Impact of Comprehensive, Minimally Invasive, Multimodal Aesthetic Treatment on Satisfaction With Facial Appearance: The HARMONY Study

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Abstract

Background: Individuals seeking aesthetic treatment have concerns regarding multiple facial areas.

Objectives: Assess the aesthetic impact and satisfaction achieved with a multimodal approach to aesthetic treatment using a combination of minimally invasive treatments.

Methods: Prospective, multicenter, rater-blinded, 4-month HARMONY study evaluated patient satisfaction and aesthetic impact of a combination of fillers (VYC-20L, HYC-24L, and HYC-24L+), onabotulinumtoxinA, and bimatoprost. Males and females aged 35 to 65 years received on-label, staged treatment with fillers, as needed per investigator assessment, on day 1, with touch ups allowed on day 14. Bimatoprost was self-administered once daily for 17 weeks. OnabotulinumtoxinA was injected into glabellar lines, crow's feet lines, or both at month 3. Primary effectiveness measure was mean change from baseline on the FACE-Q 10-item Satisfaction with Facial Appearance Overall Scale.

Results: Of 100 patients treated, 93 underwent at least the 4-month posttreatment assessment and were assessed for efficacy. The FACE-Q Satisfaction with Facial Appearance Overall Scale total score increased from baseline (41.2) to month 4 (72.9; $P < 0.00001$; effect size, 2.7). Improvement following multimodal treatment was observed on FACE-Q individual items. Self-perceived age decreased from 0.2 years older than actual age at baseline to 4.6 years younger at month 4. Nearly all patients (99%) rated themselves as improved or much improved on the Global Aesthetic Improvement Scale. Investigator assessments also demonstrated improvement. Mild to moderate adverse events occurred in 42 patients.

Conclusions: Minimally invasive, multimodal treatment resulted in improvements in FACE-Q scores and perceived age, indicating a high degree of patient satisfaction and a younger facial appearance.

Level of Evidence: 4

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Individuals presenting for aesthetic treatment often have concerns regarding multiple facial areas and features and seek noninvasive treatments[1] to achieve a look that is rested and relaxed, yet natural.[2] Patients seeking facial aesthetic treatment represent a clinically heterogeneous group, each presenting with an individual set of perceived needs.[3] However, they often express a level of psychological dissatisfaction with their appearance.[4,5] In a survey conducted in 10 countries of women's attitudes to beauty and physical appearance, the vast majority of the 3200 respondents were more comfortable describing their appearance as natural or average and less comfortable describing themselves as beautiful.[6] Such attitudes on physical appearance have a wide-ranging impact on well-being and satisfaction with appearance. Almost half of women surveyed reported that when they felt less beautiful, they felt worse about their self-esteem and happiness, and more than half were only somewhat satisfied with their appearance.[6] Studies of individuals seeking cosmetic plastic surgery procedures ranging from rhinoplasty and face lifts, breast augmentation and mammoplasty, abdominoplasty, and liposuction have shown that appropriate treatment can result in improved psychological well-being and psychosocial outcomes and may have a positive impact on emotional and affective aspects of psychological health.[7-9]

As facial aesthetic medicine evolves, clinicians increasingly recognize that achieving optimal results requires viewing the face as a whole, with each facial region being interconnected; treating one facial area may impact other areas.[10] Thus, the management of the aging face should employ multiple techniques to address surface changes, such as lines and wrinkles, as well as volume changes and their visible consequences. To meet their patients' aesthetic goals, many clinicians have adopted this global approach to facial rejuvenation, with patients commonly receiving treatment in multiple areas in a single treatment session or in staged sessions, based on an agreed-upon treatment plan.[11-15]

Large, well-designed clinical trials have not systematically evaluated this multimodal approach to aesthetic treatment. Previous studies generally focused on treating one or two facial areas, using products of the same type (eg, dermal fillers).[16-20] However, a Canadian/US multicenter, single-blind, randomized trial in which 30 patients received combination therapy with a neurotoxin in the lower face plus a dermal filler to rejuvenate the perioral area demonstrated synergistic benefits.[21] Another study, a 6-month, open-label, multicenter trial, assessed the effects of facial rejuvenation with a range of hyaluronic acid (HA) fillers in 77 patients, but the approach was not truly multimodal, as only HA fillers were utilized.[22]

Past studies have typically evaluated the efficacy and safety of specific products or devices using rating scales that measure physical, objective changes in specific facial features.[16-18] These individual outcomes have been examined from the perspective of clinician-assessed endpoints, typically with the aim of achieving regulatory authority approval rather than focusing on the overall benefit provided to the patient. In light of the importance of dissatisfaction with aging facial appearance as a central factor driving patients to seek aesthetic treatment,[4,5] patient-reported outcomes (PROs) that assess satisfaction with the amelioration of the undesirable aspect of their appearance are increasingly viewed as essential indicators of aesthetic treatment benefit. Although some studies have assessed PROs following treatment with onabotulinumtoxinA or with HA fillers and reported benefits with regard to self-esteem, self-perception of age, and patient satisfaction,[22-28] these studies did not evaluate PROs in association with a comprehensive approach using multiple treatment modalities. Recently, one study evaluated the results of facial aesthetic treatment of multiple facial regions with a neurotoxin and with HA fillers, utilizing investigator-assessed global improvement and patient-assessed satisfaction as endpoints.[29]

The HARMONY study was designed to assess the aesthetic impact of a multimodal treatment approach, using a combination of treatment modalities. The assessments consisted of a range of validated PROs for patient satisfaction, self-esteem, psychological well-being, social confidence, and perception of age. The key outcome assessments were selected from the validated FACE-Q set of PRO instruments. The FACE-Q is composed of more than 40 independent scales and checklists,[30] which allows for selection of measures that are relevant to the study procedures and provides relevant data on outcomes important to both patients and clinicians.[3,30] Additionally, effect sizes were calculated for key outcomes to allow for comparison across studies and methodologies. This report describes the findings for patient satisfaction with facial appearance, for the clinical effectiveness on individual facial areas, and for safety.

METHODS

Study Design and Ethics

The HARMONY study (clinicaltrials.gov identifier: NCT02176356) was a multicenter, single-blind, 4-month study conducted in the United States between July 1, 2014, and February 17, 2015, that evaluated patients receiving combined treatment with: onabotulinumtoxinA (Botox Cosmetic) for treatment of rhytids; HA dermal fillers for treatment of facial lines and folds using HYC-24L (Juvéderm Ultra XC) and/or HYC-24L+ (Juvéderm Ultra Plus XC) and, for volume restoration, VYC-20L (Juvéderm Voluma XC); and bimatoprost 0.03% ophthalmic solution (Latisse) for treatment of eyelash hypotrichosis (all products, Allergan plc; Dublin, Ireland). The study was conducted in accordance with the US Food and Drug Administration regulations and guidelines, the International Council for

Harmonisation (ICH) Good Clinical Practice guidelines, and local laws and regulations. The protocol was approved by a central Institutional Review Board (Schulman Associates IRB; Cincinnati, OH), and all patients provided written informed consent before study participation. Patients were reimbursed for their study-related expenses. Source documents were identified with the patient's unique identifier (ie, patients were anonymous).

Detailed information on study methodology, including patient selection, study design and conduct, and outcome measures, were previously reported[31] and are briefly summarized here.

Patients

Eligible patients were males or females aged 35 to 65 years who were naive to treatment with botulinum toxins, dermal fillers, and eyelash growth products. Patients met the following criteria: had moderate or severe glabellar lines (GL) and/or crow's feet lines (CFL); presented with at least 2 of the following, which, in the opinion of the investigator and patients, required treatment with dermal fillers: moderate or severe nasolabial folds (NLF), oral commissures (OC), perioral lines (POL), marionette lines (ML), and/or radial cheek lines (RCL), and/or moderate to substantial midface volume deficit (MFVD); and had minimal or moderate eyelash hypotrichosis on the 4-point Global Eyelash Assessment (GEA) scale, as determined by the treating investigator. Full study design and inclusion and exclusion criteria are described in Appendix A (available online as Supplementary Material at www.aestheticsurgeryjournal.com) and have been summarized previously.[31]

Treatment

Injectable treatments were administered by the treating investigators. For hypotrichosis, patients applied bimatoprost to the upper eyelid margins once daily in the evening from day 1. On days 1 and 14, for initial and touch-up treatments, respectively, HYC-24L and/or HYC-24L+ were injected as needed for NLF, OC, POL, ML, and/or RCL, with a maximum total volume of 6.0 mL (initial and touch up). On days1 and 14 for initial and touch-up treatments, respectively, VYC-20L was injected, as needed, for MFVD, with a maximum total volume of 4.0 mL (initial and touch up). At month 3, onabotulinumtoxinA was injected for GL and/or CFL, according to the FDA-approved injection pattern and doses for each indication. Patients received all treatment products on a complimentary basis.

Assessments

All effectiveness assessments were conducted at month 4. The primary effectiveness measure was the mean change from baseline on the FACE-Q 10-item Satisfaction with Facial Appearance Overall Scale.[3,32] Patients completed the scale in writing in the treating investigator's office. Each item was evaluated on a 4-point scale (very dissatisfied to very satisfied). Additional FACE-Q assessments, including the FACE-Q Aging Appearance Appraisal, FACE-Q Age Appraisal Visual Analog Scale, FACE-Q Social Confidence Scale, and FACE-Q Psychological Well-Being Scale, were evaluated, and results are reported separately.

The single-item, validated, Self-Perception of Age (SPA) measure[33] was based on a numeric estimation from the question, "How do you think your facial appearance looks compared to your age TODAY?" Response options included selecting the statement "I look my current age" or entering a value into one of the following statements: "I look __ years older" or "I look __ years younger." Responders were defined as those achieving a younger category at month 4 compared with that at baseline. Patient self-assessed and investigator-assessed global aesthetic improvement on the Global Aesthetic Improvement Scale (GAIS) at month 4 was scored using a 5-point scale wherein 2 = much improved (marked improvement in appearance), 1 = improved (improvement in appearance but a touch-up or re-treatment is indicated), 0 = no change (appearance essentially the same as original condition), −1 = worse (appearance worse than original condition), and −2 = much worse (appearance much worse than original condition).

Investigator-assessed secondary effectiveness measures, performed by an evaluating investigator who remained blinded to treatment assignment throughout the study, included mean change from baseline for the following: overall MFVD on the 6-point photometric Midface Volume Deficit Scale (MFVDS)[16]; severity of NLF, OC, and POL, using the 5-point NLF Severity Scale (NLFSS),[34] the 4-point OC Severity Scale, and the 4-point POL Severity Scale, respectively[18,35]; GL and/or CFL at maximum contraction using the appropriate Facial Wrinkle Scale (FWS) with a photonumeric guide[36]; and GEA, based on a 4-point scale.[37] For each of these assessments, responders were defined as patients achieving at least a 1-grade improvement from baseline.

Safety assessments included monitoring adverse events (AEs) and common injection site responses, which were recorded daily by patients in provided study diaries. Adverse events were categorized by the investigators as either procedure related (eg, bruising) or product related (eg, eyelid irritation).

Statistical Analysis

Efficacy analyses were conducted on the modified intent-to-treat (mITT) population, which included all patients who received treatment with all products and completed at least the month 4 posttreatment efficacy assessment. For

the FACE-Q Satisfaction with Facial Appearance Scale, raw scores of the individual items for each scale were summed to provide the total raw scores for the original scales. Raw data were transformed by Rasch measurement methods to a 0- to 100-point scale, with higher scores indicating greater satisfaction.[38,39] Transformed score ranges for each response category for all items were calculated based on threshold estimates.[40] Data were analyzed using a paired *t* test (or Wilcoxon signed-rank test, depending on the distribution of the data). Analyses were performed using the RUMM2030 software (RUMM Laboratory; Perth, Australia).

Effect size (Cohen's d) associated with mean change was calculated.[41,42] Effect sizes of 0.20, 0.50, and 0.80 are considered small, medium, and large, respectively,[41] whereas effect sizes greater than 0.80 are considered very large. Additionally, outcomes were assessed for the subgroup of patients with significant improvement on the FACE-Q Satisfaction with Facial Appearance Scale. Differences were examined at the individual patient level by determining which patients had a posttreatment FACE-Q score that fell outside the 95% confidence intervals for the baseline scores. The 95% confidence intervals around the baseline FACE-Q scores were computed as baseline score ± 1.96 × SE baseline. Therefore, patients with calculated values of at least 1.96 were considered to have significant improvement and were included in this subgroup analysis.

Safety analyses were conducted in the safety population, defined as all patients who were treated with any study product. Adverse events were summarized by system organ class, preferred term, and severity, as well as by their relationship to treatment and the number and percentage of patients with each AE were summarized.

RESULTS

Of the 116 enrolled patients, 100 received treatment and constituted the safety population (Figure 1). Sixteen patients were enrolled but failed screening and were not eligible for treatment. The mITT population for the overall analysis of effectiveness outcomes comprised 93 patients. Among patients in the safety population who were not also included in the mITT population, 4 were lost to follow up and not treated with all products and 3 discontinued early for personal reasons. Seventy-nine patients were classified as achieving significant improvement in FACE-Q Satisfaction with Facial Appearance Overall score from baseline to month 4.

Detailed demographics and baseline characteristics were previously reported.[31] Patients were predominantly white (86%) and female (96%) and had a mean (standard deviation [SD]) age of 52.5 (7.4) years (range, 37-65 years). As assessed by the treating investigator, for most facial

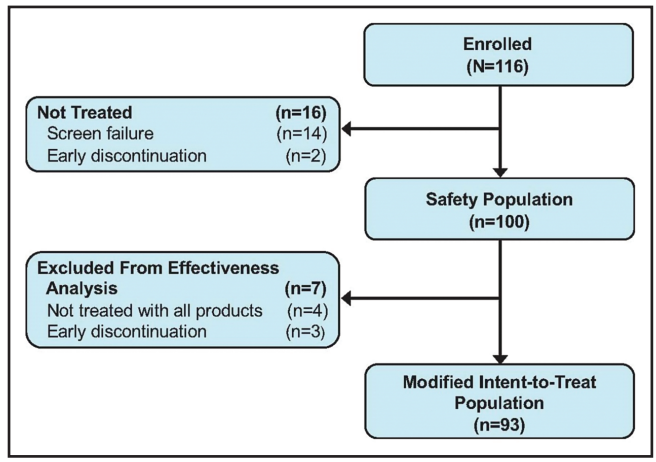

Figure 1. Patient disposition.

regions, the majority of patients had a baseline rating of at least moderate for age-related facial appearance (Table 1). The MFVDS ratings were moderate or significant in 96% of patients, with a mean rating of 3.1. In addition, NLFSS ratings were moderate to extreme in 96% of patients, with a mean rating of 2.6, Oral Commissure Severity Scale ratings were moderate or severe in 88% of patients, with a mean rating of 2.1, and ratings on the Perioral Lines Severity Scale were moderate or severe in 62% of patients, with a mean rating of 1.6.

Patient Satisfaction

The total score for the primary measure, the FACE-Q Satisfaction with Facial Appearance Overall Scale, increased from a mean (SD) score of 41.2 (12.0) to 72.9 (18.3), indicating that, on average, baseline scores for most patients were associated with somewhat dissatisfied or somewhat satisfied responses, and scores at month 4 were associated with somewhat satisfied or very satisfied responses. The change was significant ($P < 0.0001$) and demonstrated a very large effect size (2.7; Figure 2A).

For the subgroup of patients with significant individual improvements (n = 79), the mean (SD) baseline score was slightly lower (39.4 [11.2]), indicating that, on average, baseline scores for most patients were associated with very dissatisfied or somewhat dissatisfied responses with their facial appearance. At month 4, the mean (SD) score was higher (76.4 [15.3]), indicating that most patients' scores were associated with somewhat satisfied or very satisfied responses with their facial appearance after treatment (Figure 2B).

For each of the 10 individual FACE-Q item questions, patients in the mITT group reported mean improvement of 1 response category from their baseline ratings (Figure 3A). At baseline, patients were either somewhat

Table 1. Baseline Severity of Facial Areas Injected for the Overall Population (n = 100). Reprinted With Permission From Wolters Kluwer Health, Inc[31]

Treatment facial area treated	Mean Score	Patients per scale rating, n						Data missing
Dermal filler								
Midface*	3.1	None	Minimal	Mild	Moderate	Significant	Severe	0
		0	1	3	80	16	0	
Nasolabial folds†	2.6	None	Mild	Moderate	Severe	Extreme	—	0
		0	4	36	59	1		
Oral commissures‡	2.1	None	Mild	Moderate	Severe	—	—	1
		0	11	67	21			
Perioral lines§	1.6	None	Mild	Moderate	Severe	—	—	2
		12	24	52	10			
OnabotulinumtoxinA								
Glabellar lines at maximum frown‖	2.5	None	Mild	Moderate	Severe	—	—	3
		0	1	44	52			
Glabellar lines at rest‖	1.7	None	Mild	Moderate	Severe	—	—	3
		1	33	55	8			
Crow's feet lines at maximum smile‖	2.5	None	Mild	Moderate	Severe	—	—	3
		0	0	50	47			
Crow's feet lines at rest‖	1.9	None	Mild	Moderate	Severe	—	—	3
		0	26	52	19			

*Scores based on the Midface Volume Deficit Scale. †Scores based on the Nasolabial Fold Severity (NLFS) Scale. ‡Scores based on the Oral Commissure Severity Scale. §Scores based on the Perioral Lines Severity Scale. ‖Scores based on the Facial Wrinkle Scale with photonumeric guide.

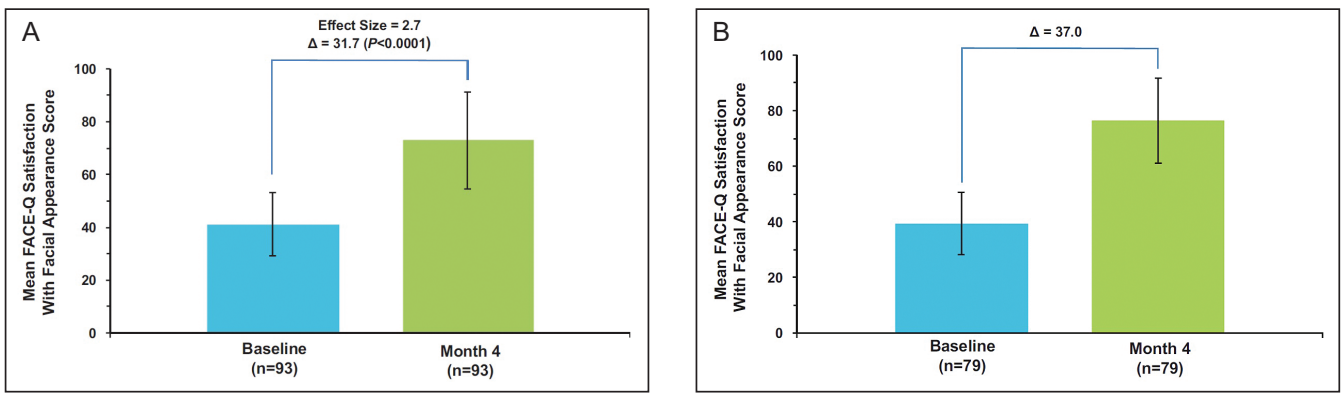

Figure 2. Mean (standard deviation) FACE-Q Satisfaction with Facial Appearance total score for (A) the intent-to-treat population (n = 93) and (B) patients with significant individual improvements (as defined in the Methods; n = 79). Raw scores for patient responses were Rasch-transformed to a 0 to 100 score range.

dissatisfied or somewhat satisfied with all items on the Satisfaction with Facial Appearance Overall scale. After treatment, they improved on all items (from somewhat dissatisfied to somewhat satisfied or from somewhat satisfied to very satisfied) on all items of the FACE-Q. For the subgroup of patients with significant improvement

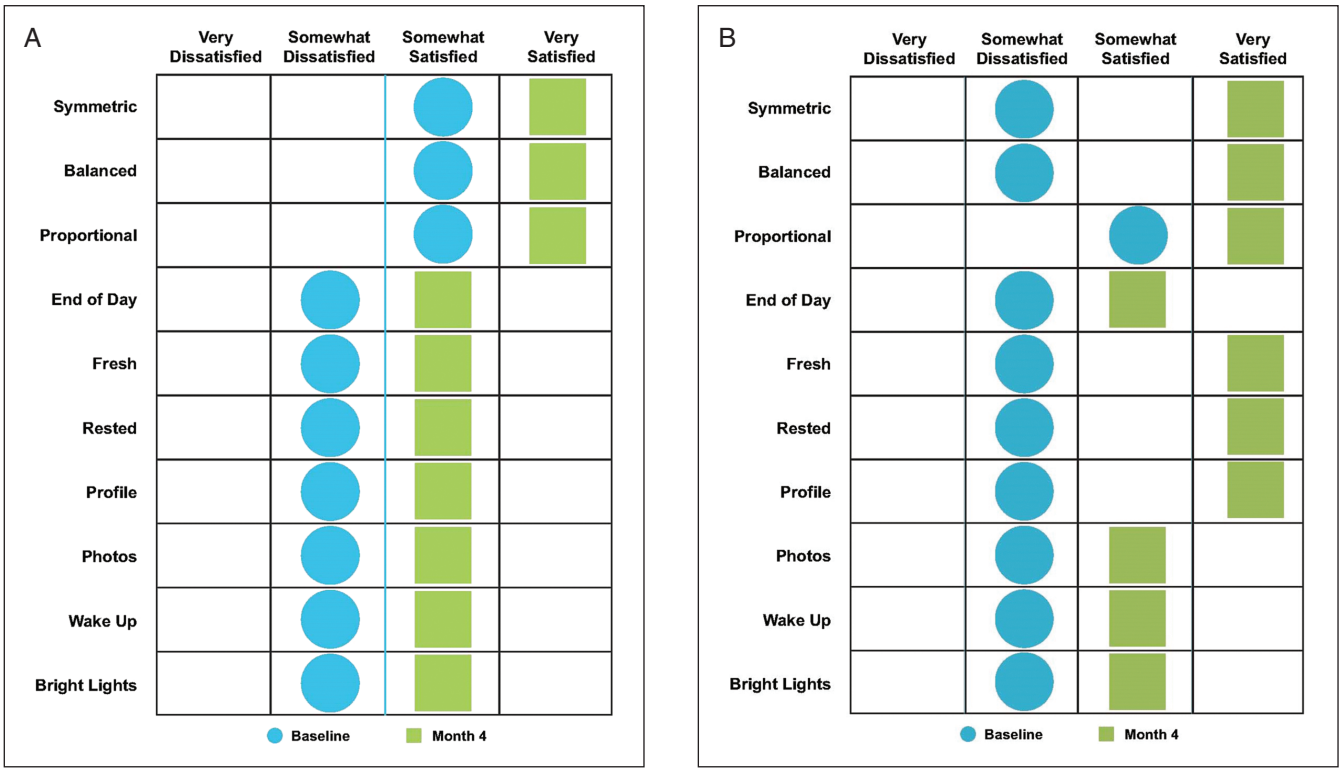

Figure 3. FACE-Q Satisfaction with Facial Appearance responses, by item and response category, for (A) the intent-to-treat population (n = 93) and (B) patients with significant improvement (as defined in the Methods section; n = 79).

on the overall scale, half of the items, including facial symmetry and balance and looking fresh and rested, demonstrated a 2-category improvement; all of the remaining items showed a 1-category improvement (Figure 3B).

Overall, at baseline, patients perceived themselves to look, on average, 0.2 (SD, 4.08) years older relative to their actual age but reported looking 4.6 (SD, 4.19) years younger at month 4. At month 4, 73 patients (78%) reported looking an age that was younger than at baseline by a mean (SD) decrease in perceived age of 6.4 (3.63) years, 12 patients (13%) reported that they looked their current age, and 8 patients (9%) felt they looked an age that was a mean (SD) of 2.9 (2.47) years older than their current age (Figure 4).

On the GAIS, patients and investigators independently assessed their satisfaction with treatment outcomes at month 4, with reference to a baseline photograph. Investigators rated the facial appearance of 99% of patients as improved or much improved from baseline. Likewise, 99% of patients rated themselves as improved or much improved (Figure 5).

Figures 6 and 7 show representative patient photographs at baseline and at month 4, demonstrating aesthetic outcomes following treatment.

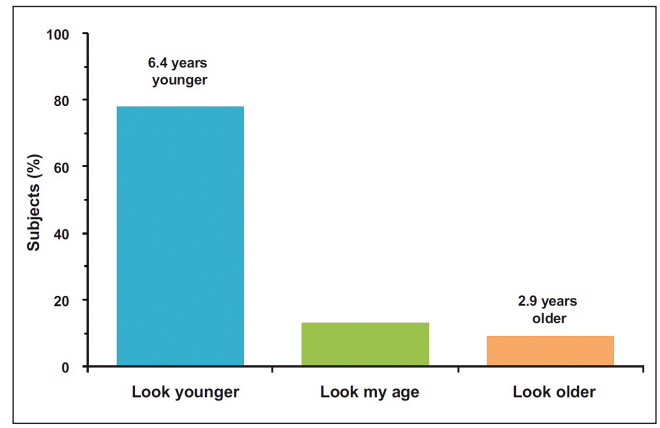

Figure 4. Patients' responses on the Self-Perception of Age questionnaire at month 4 (modified intent-to-treat population).

Blinded Investigator-Rated Assessment of Effectiveness

Dynamic facial wrinkles (GL and CFL) improved after treatment with onabotulinumtoxinA. The proportion of responders (≥1-grade improvement from baseline at month 4) for GL on the FWS at maximum frown was 96%. The GL

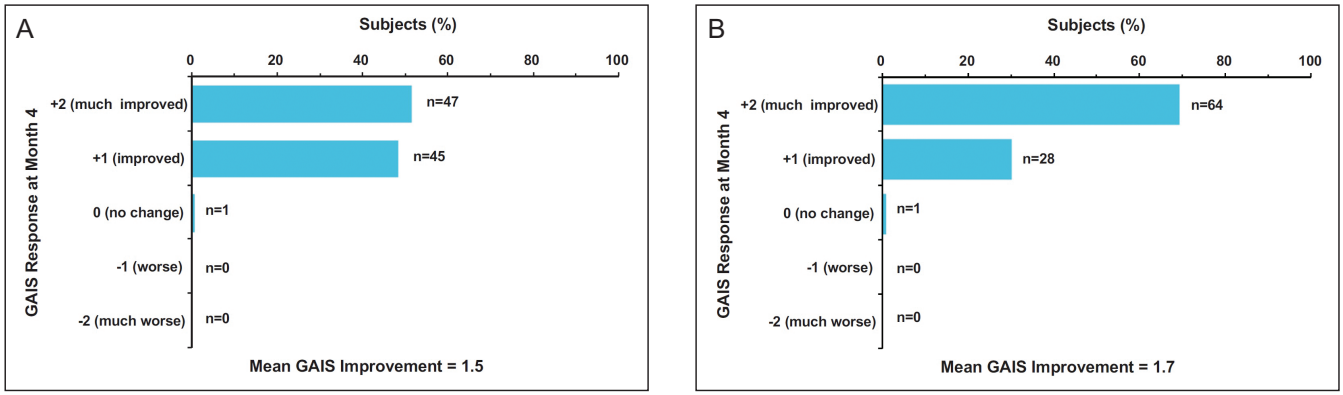

Figure 5. Global Aesthetic Improvement Scale responses at month 4, (A) as rated by the investigators and (B) as self-rated by the patients (modified intent-to-treat population). GAIS, Global Aesthetic Improvement Scale.

severity scores at maximum frown decreased from a mean of 2.6 at baseline to 0.9 at month 4 ($P < 0.001$; Figure 8A) The CFL severity score was assessed independently for the right and left sides; however, a high degree of side-to-side consistency was observed. Nearly three fourths of patients were rated as responders for CFL on the FWS at maximum smile, and CFL severity decreased from a mean of 2.5 at baseline to 1.5 at month 4 ($P < 0.001$; Figure 8B).

Based on investigator assessments, MFVDs, facial folds, and static wrinkles improved after treatment with HA fillers. The MFVD decreased significantly ($P < 0.001$) from a mean overall MFVD severity score of 3.1 at baseline to 1.4 at month 4 in those who received treatment in the midface (Figure 9); 97% of patients were considered responders. Significant improvements from baseline to month 4 in NLF, OC, and POL severity scores (all, $P < 0.001$) were observed (Figure 10), and the proportion of responders for NLF, OC, and POL ranged from 72% to 81%.

Eyelash fullness increased significantly ($P < 0.001$) from a mean GEA score of 1.8 at baseline to 3.3 at month 4 (Figure 11), and 94% of patients were rated as responders.

Safety

Forty-two patients (42%) experienced a total of 130 AEs (Table 2). All AEs were mild to moderate in intensity, and no serious AEs or delayed-onset AEs related to fillers were reported. Ninety-one procedure-related AEs occurred; the most common were bruising (60 events), injection site pain (12 events), injection site redness (8 events), and swelling/edema (7 events). Twelve adverse events in 11 patients were deemed to be primarily related to a product and included itching, burning, irritation, rash, or hyperpigmentation in the eye or orbital areas related to bimatoprost (n = 6), eyelid ptosis related to onabotulinumtoxinA (n = 1), and skin induration, discomfort, edema, or lumps in isolated facial areas of filler injections (n = 5). Up to 92% of patients experienced at least 1 injection site response, with the majority being mild to moderate in severity (Table 3). The most commonly reported injection site responses (≥80% of patients), based on the daily diary entries, were bruising, tenderness, swelling, and lumps. No patients discontinued the study because of an AE.

DISCUSSION

The HARMONY study demonstrated the benefit of comprehensive minimally invasive, multimodal treatment with considerable improvements in patient-reported satisfaction with their facial appearance. The study aimed to determine the impact of a comprehensive, minimally invasive approach to facial rejuvenation on patients' self-perceptions. Using the rigorously developed and validated PRO measure, the FACE-Q Satisfaction with Facial Appearance Overall Scale, we found that patient satisfaction with their face overall almost doubled following treatment. The very large effect size for overall patient satisfaction with facial appearance indicates the robust nature of this finding. These results demonstrate the potential for this minimally invasive, multimodal approach to achieve the positive outcomes sought by patients.

Patients who undergo facial aesthetic treatment are a highly diverse group.[3] From the patients' perspective, satisfaction constitutes a critical and most important means of assessing the outcome for aesthetic dermatology procedures.[2] To capture this qualitative improvement the FACE-Q Satisfaction with Facial Appearance Overall Scale was chosen as the primary endpoint of the study. This validated scale was designed for patients undergoing any type or number of aesthetic facial procedures.[3,30,43] The FACE-Q Satisfaction with Facial Appearance Overall Scale assesses patient-rated global impressions of facial appearance. Three recent studies reported improved satisfaction using the FACE-Q Satisfaction with Appearance Overall Scale after

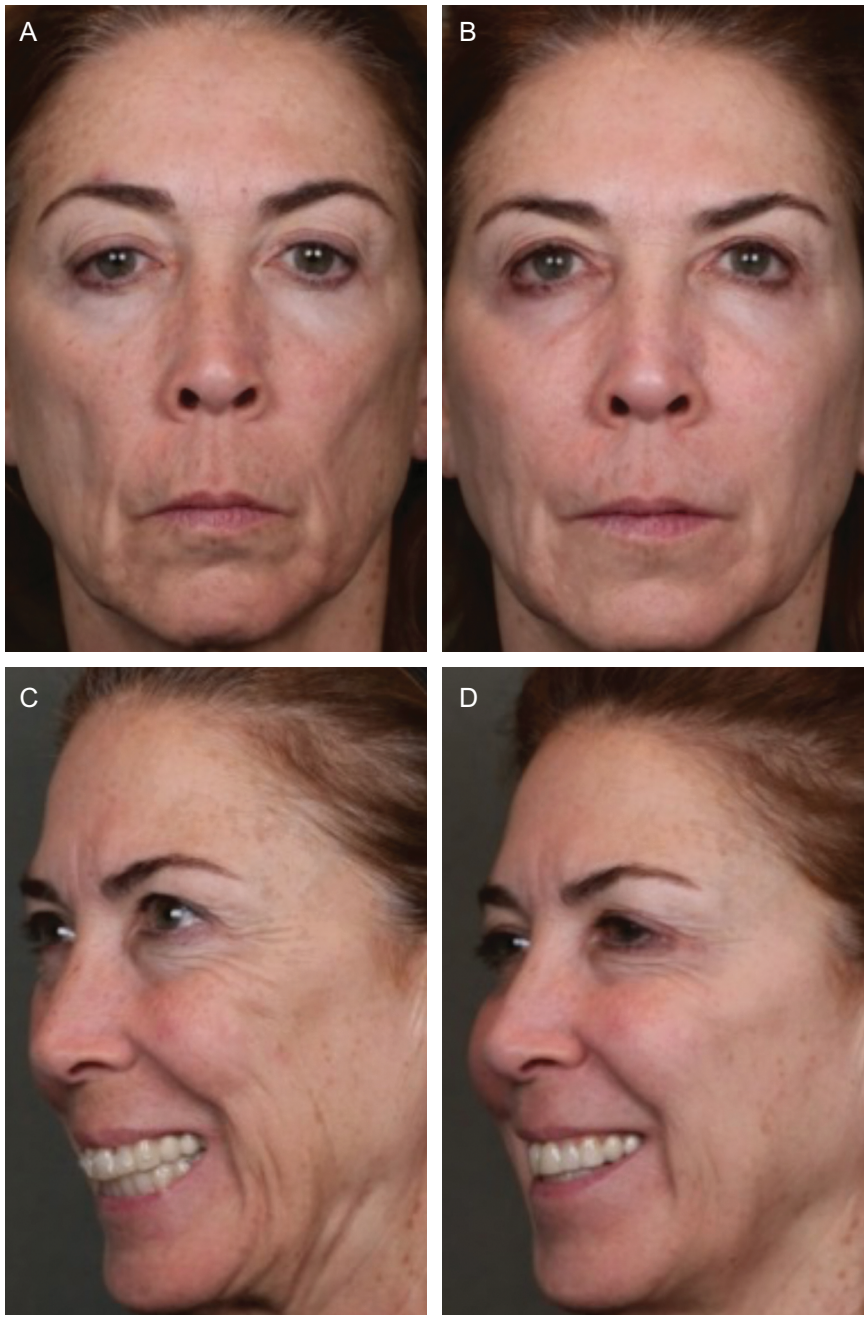

Figure 6. Frontal and left profile photographs of a 57-year-old female at baseline (A, C) and at month 4 (B, D). The patient received treatment with bimatoprost for eyelash hypotrichosis, with VYC-20L for midface volume deficiency; HYC-24L for nasolabial folds, oral commissures, and perioral lines; and HYC-24L+ for oral commissures and marionette lines. Glabellar lines and crow's feet lines were treated with onabotulinumtoxinA. At month 4, the patient's raw (not Rasch transformed) FACE-Q Satisfaction With Facial Appearance Overall Scale score improved 9 points from baseline, and the patient scored herself on the Self-Perception of Aging questionnaire as looking 3 years younger than her actual age. The GAIS-investigator assessment was 2 (much improved) and the GAIS-patient assessment was 1 (improved). GAIS, Global Aesthetic Improvement Scale.

treatment with minimally invasive cosmetic procedures. A 28% improvement from baseline in scores following treatment of GL with neuromodulators was reported in one study.[44] A separate study found an improvement from baseline of 15% at 1 month and 28% at 6 months after facial skin rejuvenation with multifractional microablative laser

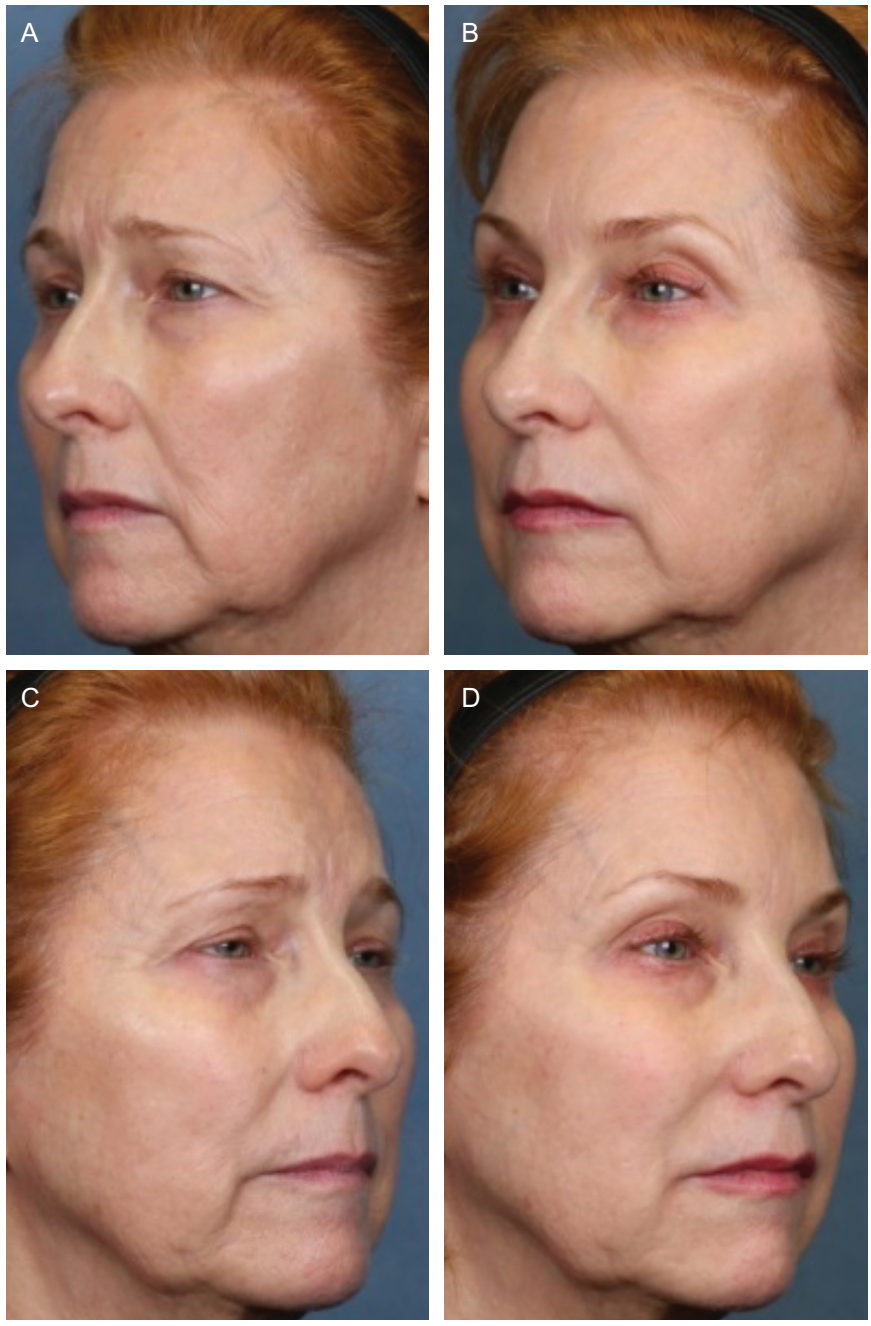

Figure 7. Left and right profile photographs of a 61-year-old female at baseline (A, C) and at month 4 (B, D). The patient applied bimatoprost daily to her eyelid margins and was treated with HYC-24L for nasolabial folds, oral commissures, perioral lines, and marionette lines and HYC-24L+ for nasolabial folds. Glabellar lines and crow's feet lines were treated with onabotulinumtoxinA. At month 4, the patient's FACE-Q raw (not Rasch transformed) Satisfaction With Facial Appearance Overall Scale score improved 14 points from baseline, and the patient scored herself on the Self-Perception of Aging questionnaire as looking 2 years younger than her actual age. The GAIS-investigator and GAIS-patient assessments were each 2 (much improved). GAIS, Global Aesthetic Improvement Scale.

treatment combined with spacially modulated ablation,[45] while a third reported an approximately 51% improvement from baseline in scores after laser resurfacing, injectable neuromodulator, or injectable filler, as appropriate.[46] Of note, these studies of single modality treatments in isolated facial areas report overall facial appearance improvements that are substantially less than the almost 2-fold improvement reported here, providing support for the notion

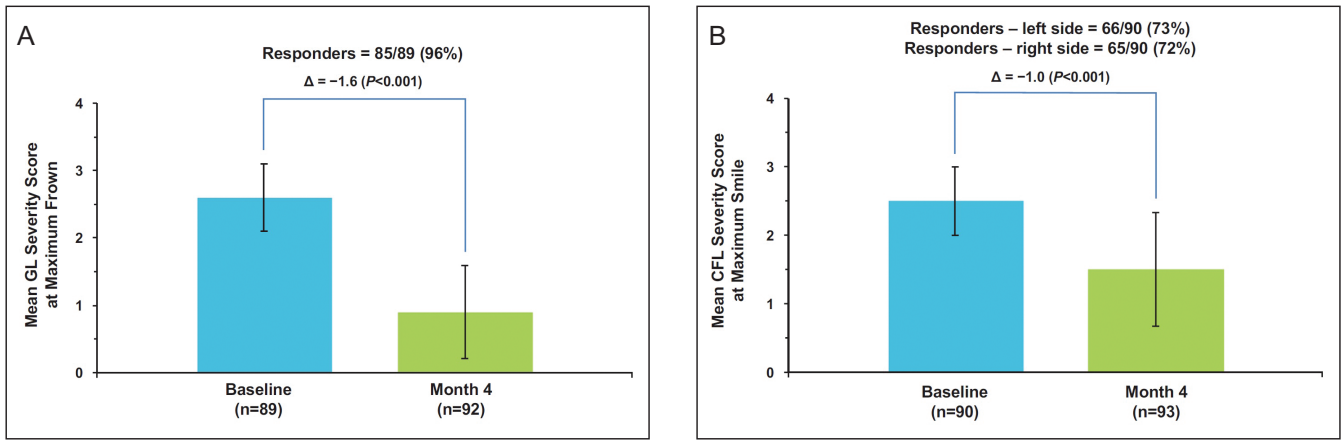

Figure 8. Investigator assessment of (A) glabellar line severity at maximum frown (n = 89) and (B) right and left crow's feet lines severity at maximum smile (n = 90). Assessments were made using the Facial Wrinkle Scale with photonumeric guide. Severity was assessed using a 4-point scale, wherein 0 = none, 1 = mild, 2 = moderate, and 3 = severe. N values indicate the number of evaluable patients at each time point. A responder was defined as achieving at least a 1-point improvement from baseline. Values for the right and left sides were identical. CFL, crow's feet lines; GL, glabellar lines.

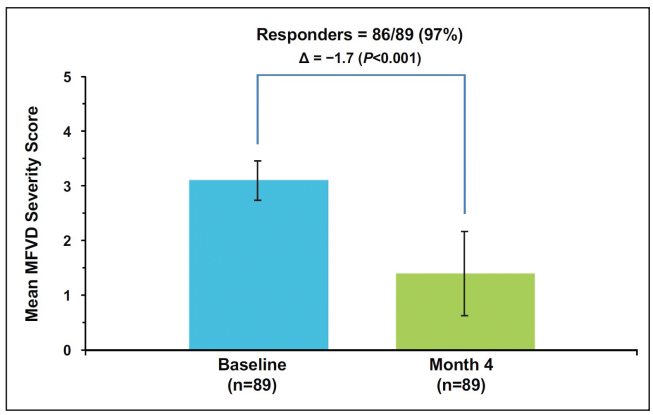

Figure 9. Investigator assessment of midface volume deficit (modified intent-to-treat population; n = 93) using the 6-point Midface Volume Deficit Severity Scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = significant, and 5 = severe). N values indicate the number of evaluable patients at each time point. A responder was defined as achieving at least a 1-point improvement from baseline. In patients who received treatment with VYC-20L, the overall mean volume injected in the right and left cheeks was 1.6 mL each. MFVD, midface volume deficit.

that minimally invasive, multimodal treatment results in enhanced benefit compared with isolated treatments. Additionally, more than 98% of patients rated themselves as being somewhat or very satisfied with treatment on the GAIS, providing strong support for the patient-perceived benefit of the multimodal treatment approach.

FACE-Q modules have also been used to demonstrate patient-reported benefits of plastic surgery procedures, such as rhinoplasty[47] and facelifts,[48] for both overall satisfaction and psychosocial outcomes. For patients undergoing rhinoplasty, mean scores on the FACE-Q Satisfaction with Appearance Overall Scale before and after treatment were 44.9 and 70.4, respectively.[47] While baseline scores were not reported for those undergoing facelifts, the mean FACE-Q Satisfaction with Appearance Overall Scale score after surgery was 80.7.[48] The current study found results on the FACE-Q to be similar to those reported for plastic surgery procedures, suggesting that a multimodal approach utilizing minimally invasive, nonsurgical aesthetic procedures may produce facial aesthetic improvements as large in magnitude as those achieved with traditional surgical techniques.

As originally developed using Rasch Measurement Theory methods, the FACE-Q Satisfaction with Facial Appearance Overall Scale allows for an item analysis at the response option level. This feature, which is rarely possible with PRO measures, maximizes the ability to interpret findings.[3,32] This item analysis showed that patients perceived improvement for all scale items. At month 4, patients were very satisfied with facial symmetry, balance, and proportions. A substantial majority (85%; 79/93) of patients experienced significant individual improvements on the FACE-Q Satisfaction with Facial Appearance Overall Scale. In addition, patients who showed significant individual improvements were also "very satisfied" with the extent that their faces looked fresh and rested and with their profiles. Looking fresh and rested are important goals for patients undergoing aesthetic dermatology procedures.[2] Rather than focusing on the appearance of individual facial features, patients tend to focus on more global impressions of appearance and on looking natural.

The mean total score for the FACE-Q Satisfaction with Facial Appearance Overall Scale was slightly lower at baseline for the subgroup of patients with significant individual improvements compared with the mITT group (39.4

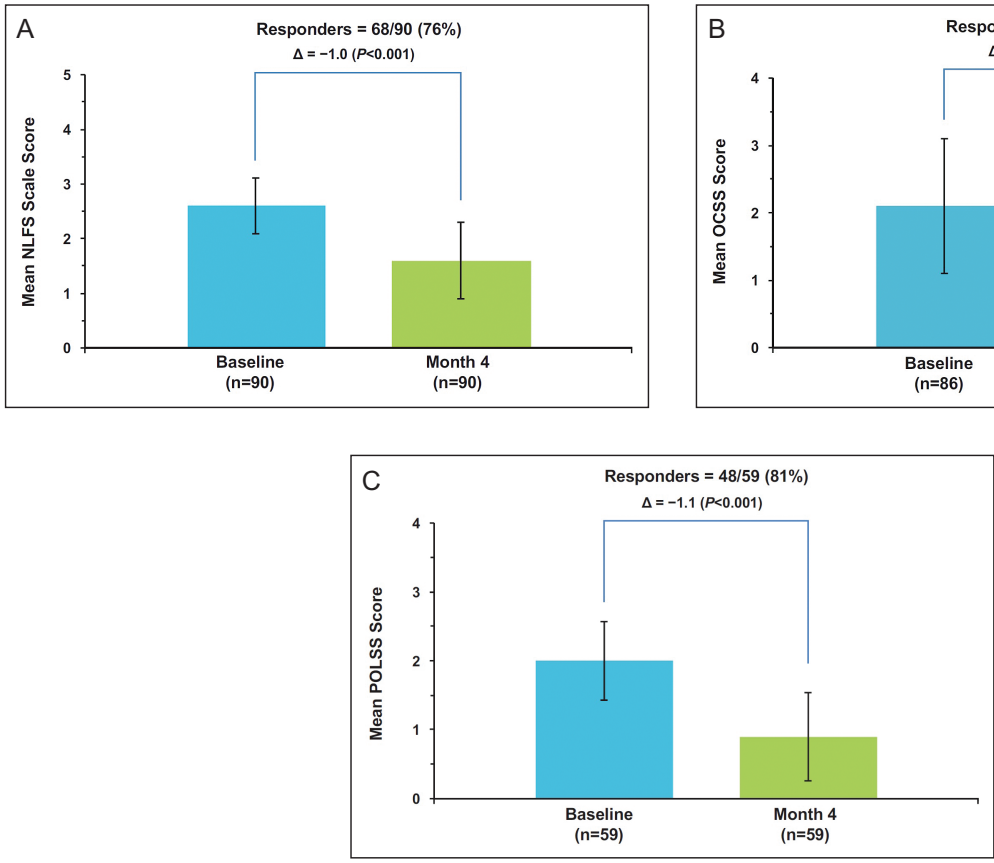

Figure 10. Investigator assessments in the intent-to-treat population (n = 93). (A) Nasolabial fold (NLF) severity, based on the 5-point NLF Severity Scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = extreme). A responder was defined as having at least a 1-point improvement from baseline. In the 59 patients who received treatment with HYC-24L, the overall mean volume injected in the right and left nasolabial folds was 0.7 mL each; for the 59 patients who received HYC-24L+, the overall mean volume injected was 0.6 and 0.7 mL, respectively. (B) Oral commissure (OC) severity was based on the 4-point OC Severity Scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe). N values indicate the number of evaluable patients at each time point. A responder was defined as having at least a 1-point improvement from baseline. In the 58 patients who received treatment with HYC-24L, the overall mean volume injected in the right and left OC was 0.3 mL each; for the 55 patients who received HYC-24L+, the overall mean volume injected was 0.6 and 0.5 mL, respectively. (C) Perioral line (POL) severity was based on the 4-point POL Severity Scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe). A responder was defined as having at least a 1-point improvement from baseline. In the 58 patients who received treatment with HYC-24L, the overall mean volume injected in the right and left POL was 0.5 and 0.4 mL, respectively; for the 7 patients who received HYC-24L+, the overall mean volume injected was 0.3 mL each. NLFS, Nasolabial Fold Severity; OCSS, Oral Commissure Severity Scale; POLSS, Periorbital Lines Severity Scale.

vs 41.2, respectively) and increased to a higher mean score at month 4 (76.4 vs 72.9). Thus, as a group, the patients who demonstrated significant individual improvements with treatment were somewhat less satisfied than the entire study group with their facial appearance before treatment and were somewhat more satisfied with their facial appearance after treatment.

Effect size conveys information about the magnitude and direction of treatment effects, independent of sample size[42] and, therefore, allows for comparison across studies and treatments with varying design features and characteristics. The current study demonstrated an effect size of 2.7 for change from baseline to month 4 for the mean total score on the FACE-Q Satisfaction with Facial Appearance Overall Scale. Although effect size analyses have not been reported extensively for aesthetic or dermatologic interventions, several studies using PROs have included effect size analyses. As part of an international field test of the FACE-Q, 77 patients completed the FACE-Q Satisfaction with Appearance Overall Scale before and after surgical (n = 50) or nonsurgical (n = 22) facial aesthetic procedures.[43] The effect size was 2.12 for facial surgery and 0.68 for nonsurgical aesthetic procedures. Two studies that used the FACE-Q Satisfaction with Appearance Overall Scale to

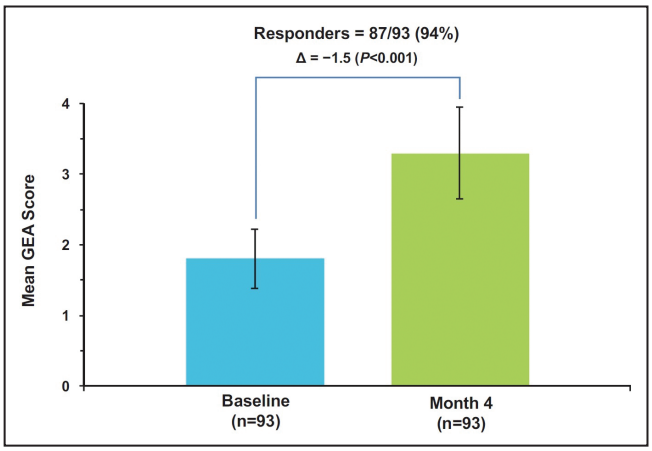

Figure 11. Investigator assessment of eyelash fullness using the 4-point Global Eyelash Assessment in the intent-to-treat population (n = 93; 1 = minimal, 2 = moderate, 3 = marked, 4 = very marked. N values indicate the number of evaluable patients at each time point. A responder was defined as achieving at least a 1-point improvement from baseline. GEA, Global Eyelash Assessment.

assess patient-reported satisfaction following rhinoplasty reported effect sizes of 1.5[49] and 1.9,[47] respectively. Effect sizes ranging from 1.3 to 2.1 have been reported for the impact on body image of a body image modification intervention program for patients with systemic lupus erythematosus.[50] Effect sizes of 1.7 to 2.4 were shown for the impact of breast augmentation, determined using the BREAST-Q Augmentation module.[51] Thus, the effect size reported in the current study was comparable to or larger than those observed following facial surgery and other aesthetic interventions, suggesting that more robust results may be possible with comprehensive, multimodal treatment than with single treatments in individual facial areas.

This global approach to aesthetic treatment was also associated with substantial improvements in perception of age. Patients perceived that they looked a mean of 4.6 years younger following treatment. Overall facial appearance contributes to perceptions of age[52]; ie, patients who reported greater satisfaction with their facial appearance typically also reported perceiving that they looked younger than their chronologic age. In a retrospective analysis of 207 patients who had received treatment with onabotulinumtoxinA for GL as well as other facial aesthetic treatments with dermal fillers, dermal creams, and other products over a 9.1-year period, the patients' perceived age improved by 6.9 years for those who, when asked, saw themselves as looking younger than their actual age.[28] These improvements in perceived age tended to be greater with longer treatment periods. Importantly, perceived age in the current study improved by 4.6 years at 4 months after only 1 cycle of treatment.

Table 2. Adverse Events

Parameter, n	Events
All AEs	130
Procedure-related AEs	91
Product-related AEs	12
Unrelated AEs	27

AE, adverse event.

As expected, significant improvements were also observed in specific areas of the face as assessed by the investigator, including eyelashes, midface volume, NLF, OC, and POL, GL, and CFL. These findings reinforce positive results previously reported for treatment with the individual agents used in this study.[16,18,20,36,53-55] It is striking to note that in the current study, the magnitude of improvement observed for specific treatments of facial regions, such as midface volumization or correction of NLF, is similar to that reported in previous studies,[16,18] while injection volumes in this study were lower. In the current study, injection volume for NLF correction was approximately 1.6 mL (0.8 mL for each side), while in a previous study of NLF treatment alone, injection volume was approximately 1.6 mL in only 1 NLF for each patient.[18] Similarly, in the pivotal study of midface volumization alone, injection volume was approximately 6.7 mL[16] while it was only 3.1 mL in the current study. These findings support and extend our understanding of the previously reported interrelationship between age-related deficits in contiguous facial regions that showed that progression of midface volume loss is associated with greater severity of NLFs and infraorbital hollowing.[56] Further, these intriguing results suggest that, along with the efficiency gained through experience by injectors, this approach to aesthetic facial treatment utilizing multiple techniques may allow for efficient product use.

The minimally invasive, multimodal approach used in this study was generally well tolerated. The safety profile was consistent with that of the individual products,[57-61] and no new safety concerns were reported. Of note, no serious AEs were reported, no patients discontinued the study because of an AE, and no delayed onset of AEs related to dermal fillers was reported.

While other studies have used a combination of noninvasive aesthetic modalities to treat 1 or 2 facial areas,[21,62] we were able to identify only 1 other study that employed a full-facial approach using a combination of noninvasive techniques and that reported patient- and/or investigator-rated outcomes. A 6-month, multicenter, open-label study (N = 60) evaluated efficacy and patient satisfaction following multimodal rejuvenation using a combination of botulinum toxin type A and a range of 5 HA fillers.[29]

Table 3. Incidence, Duration, and Severity of Common Injection Site Responses (Safety Population; n = 100)

Event	Patients, n (%)	Mean duration, days (median; range)
Redness	77 (77)	5.8 (4.0; 1-30)
Mild	27 (27)	—
Moderate	32 (32)	—
Severe	18 (18)	—
None	20 (20)	—
Missing	3 (3)	—
Pain	75 (75)	4.3 (2.0; 1-18)
Mild	38 (38)	—
Moderate	25 (25)	—
Severe	12 (12)	—
None	22 (22)	—
Missing	3 (3)	—
Tenderness	91 (91)	8.9 (6.0; 1-30)
Mild	45 (45)	—
Moderate	28 (28)	—
Severe	18 (18)	—
None	6 (6)	—
Missing	3 (3)	—
Firmness	78 (78)	8.9 (5.0, 1-41)
Mild	30 (30)	—
Moderate	34 (34)	—
Severe	14 (14)	—
None	19 (19)	—
Missing	3 (3)	—
Swelling	88 (88)	8.6 (7.0; 1-44)
Mild	33 (33)	—
Moderate	33 (33)	—
Severe	22 (22)	—
None	(9)	—
Missing	3 (3)	—
Lumps	85 (85)	12.3 (9.0; 1-45)
Mild	37 (37)	—
Moderate	32 (32)	—
Severe	16 (16)	—
None	12 (12)	—
Missing	3 (3)	—
Bruising	92 (92)	11.8 (10.0; 1-44)
Mild	31 (31)	—
Moderate	32 (32)	—
Severe	29 (29)	—
None	5 (5)	—
Missing	3 (3)	—
Itching	45 (45)	2.6 (2.0; 1-12)
Mild	26 (26)	—
Moderate	17 (17)	—
Severe	2 (2)	—
None	52 (52)	—
Missing	3 (3)	—
Discoloration	73 (73)	8.7 (6.0; 1-35)
Mild	29 (29)	—
Moderate	26 (26)	—
Severe	18 (18)	—
None	24 (24)	—
Missing	3 (3)	—
Other	26 (26)	4.9 (2.0; 1-30)
Mild	16 (16)	—
Moderate	8 (8)	—
Severe	2 (2)	—
None	51 (51)	—
Missing	23 (23)	—

Although effect sizes were not reported, the study observed high levels of patient satisfaction at 3 weeks and at 6 months, based on investigator and patient GAIS assessments.

Several aspects of treatment should be considered when employing such an approach to aesthetic rejuvenation. The treating physician must assess the patient's individual facial characteristics, needs, and goals for treatment. Individual patient's facial features age over a varied time course based on a variety of intrinsic and extrinsic factors, including gender and race or ethnicity.[63] Additionally, consideration of each facial area and feature in conjunction with surrounding areas and in the overall context of

facial symmetry is an important component to designing a treatment regimen that addresses each patient's needs and expectations. A previously published paper[31] provided a comprehensive description of the techniques used for the minimally invasive, multimodal approach utilized in the HARMONY study, as well as treatment characteristics (eg, filler volumes used and placement of injections), precautions taken by the investigators, and comments on the areas/anatomical structures to watch for and avoid.

Several limitations of the current study should be noted. The study primarily enrolled white females, limiting generalizability of the findings to males and to other racial groups. The open-label design of this study did not allow blinded assessment by patients, although the evaluating investigators were blinded to treatment assignment. It is conceivable that because patients were not blinded to treatment, they may have had a more positive response to treatment than if they had been blinded. While blinded designs are typically preferred, accomplishing the goal of assessing the aesthetic impact of a multimodal treatment approach, using a combination of treatment modalities individualized for each patient's needs, would not be possible with such a study design. As is customary in interventional studies, patients in the current study received treatment products on a complimentary basis, which may have influenced their assessments and satisfaction with treatment. However, the clinically meaningful improvements in most patients and the blinded independent rater results generally aligned with patient satisfaction scores, suggesting that the potential influence of bias was minimal. The 4-month duration of this study did not allow for assessment of the duration of the effects of global treatment and did not permit a full assessment of potential late-onset adverse events arising from treatment. However, no serious AEs or delayed-onset AEs related to fillers were reported within the time period studied. Previous studies showed that the individual treatment modalities provide durable effects from 15 to 24 months for dermal fillers[64] and 4 or more months for onabotulinumtoxinA.[65,66] As these patients were naive to aesthetic treatment, extrapolation of the conclusions of this study to individuals with ongoing experience with aesthetic treatment should be made with caution.

CONCLUSIONS

In this study, the comprehensive, minimally invasive, multimodal aesthetic approach resulted in substantial improvements in patient satisfaction with facial appearance, and provided a rested and fresh facial appearance in the majority of patients. Recent FACE-Q data on patient satisfaction with treatment outcomes for individuals undergoing aesthetic surgical procedures on their faces demonstrated effect sizes that were similar to or lower than that observed in the current study. While direct comparison with the current findings may not be appropriate, these results suggest that substantial improvements in patient satisfaction can be achieved with these minimally invasive techniques. Overall, the findings of this study underscore the benefits of a holistic approach to assessment and treatment. This approach may help to limit the potential for overtreatment of individual areas and to provide a more balanced, rested, and youthful appearance.

Supplementary Material

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

Disclosures

Dr Werschler has served as a clinical investigator, consultant, speaker, and advisory board member for, and/or has received research support, from Allergan plc, Medicis, Merz, Suneva, and Sanofi-Aventis. Dr Shamban serves as an investigator for Allergan plc, Medicis, Galderma, and Kythera, and as a consultant for Allergan plc. Dr Rivkin serves as a consultant and investigator for Allergan plc and Merz Aesthetics USA. Dr Narurkar serves as an investigator for Allergan plc, Merz Aesthetics, Solta Medical, Myoscience, Polyremedy LLC, and Syneron Candela; as a consultant for Allergan plc, Philips, and Revance; and on advisory boards for Cabochon Aesthetics and Clarisonic, and is a cofounder of Cosmetic Boot Camp LLC. Dr Dayan has received research support, speaking fees, or consulting fees from Allergan plc, Galderma, Merz, and Valeant. Dr Cohen has served as a consultant and investigator for Allergan plc, Medicis, and Merz. Dr Gallagher is an employee of Allergan plc and owns stock or stock options in the company. Drs Kaminer, Sykes, Teller, and Weinkle declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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