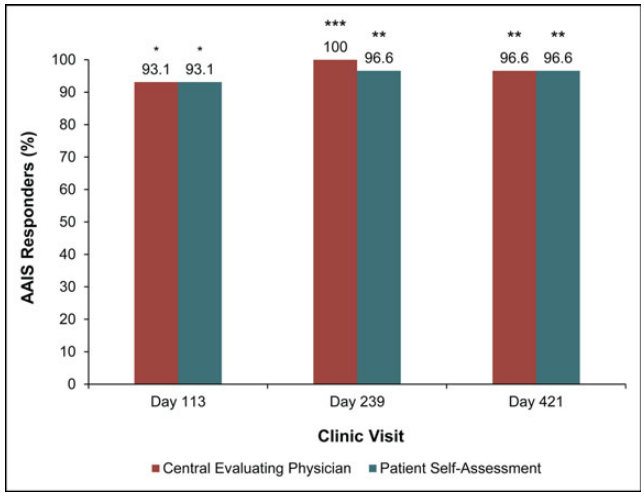

Figure 2. Proportion of patients responding to treatment with study filler (≥ 1 grade improvement in AAIS), as independently assessed by the central evaluating physician and the patients, respectively (n = 29). P value based on binominal test with 80% probability of ≥1 grade improvement. *P = .04; **P = .01; ***P = .004. Co-primary endpoint was at first post-treatment visit (Day 113). AAIS, Assessment of Aesthetic Improvement Scale.

for both the independent central evaluating physician assessment and the patients' self-evaluation. At the first post-treatment follow-up visit (Day 113; primary endpoint), 27 (93.1%) patients were AAIS responders, based on both the central evaluating physician's rating and the patient's self-assessment. At the second follow-up visit (Day 239), the central evaluating physician determined that all (100%) patients were responders, while 28 (96.6%) patients considered that they were still responders. At the final follow-up visit (Day 421), the central evaluating physician concluded that the 1 grade or better improvement was maintained in 28 (96.6%) patients, which was consistent with the patient's self-assessment.

By illustration, the patients in Figures 3 and 4 maintained a 1-grade improvement in the AAIS, relative to their baseline score, for the duration of the study as determined independently by the central evaluating physician and the patient.

Patient Satisfaction with Nose Appearance; Satisfaction with the Study Filler Treatment

Prior to the study filler administration, all (100%) patients scored themselves with either a grade of −1 (dissatisfied) or −2 (very dissatisfied) for the appearance of their nose, based on the Nose Satisfaction Scale (Figure 5). At Day 113, 27 (93.1%) patients scored themselves as satisfied or very satisfied with their nose appearance, with 2 (6.9%)

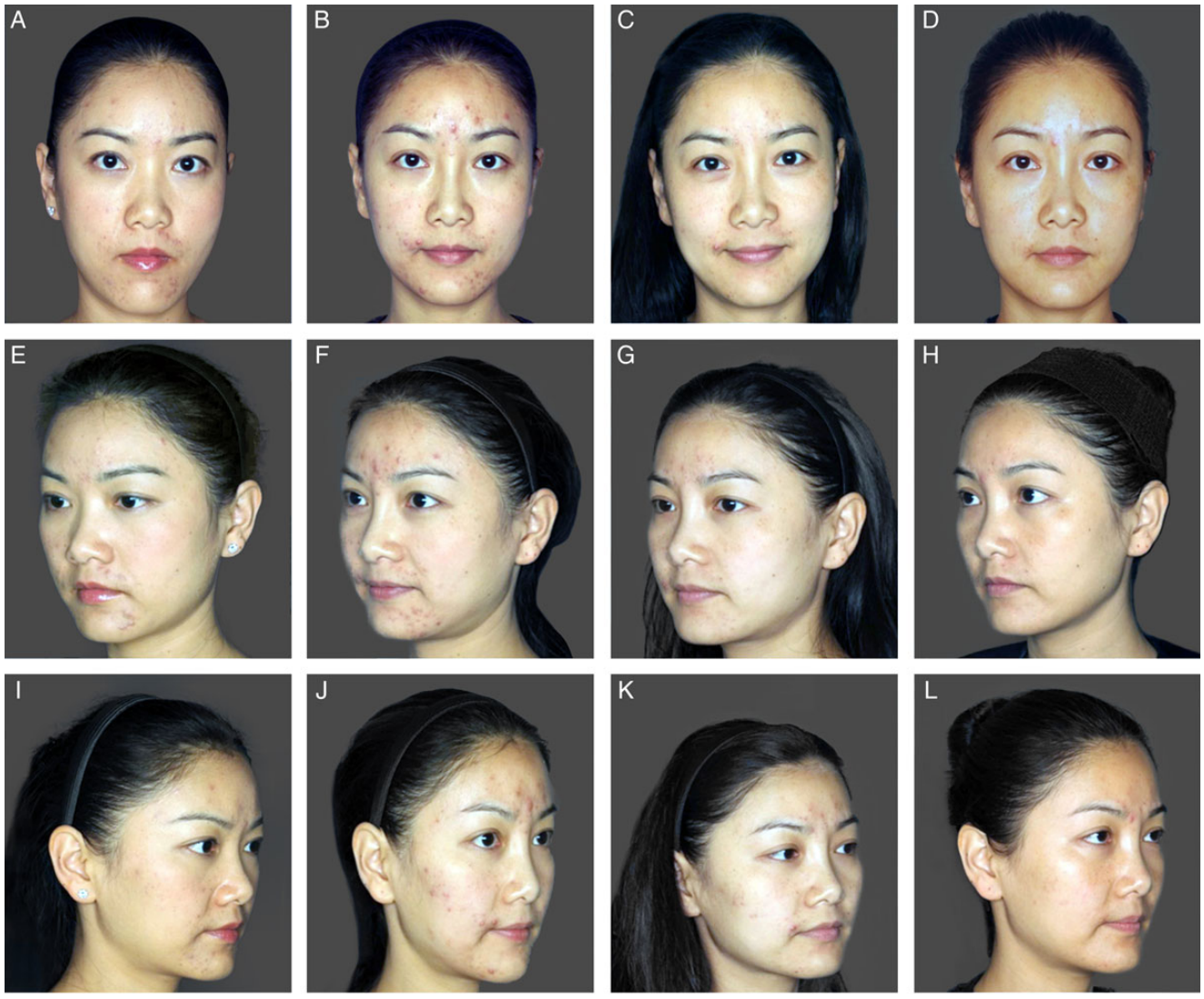

Figure 3. (A, E, I) Day 0 pre-treatment, (B, F, J) Day 113 post-treatment, (C, G, K) Day 239 post-treatment, and (D, H, L) Day 421 post-treatment photographs of a 35-year-old woman (at enrollment). This woman maintained a ≥1 grade improvement in her AAIS score from baseline (Day 0) at each of the scheduled post-treatment clinic visits (Days 113, 239, and 421), as independently assessed by the patient and the central evaluating physician. AAIS, Assessment of Aesthetic Improvement Scale.

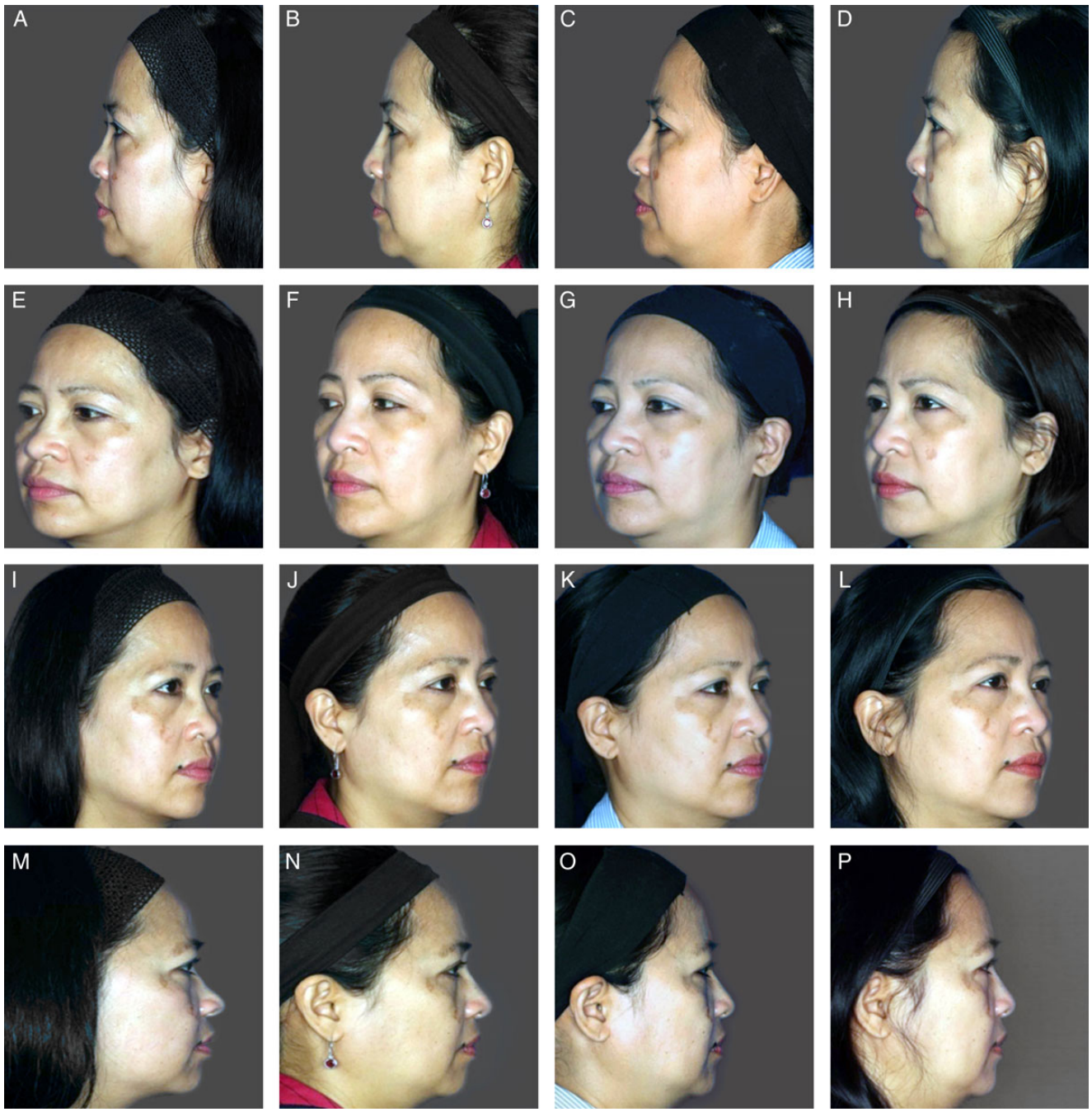

Figure 4. (A, E, I, M) Day 0 pre-treatment, (B, F, J, N) Day 113 post-treatment, (C, G, K, O) Day 239 post-treatment, and (D, H, L, P) Day 421 post-treatment photographs of a 41-year-old woman (at enrollment). This woman maintained a ≥1 grade improvement in her AAIS score from baseline (Day 0) at each of the scheduled post-treatment clinic visits (days 113, 239, and 421), as independently assessed by the patient and the central evaluating physician. AAIS, Assessment of Aesthetic Improvement Scale.

documenting a neutral opinion (grade = 0). At Days 239 and 421, 26 (89.7%) patients were satisfied or very satisfied with their nose, while 3 (10.3%) patients had a neutral opinion. No patient was dissatisfied or very dissatisfied with their nose appearance at any point during the post-treatment follow-up. Furthermore, 24 (82.8%) patients were satisfied or very satisfied with the study filler based on the Treatment Satisfaction Scale at Day 113, while 2 (6.9%) were very unsatisfied, with this assessment not performed in the remaining 3 patients (Figure 6). This outcome was

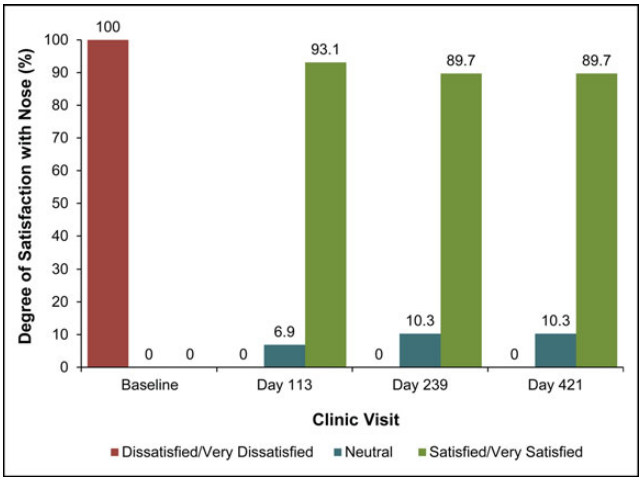

Figure 5. Degree of satisfaction with nose appearance, based on the NSS (patient self-evaluation; $n = 29$). Baseline is prior to treatment. NSS, Nose Satisfaction Scale.

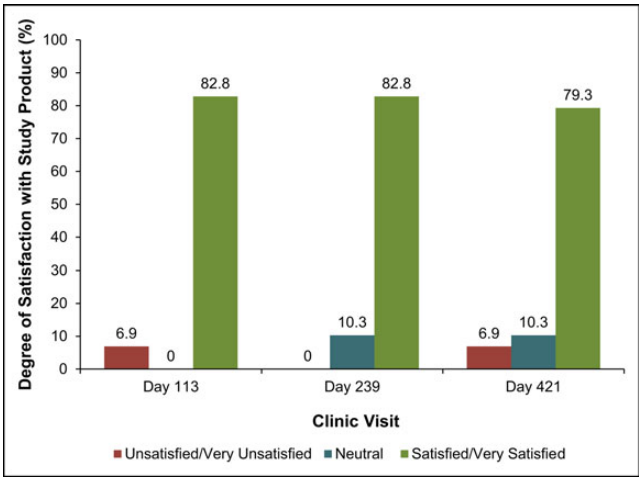

Figure 6. Degree of satisfaction with the treatment of their nose with the study product, based on the TSS (patient self-evaluation; $n = 29$). Day 113 assessment not available for 3 patients; Day 239 assessment not available for 2 patients; Day 421 assessment not available for 1 patient. TSS, Treatment Satisfaction Scale.

maintained at Day 239, with 24 (82.8%) patients again documenting that they were satisfied or very satisfied with the treatment, with 3 (10.3%) recording a neutral opinion, with no response documented for 2 patients. At the final visit, 23 (79.3%) patients were satisfied or very satisfied, 3 (10.3%) were neutral, with 2 (6.9%) very unsatisfied, with the response missing for 1 patient. Finally, 26 (89.7%) patients affirmed at Days 113 and 239 that they recommend the study filler treatment of the nose to others (response missing for 2 patients), with 25 (86.2%) patients also recommending the study filler at Day 421 (response missing for 3 patients). Only 1 (3.4%) patient documented a negative opinion to this question throughout the post-treatment period of the study (Figure 7).

Exploratory Assessments: Change in NPAS

At Day 113, 27 (93.1%) patients had achieved a 1 grade or better improvement in the appearance of their nose, based on the NPAS (Table 2), as independently documented by the central evaluating physician and injecting physicians. At Day 239, all 29 (100%) patients had achieved this outcome, as confirmed by the same physicians. At the final visit (Day 421), 28 (96.6%) and 29 (100%) patients had maintained this improvement, again as documented by the injecting physicians and the central evaluating physician, respectively.

Treatment Goal Attainment: Primary and Secondary Goals

Prior to the administration of the study filler, the injecting physicians identified improvement in the radix break point position, dorsal width/height, and surface contour (*Goal B from the NTGAS;* Table 1) as the primary treatment goal in 28 of the 29 patients. Improvement in the nasofrontal angle (*Goal A*) was the primary goal in the remaining patient.

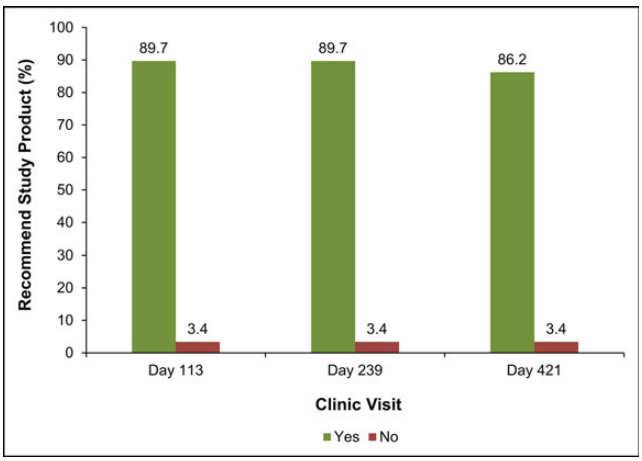

Figure 7. Proportion of patients who would recommend the study product to treat the nose of others (patient self-evaluation; $n = 29$). Day 113 and 239 assessments not available for 2 patients; Day 421 assessment not available for 3 patients.

The injecting physicians subsequently documented attainment of Goal A in the single patient and Goal B in 27 of 28 (96.4%) patients, when evaluated at Day 113, with the evaluation not performed for one patient. The central evaluating physician independently affirmed goal attainment in all 29 (100%) patients at Day 113 (Figure 8A).

For the secondary treatment goal, the injecting physicians determined that improvement in the nasal tip, columella and nasolabial angle (*Goal D*) was a secondary goal in 17 (58.6%) patients, while alar base narrowing and/or alteration of nostril shape (*Goal C*) and improvement in the nasofrontal

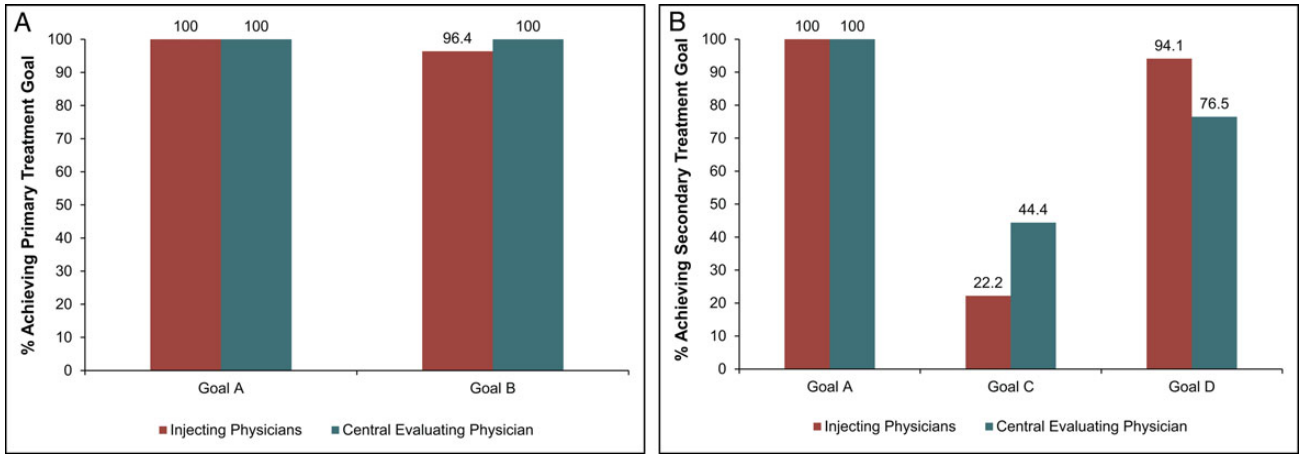

Figure 8. (A) Proportion of patients achieving the primary treatment goal at the first post-treatment visit (Day 113) based on the NTGAS (n = 29), as independently assessed by the injecting physicians and central evaluating physician. Goal A: Correction of nasofrontal angle; Goal B: Correction of radix break point position, dorsal width/height and/or surface contour (Goal B injecting physician assessment unavailable for 1 patient). (B) Proportion of patients achieving the secondary treatment goal at the first post-treatment follow-up visit (Day 113), based on the NTGAS (n = 29), as independently assessed by the injecting physicians and central evaluating physician. Goal A: Correction of nasofrontal angle; Goal C: Correction of alar base width and/or nostril shape; Goal D: Correction of nasal tip, columella and/or nasolabial angle (Goal D injecting physician assessment unavailable for 1 patient). NTGAS, Nose Treatment Goal Attainment Scale.

angle (*Goal A*) were the secondary treatment goals in 9 (31%) and 3 (10.3%) patients, respectively. At Day 113, all 3 patients attained Goal A, according to the injecting physicians, who also confirmed that 16/17 (94.1%) patients had achieved Goal D, with this evaluation not completed in one patient. By contrast, the same physicians documented attainment of Goal C in only 2/9 (22.2%) of patients. The central evaluating physician also reported that all 3 patients had achieved Goal A. Furthermore, 13/17 (76.5%) patients were judged to have sufficient correction to realize Goal D. Finally, the central evaluating physician scored 4/9 (44.4%) patients achieving Goal C (Figure 8B).

Safety and Tolerability

The study treatment was well tolerated, with all AEs being mild to moderate in severity. There were no serious AEs or AEs leading to early termination. Other than unrelated conditions, such as respiratory infections and seasonal allergies, all AEs were localized to the injection site. These events were principally transient cases of swelling, erythema, bruising, or pain/discomfort and are presented in Table 3. All of these AEs were associated with the injection procedure and not the study filler, in the opinion of the injecting physicians. Further, no specific medical intervention was required with 2 exceptions. In the first case, a discrete deposit of the filler to the lateral dorsum became displaced following its administration. It was gently molded into the correct position by the injecting physician at the subsequent clinic visit. In the second case, the displaced filler on the dorsum had to be molded into place at the first follow-up visit. This was attributed to the pressure of the nose pads of the patient's reading glasses. In both cases, the events resolved with no further intervention.

DISCUSSION

When individuals view themselves in the mirror, they may critically compare themselves to others and, indeed, to an idealized concept of what they should look like.[29,30] For Asians, their greatest focus is most likely at their nose. Not surprisingly, features of the nose which are perceived as aesthetically detracting and/or deficient are the catalyst for most Asian patients seeking a consultation with aesthetic specialists[2-10] Notably, however, for many patients a non-surgical approach to correct these features is more appealing than surgical rhinoplasty, due to concerns over the risks of the surgery and the significant predicted downtime for recovery.[6,10-15]

In our study, we were able to demonstrate that a safe and effective correction of the nose was achieved with the study filler. Importantly, this correction was durable for over 12 months, as documented by a series of qualitative scales and 2D images, independently scored by the central evaluating physician, the injecting physician, and/or through patient self-evaluation (Figures 2-7).

The procedure utilized to administer the study filler in the current study, which featured a specific injection sequence combined with a structured goal-setting exercise and strict eligibility criteria (see Methods), was developed to address the common structural deficiencies seen in Asians and to also minimize the risk for AEs. Indeed, the

Table 3. Incidence of Injection Site Reactions During the Study

Injection Site Reactions	n (%)
Swelling	28 (96.6)
Erythema	20 (69.0)
Bruising	16 (55.2)
Pain	11 (37.9)
Discomfort	8 (27.6)
Hypoesthesia	2 (6.9)
Injection site reaction	1 (3.4)
Pruritis	1 (3.4)

Frequency of injection site reactions reported in a total of 29 subjects. All events were mild to moderate in presentation, with all related to the injection procedure and not the study product.

treatment-emergent AEs in our study were mild to moderate and transient injection site reactions, all of which were deemed by the injecting physicians to be related to the injection procedure and not the study filler.

As is the case with all aesthetic treatments of the face, a comprehensive understanding of the associated risks is mandatory. As such, injecting physicians are required to explain these risks carefully to the prospective study patient and indeed to screen these patients carefully prior to treatment, including a history of nose trauma, prior surgery, and/or any other procedure to the nose. Further, an understanding of standard vascular anatomy and its variants is essential. The facial artery is the principal source of blood supply to the external nose, with the main branches—the superior labial and angular arteries—supplying the nose tip by forming the columellar and lateral nasal branches, with the latter located superior to the alar groove. The dorsal nasal and external nasal arteries are also branches of the ophthalmic artery, which also provides collateral flow to the nasal tip.[31,32] Isolated reports of tip necrosis or visual disturbance have been documented in the literature following the use of fillers of all types, including fat, polylactic acid, and hyaluronic acid, and indeed have been documented as a rare complication of surgical rhinoplasty. The mechanism for this is assumed to be compression, occlusion, and/or through embolization of these vessels. These events are clearly not unique to the nasal vasculature, with similar reports following the administration of fillers in the forehead, glabellar, temple, and nasolabial regions.[14,33-39] We used a needle in our study, as we considered that the study filler could be more effectively and accurately injected in the nose. Additionally, the standardized injection procedure employed in the study was designed to minimize the risk of the aforementioned vascular complications.

One possible limitation of the study was its non-comparative and open-label design. To enable an independent evaluation of the treatment results, a single central evaluating physician was utilized. He was not an injecting physician and was not involved in the initial clinical assessment or the treatment goal setting of each study patient. Furthermore, he was unaware of which physician had injected the study filler in each patient, or the number, sites, or volume of the injections.

Notably, the scores independently documented by the central evaluating physician and the study patients were found to be very consistent (Figure 2).

Another possible limitation in the current study was the absence of a quantitative outcome parameter. In a future study, we would aim to formally quantify the results of the current study by utilizing 3D imaging to accurately assess volumetric change over time.

The treatment goal of alar base narrowing and/or nostril shape alteration was identified in the current study as the most difficult outcome to achieve, as documented on the NTGAS, with only 4/9 (44.4%) and 2/9 (22.2%) patients attaining this goal, according to the central evaluating physician and the injecting physicians, respectively (Figure 8B). As this treatment goal is technically difficult to achieve effectively with surgical rhinoplasty, even when utilizing a cartilaginous graft and an excision technique, this is perhaps not unexpected.[40] In the future, the possible development of new HA fillers with better lift capacity may assist in achieving these treatment goals through the provision of more sustained projection and support.

CONCLUSIONS

The administration of the study filler, utilizing a standardized injection protocol and a structured goal-setting procedure with strict eligibility criteria, successfully and safely corrected aesthetically deficient and/or detracting features in the Asian nose. Notably, this correction was maintained for over 12 months, providing evidence for the utility of this HA filler as a non-surgical alternative in carefully selected Asian patients unwilling or unable to have surgery.

Supplementary Material

This article contains supplementary material located online at www.aestheticsurgeryjournal.com.

Acknowledgments

The data management and statistical analysis were conducted independently by Datalytics Pty Ltd (Sydney, Australia). The digital imaging equipment and software applications were provided by Canfield Scientific, Inc. (Fairfield, NJ). The study coordination at the investigational sites was performed by Louise Hart-Brown and Nola Campbell.

Disclosures

Dr Liew is a Consultant and an Advisory Board Member for Allergan, Galderma, and Kythera. Dr Scamp is a Consultant and an Advisory Board Member for Allergan, Galderma, and Canfield Scientific. Dr de Maio is a Consultant and an Advisory Board Member for Allergan. All have received honoraria for providing lectures on behalf of these companies. Dr Rogers, Mr Halstead, Dr Silberberg, and Ms Johnston were full-time employees of Allergan at the time the study was designed and conducted. Dr Rogers, Dr Silberberg, and Mr Halstead were also Allergan stockholders during this time.

Funding

The clinical study was sponsored by Allergan plc, Dublin, Ireland. While the authors did not receive financial support for the writing of this article and none of the authors received payment for the preparation of this manuscript, Drs Liew, Scamp, and de Maio received compensation as clinical investigators for this study.

REFERENCES

1. Cosmetic Surgery National Data Bank Statistics. *Aesthet Surg J*. 2015;35(Suppl 2):1-24.
2. Ishii CH. Current Update in Asian Rhinoplasty. *Plast Reconstr Surg Glob Open*. 2014;2(4):e133:1-8.
3. Wu WT. The Oriental nose: an anatomical basis for surgery. *Ann Acad Med Singapore*. 1992;21(2):176-189.
4. Le TT, Farkas LG, Ngim RC, Levin LS, Forrest CR. Proportionality in Asian and North American Caucasian faces using neoclassical facial canons as criteria. *Aesthetic Plast Surg*. 2002;26(1):64-69.
5. Shirakabe Y, Suzuki Y, Lam SM. A systematic approach to rhinoplasty of the Japanese nose: a thirty-year experience. *Aesthetic Plast Surg*. 2003;27(3):221-231.
6. Lam S. Asian Rhinoplasty. *Seminars in Plastic Surgery*. 2009;23(3):215-222.
7. Toriumi DM, Pero CD. Asian rhinoplasty. *Clin Plast Surg*. 2010;37(2):335-352.
8. Tanaka Y, Matsuo K, Yuzuriha S. Westernization of the Asian nose by augmentation of the retropositioned anterior nasal spine with an injectable filler. *Eplasty*. 2011;11:e7.
9. Kim P, Ahn JT. Structured nonsurgical Asian rhinoplasty. *Aesthetic Plast Surg*. 2012;36(3):698-703.
10. Bergeron L, Chen PK. Asian rhinoplasty techniques. *Semin Plast Surg*. 2009;23(1):16-21.
11. Park CH. Dorsal Augmentation for the Asian Nose. In: Shiffman MA, Di Giuseppe A. eds. *Advanced Aesthetic Rhinoplasty: Art, Science, and New Clinical Techniques*. New York, NY: Springer; 2013:1004.
12. Gu Y, McNamara JA, Sigler LM, Baccetti T. Comparison of craniofacial characteristics of typical Chinese and Caucasian young adults. *Eur J Orthod*. 2011;33(2):205-211.
13. Holt GR, Garner ET, McLarey D. Postoperative sequelae and complications of rhinoplasty. *Otolaryngol Clin North Am*. 1987;20(4):853-876.
14. Rettinger G. Risks and complications in rhinoplasty. *GMS Curr Top Otorhinolaryngol Head Neck Surg*. 2007; 6:1-14.
15. Rokhsar C, Ciocon DH. Nonsurgical rhinoplasty: an evaluation of injectable calcium hydroxylapatite filler for nasal contouring. *Dermatol Surg*. 2008;34(7):944-946.
16. de Maio M. The minimal approach: an innovation in facial cosmetic procedures. *Aesthetic Plast Surg*. 2004;28 (5):295-300.
17. Gold MH. Use of hyaluronic acid fillers for the treatment of the aging face. *Clin Interv Aging*. 2007;2(3):369-376.
18. Dayan SH, Bassichis BA. Facial dermal fillers: selection of appropriate products and techniques. *Aesthet Surg J*. 2008;28(3):335-347.
19. Bray D, Hopkins C, Roberts DN. A review of dermal fillers in facial plastic surgery. *Curr Opin Otolaryngol Head Neck Surg*. 2010;18(4):295-302.
20. Goodman GJ, Bekhor P, Rich M, Rosen RH, Halstead MB, Rogers JD. A comparison of the efficacy, safety, and longevity of two different hyaluronic acid dermal fillers in the treatment of severe nasolabial folds: a multicenter, prospective, randomized, controlled, single-blind, within-subject study. *Clin Cosmet Investig Dermatol*. 2011;4: 197-205.
21. Muhn C, Rosen N, Solish N, et al. The evolving role of hyaluronic acid fillers for facial volume restoration and contouring: a Canadian overview. *Clin Cosmet Investig Dermatol*. 2012;5:147-158.
22. Callan P, Goodman GJ, Carlisle I, et al. Efficacy and safety of a hyaluronic acid filler in subjects treated for correction of midface volume deficiency: A 24 month study. *Clin Cosmet Investig Dermatol*. 2013;6:81-89.
23. Tezel A, Fredrickson GH. The science of hyaluronic acid dermal fillers. *J Cosmet Laser Ther*. 2008;10(1):35-42.
24. Jones D, Tezel A, Borrell M. In vitro resistance to degradation of hyaluronic acid fillers by ovine testicular hyaluronidase. *Dermatol Surg*. 2010;36:804-809.
25. Borrell M, Leslie DB, Tezel A. Lift capabilities of hyaluronic acid fillers. *J Cosmet Laser Ther*. 2011;13(1):21-27.
26. Maloney BP. Nasal contouring using fillers. *Operative Techniques in Otolaryngology*. 2007;18:302-306.
27. Redaelli A. Medical rhinoplasty with hyaluronic acid and botulinum toxin A: a very simple and quite effective technique. *J Cosmet Dermatol*. 2008;7(3):210-220.
28. Xue K, Chiang CA, Liu K, Gu B, Li Q. Multiplane hyaluronic acid rhinoplasty. *Plast Reconstr Surg*. 2012;129 (2):371e-372e.
29. Pearson DC, Adamson PA. The ideal nasal profile: rhinoplasty patients vs. the general public. *Arch Facial Plast Surg*. 2004;6(4):257-262.
30. Swift A, Remington K. BeautiPHIcation™: A global approach to facial beauty. *Clin Plast Surg*. 2011;38(3):347-377.
31. Rohrich RJ, Gunter JP, Friedman RM. Nasal tip blood supply: an anatomic study validating the safety of the transcolumellar incision in rhinoplasty. *Plast Reconstr Surg*. 1995;95(5):795-799; Discussion: 800-801.
32. Koppe T, Giotakis EI, Heppt W. Functional anatomy of the nose. *Facial Plast Surg*. 2011;27(2):135-145.

33. Grunebaum LD, Bogdan Allemann I, Dayan S, Mandy S, Baumann L. The risk of alar necrosis associated with dermal filler injection. *Dermatol Surg*. 2009;35 Suppl 2:1635-1640.
34. Lazzeri D, Agostini T, Figus M, Nardi M, Pantaloni M, Lazzeri S. Blindness following cosmetic injections of the face. *Plast Reconstr Surg*. 2012;129(4):995-1012.
35. Park SW, Woo SJ, Park KH, Huh JW, Jung C, Kwon OK. Iatrogenic retinal artery occlusion caused by cosmetic facial filler injections. *Am J Ophthalmol*. 2012;154(4):653-662.
36. Carruthers JD, Fagien S, Rohrich RJ, Weinkle S, Carruthers A. Blindness caused by cosmetic filler injection: a review of cause and therapy. *Plast Reconstr Surg*. 2014;134(6): 1197-1201.
37. Carle MV, Roe R, Novack R, Boyer DS. Cosmetic facial fillers and severe vision loss. *JAMA Ophthalmol*. 2014; 132(5):637-639.
38. DeLorenzi C. Complications of injectable fillers, part 2: vascular complications. *Aesthet Surg J*. 2014;34(4):584-600.
39. Manafi A, Barikbin B, Manafi A, Hamedi ZS, Ahmadi Moghadam S. Nasal alar necrosis following hyaluronic Acid injection into nasolabial folds: A case report. *World J Plast Surg*. 2015;4(1):74-78.
40. Gruber RP, Nathan N, Endress RD. Nasal Base Reduction. In: Rohrich RJ, Adams WP, Ahmad J, Gunter J, eds. *Dallas Rhinoplasty: Nasal Surgery by the Masters*, 3rd edn. CRC Press 2014:675.