A Comprehensive Approach to Multimodal Facial Aesthetic Treatment: Injection Techniques and Treatment Characteristics From the HARMONY Study

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BACKGROUND The HARMONY study is the first clinical trial to assess the impact of a global approach to facial rejuvenation with several minimally invasive modalities, using patient-reported outcome measures.

OBJECTIVE Provide details of this treatment approach and describe investigators' experiences and recommendations based on this study.

METHODS This multicenter, 4-month study evaluated subject satisfaction with and psychological impact of combined treatment with VYC-20L (Juvéderm Voluma XC), HYC-24L (Juvéderm Ultra XC), HYC-24L+ (Juvéderm Ultra Plus XC), onabotulinumtoxinA (Botox), and bimatoprost 0.3% ophthalmic solution (Latisse). Treatment-naive adults with moderate-to-severe facial lines and folds and eyelash hypotrichosis received on-label, staged treatment with fillers. Bimatoprost was self-administered once daily for 17 weeks from day 1. OnabotulinumtoxinA was administered for glabellar lines, crow's feet lines, or both at month 3.

RESULTS Overall, 100 subjects received bimatoprost for eyelash hypotrichosis, 96 received onabotulinumtoxinA for glabellar lines and/or crow's feet lines, and 96 received VYC-20L for midface volume deficit. From 17 to 96 subjects received HYC-24L and/or HYC-24L+ for nasolabial folds, oral commissures, marionette lines, perioral lines, or radial cheek lines. Injections of filler generally progressed from cranial to caudal, with midface injected first. Investigator-reported factors that may have contributed to the potential benefits of this approach include the critical role of the midface in facial aesthetics, use of lower volumes of filler in individual facial areas, and anesthetic effects.

CONCLUSION The investigators' perspectives and experience with the injection pattern, sequencing, volumes, and techniques may provide valuable guidance for a multimodal approach to facial aesthetic treatment.

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During aesthetic consultations, many individuals identify concerns with multiple facial areas and features that they would like to have treated or softened.[1] A global approach to aesthetic treatment for facial rejuvenation is being more widely incorporated into standard clinical practice, and patients now

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commonly receive treatment in multiple facial areas.[2–6] This approach, which considers the face as a whole, employs a variety of treatment modalities to address multiple aspects of facial appearance. By balancing correction of volume loss with treatment of dynamic lines, static facial folds, and eyelash loss, clinicians are able to achieve a harmonious balance of aesthetic features with a more natural, rested appearance.

Well-designed clinical trials examining the panfacial (i.e., global) approach to aesthetic treatment that employ a combination of treatment modalities have not been conducted or reported in the literature. Previously, clinical studies have examined individual products, most commonly used in 1 or 2 facial areas.[7–11] Dual combination therapy with botulinum toxin plus dermal filler has been studied in the perioral area and lower face, where it demonstrated synergistic benefits.[12]

Typically, studies have focused on assessing the pharmacologic effects of a drug or device using ratings scales that measure objective physical changes in specific facial features. Such assessments do not provide a comprehensive perspective on benefits that may extend beyond the amelioration of specific facial lines and folds. Further, patient-reported outcomes (PROs) are generally not used as a primary end point in filler and toxin studies. However, recent data indicate broad psychological benefits associated with aesthetic treatment.[13–15] In a multicenter, single-blind, randomized controlled (no treatment) study, treatment of moderate-to-severe age-related midface volume deficit with VYC-20L (Juvéderm Voluma XC; Allergan plc, Dublin, Ireland), an injectable hyaluronic acid (HA) filler, resulted in high rates of improvement in subject-assessed satisfaction with facial appearance and with self-perception of appearing to be younger than their actual age.[13] The psychological benefits associated with onabotulinumtoxinA (Botox Cosmetic; Allergan plc, Dublin, Ireland) injections to the glabellar area, forehead, and crow's feet lines (CFL) are supported by results from a randomized, double-blind, placebo-controlled health outcomes survey, which reported significantly greater quality of life and self-esteem values with onabotulinumtoxinA versus placebo.[14] Additionally, an analysis of data from 2 phase 3 trials on the efficacy of onabotulinumtoxinA treatment for CFL demonstrated consistent positive effects on several PROs, including psychological impact, perception of age, appearance, and satisfaction.[15] Although results of these studies are compelling, their interpretation is limited to benefits of treatment in specific facial regions.

A 6-month, open-label, multicenter study evaluated the effects of facial rejuvenation (including treatment of periorbital lines, tear troughs, cheeks, cheek folds, nasolabial folds, upper lip lines, lips, and marionette lines) with a range of HA fillers on investigator-rated aesthetic improvement (both global and site specific) and patient satisfaction.[16] Results demonstrated high rates of patient satisfaction, suggesting benefits of panfacial treatment on self-esteem, because 63% of patients reported that they felt a lot or much better about themselves 6 months following the first injection. However, this study was not truly multimodal because only HA fillers were used and outcomes were assessed using nonvalidated scales.

The HARMONY study (clinicaltrials.gov identifier: NCT02176356), a multicenter, single-blind study, was prospectively designed to assess the psychological impact and holistic benefits (i.e., benefits relating to a person as a whole and not just to facial areas) achieved using a multimodal facial treatment approach. HARMONY was the first clinical trial to examine the impact of a unique combination of multiple, noninvasive facial treatments using a range of validated PROs to assess subject satisfaction, self-esteem, social confidence, and perception of age. Treatments included HA dermal fillers, onabotulinumtoxinA, and bimatoprost (Latisse; Allergan plc, Dublin, Ireland).

The complex nature of the HARMONY study's design and methodology, the amount of technical detail required to adequately describe the optimal administration of each product, and the space needed to present the investigators' recommendations related to their experience with the products used together in this study preclude the presentation of the study outcomes and the technical aspects of this study in a single publication. Thus, to present a sufficient level of detail and a comprehensive discussion of the technical

aspects of administering the products used in combination in the HARMONY study, the current report presents details of combined treatment with HA fillers for facial volumizing and contouring (VYC-20L, HYC-24L [Juvéderm Ultra XC; Allergan plc, Dublin, Ireland] and HYC-24L+ [Juvéderm Ultra Plus XC; Allergan plc, Dublin, Ireland]), onabotulinumtoxinA, and bimatoprost, along with results of post-study investigators' discussions of techniques and recommendations on how to optimize aesthetic outcomes using the multimodal treatments available in the HARMONY study. Safety and efficacy outcomes will be presented separately.

Methods

Study Design

This prospectively designed, multicenter, rater-blinded, 4-month study was conducted to evaluate subject satisfaction and the aesthetic impact of the combined use of VYC-20L, HYC-24L, HYC-24L+, onabotulinumtoxinA, and bimatoprost (Figure 1). Subjects received staged treatment with these aesthetic products according to the evaluation of need by treating investigators, followed by assessments using validated PRO measures to determine the personal, perceptual, social, and psychological impact of this integrated treatment approach. At baseline (day 1), subjects received treatment with VYC-20L, HYC-24L, and/or HYC-24L+. A touch-up treatment with VYC-20L, HYC-24L, and/or HYC-24L+ was allowed on day 14. Bimatoprost was dispensed at day 1 and was self-administered once daily according to prescribing instructions for 17 weeks. OnabotulinumtoxinA was administered in glabellar lines (GL), CFL, or both at month 3 following the last filler treatment. Primary and secondary end points were assessed at month 4.

An overall structured, sequential approach to assess and treat the midface (Figure 2) and other facial areas, including nasolabial folds (NLF), oral commissures (OC), perioral lines (POL), marionette lines (ML), and radial cheek lines (RCL), with HA dermal fillers was discussed during the investigators' protocol review. However, the investigators were able to use their own clinical judgment and experience in treating each subject.

Subjects

The study enrolled healthy men and woman aged 35–65 years who were naive to botulinum toxin therapy, dermal filler treatment in the face and neck, and prescription eyelash growth products. Eligible subjects had to meet all entry criteria to receive treatment with onabotulinumtoxinA, HA filler, and bimatoprost. Subjects must have had moderate-to-severe GL at maximum frown and/or moderate-to-severe CFL at maximum smile, and at least 2 of the following: moderate-to-severe NLF and/or OC and/or POL, as assessed using the relevant validated rating scale, and/or moderate or severe ML and RCL requiring treatment, as assessed by the treating investigator, and/or moderate to significant midface volume deficit, as assessed using the Midface Volume Deficit Scale (MFVDS). Subjects were also required to have

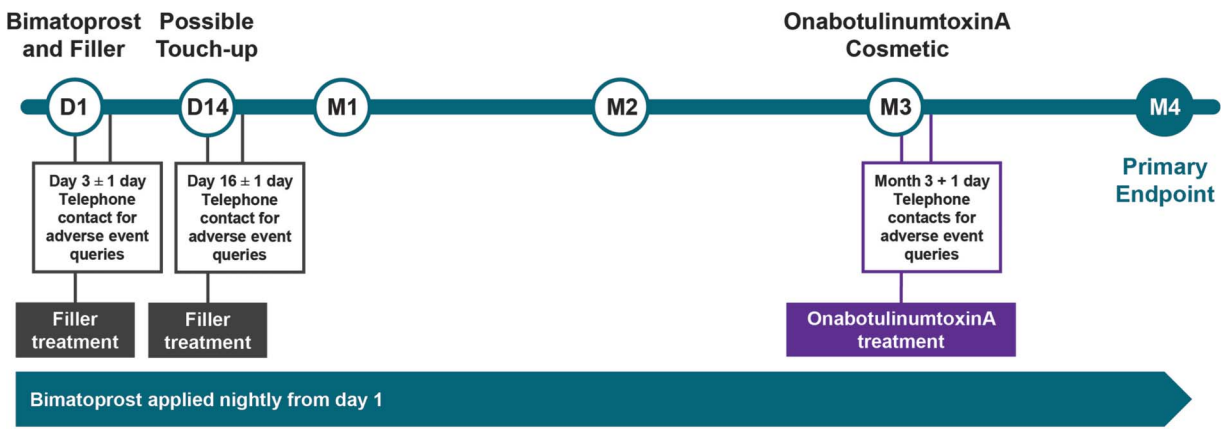

Figure 1. Study design.

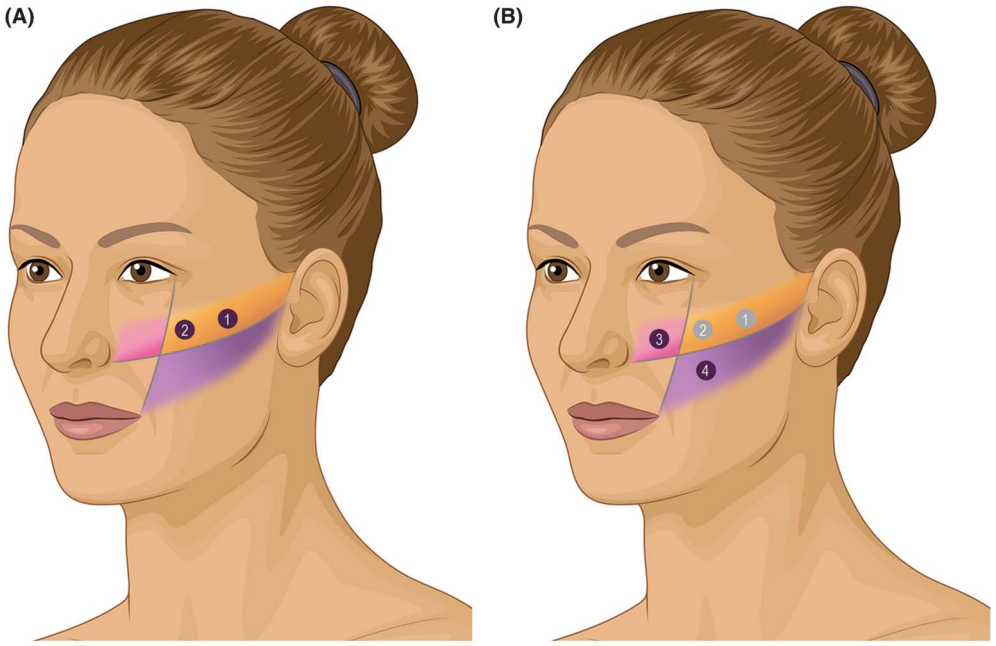

Figure 2. Injection sites V1 and V2 (A) and V3 and V4 (B), indicating injection sequence and depths for VYC-20L. For subjects treated in the V1/V2 regions, injections were made lateral to medial, and most injections were placed supraperiosteally. For subjects treated in the V3 and V4 regions, in approximately 50% of cases, injections in the V3 region followed treatment of the V1/V2 regions, and in 50% of cases, injections in the V4 region followed treatment of V1/V2 regions; approximately 50% of injections in the V3 region were supraperiosteal. Reprinted with permission from Allergan plc, Dublin, Ireland.

only minimal-to-moderate eyelash fullness, as assessed using the Global Eyelash Assessment (GEA) scale.

Study Treatments

Multiple HA fillers designed for specific facial areas and depths of injection are available.[17–19] Indications for each agent used in the HARMONY study[17–21] and their corresponding approval dates are described in Table 1. In this study, VYC-20L could be injected into the mid-face region at a total volume of up to 4 mL, including the initial and touch-up treatment. Using 30-gauge and 27-gauge needles, respectively, HYC-24L and HYC-24L+ could be injected into the NLF, POL, OC, ML, and/or RCL. The cumulative volume to be used across both HYC-24L and HYC-24L+ for an individual subject, including the initial and touch-up treatments, was limited to up to 6 mL. Investigators could inject either VYC-20L in V4 (submalar) or HYC-24L or HYC24L+ in RCL, but not in both, to avoid injection of multiple products into overlapping facial areas. Likewise, investigators could inject either HYC-24L or HYC-24L+, but not both products, into each NLF, POL, OC, and ML, and layering of fillers was not permitted.

OnabotulinumtoxinA was used in the periorbital region to treat GL, CFL, or both, with treatment consisting of 20 U total to GL area (5 injection sites [2 in each corrugator, 1 in the procerus], 0.1 mL/injection) and/or 24 U total to CFL areas (6 injection sites [3 per side], 0.1 mL/injection). As described in the physician prescribing information, 2 injection patterns were available for treating CFL, depending on investigators' assessment and varying pattern/location of the CFL.[22]

Bimatoprost was to be applied nightly to the skin of the upper eyelid margin at the base of the eyelashes bilaterally by each subject in accordance with the instructions provided in the package insert, for the duration of the study.[20]

Assessments

Efficacy Measures

All efficacy measures were assessed at month 4. The primary efficacy assessment was the FACE-Q Satisfaction with Facial Appearance Overall Scale.[23] Key secondary assessments (subject assessed) included the

TABLE 1. Treatments Used in the HARMONY Study[17–21]

Agent	*Indications (Year of Approval)*
Bimatoprost (Latisse)[20]	Treatment of hypotrichosis of the eyelashes (2008)
HYC-24L (Juvéderm Ultra XC)[17]	Injection into the mid-to-deep dermis for correction of moderate-to-severe facial wrinkles and folds, such as nasolabial folds (2010)
HYC-24L+ (Juvéderm Ultra Plus XC)[18]	Injection into the mid-to-deep dermis for correction of moderate-to-severe facial wrinkles and folds, such as nasolabial folds (2010)
VYC-20L (Juvéderm Voluma XC)[19]	Deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the midface in adults aged 21 years and older (2013)
OnabotulinumtoxinA (Botox Cosmetic)[21]	Temporary improvement in the appearance of moderate-to-severe glabellar lines associated with corrugator and/or procerus muscle activity in adults (2002)
	Temporary improvement in the appearance of moderate-to-severe lateral canthal lines associated with orbicularis oculi activity in adults (2013)

FACE-Q Aging Appraisal Scale, the FACE-Q Age Appraisal Visual Analogue Scale, the FACE-Q Social Confidence Scale, and the FACE-Q Psychological Well-Being Scale. Additional secondary outcome measures included subject-assessed satisfaction with appearance on the Periorbital Aesthetic Appearance Questionnaire (PAAQ) as well as the following investigator assessments: GL severity at maximum frown and CFL severity at maximum smile using the Facial Wrinkle Scale (FWS) with photonumeric guide; the GEA; the 6-point photometric MFVDS[8]; the 5-point Nasolabial Fold Severity (NLFS) Scale[24]; the 4-point Oral Commissure Severity Scale (OCSS)[25]; and the 4-point Perioral Lines Severity Scale (POLSS).[26,27] Other efficacy measures were subject and investigator assessments of improvement on the Global Aesthetic Improvement Scale (GAIS).

Safety Assessments

Adverse events were monitored throughout the course of the study, and common treatment site responses were assessed based on a subject diary kept for 30 days after each treatment.

Results

Efficacy and safety results were presented at the American Society of Dermatologic Surgery Annual Meeting, October 2015 (written communication, S. H. Weinkle, October 2015) and will be published separately.

Subjects

In total, the study enrolled 116 subjects at 10 study sites. Of these, 100 subjects received treatment. Of the 16 subjects who did not receive treatment, 14 were screen failures and 2 discontinued from the study before they received treatment. Ninety-three of the 100 subjects who began treatment were included in the intent-to-treat analyses. Among the 7 subjects who were not included, 4 were not treated with all products, and 3 discontinued before final outcome assessment.

Subjects were predominantly white and women (Table 2). The median age was 52 years, with ages ranging from 37 to 65 years. Most subjects were Fitzpatrick skin types II, III, or IV. In the majority of patients at baseline, age-related facial appearance for most areas was rated as moderate in severity (Table 3) and NLF and GL at maximum frown were rated as severe.

Pretreatment or Concomitant Treatments

Overall, 27 subjects received pretreatment with ice, and 6 were pretreated with arnica. In approximately 65% of dermal filler injections, topical anesthesia was used. For all RCL injections, topical anesthetics were used. Other areas were pretreated less frequently, with the lowest proportion of POL injections accompanied by topical anesthetics (69% and 50% for initial treatments with HYC-24L and HYC-24L+ and 67% and 33% for touch-up treatments with HYC-24L and HYC-24L+, respectively).

TABLE 2. Baseline Demographic Characteristics, Safety Population

Characteristic	*Subjects (n = 100)*
Age, yrs	
Mean (SD)	52.5 (7.4)
Median	52
Range	37–65
Age group, *n*	
≤50 yrs	43
>50 yrs	57
Gender, *n*	
Female	96
Male	4
Race/ethnicity	
White	86
Hispanic	10
Black	2
Asian	1
American Indian or Alaska native	1
Fitzpatrick skin type	
I	3
II	31
III	41
IV	22
V	3
VI	0

OnabotulinumtoxinA

Ninety-five subjects received onabotulinumtoxinA injections in both GL and CFL, and 1 subject who did not meet criteria for GL treatment received onabotulinumtoxinA injections in CFL only. Although both of the on-label injection patterns were available to the investigators, the injection pattern considered standard for CFL was used for all subjects; investigators felt that this pattern produced a desirable secondary effect of lifting the lateral brow. For both GL and CFL, 30-gauge or smaller needles were used for onabotulinumtoxinA injections.

Bimatoprost

All subjects began applying bimatoprost as instructed on day 1 for once-daily treatment.

Dermal Filler

Most subjects received dermal filler injections in 4 or 5 of the 6 eligible areas of the face (Figure 3). With respect to the injection sequence, assessments and treatment progression were generally similar between investigators. Investigators universally assessed and treated the midface first.

Midface

All subjects received midface VYC-20L injections at initial treatment, and approximately half (57%) received a touch-up treatment (Table 4; Figure 4).The overall mean volume injected was 3.1 mL, with approximately two-thirds of the total volume injected at initial treatment and the remaining third at touch-up treatment. Mean injection volumes were equivalent on the left and right sides. Investigators were more likely to perform touch-ups to the midface than to other areas (0%–35% for other areas). They expressed that they were cautious about using too much VYC-20L at initial treatment and chose to add more subsequently.

Focusing on the specific subregions of the midface, 92 subjects (96%) received treatment into the zygomaticomalar region (V1, V2) at initial treatment, and approximately 40% of these received touch-up treatments (Table 4). Investigators typically proceeded from lateral to medial on the zygomatic arch (V1–V2; Figure 2A). The mean (range) total volume of filler injected in the zygomaticomalar area was 1.4 (0.2–4.0) mL; 0.7 mL on each side. Data were not broken out by amounts in V1 versus V2; rather, volumes injected into V1 and V2 were tallied together. Investigators most often injected supraperiosteally in this region (80% of injections [75% at touch-up]) with injections in the subcutaneous plane in only 15 cases. Most investigators deposited small boluses (typically 0.1–0.15 mL, with a 0.20 mL maximum) through a perpendicular injection down to bone on the zygomatic arch, injecting a small amount while withdrawing the needle to lay down the gel in pyramid-shaped pillars. However, some investigators preferred to inject in columns.

Eighty-six subjects (90%) were treated in the anteromedial cheek (V3) region at initial treatment; 39 subjects (41%) received touch-up injections in this region. The mean (range) total volume of filler injected in the

TABLE 3. Baseline Severity of Facial Areas Injected Based on Investigator Assessments

Treatment Facial Area Treated	*Mean Score*	*Subjects per Scale Rating, n*						*Data Missing*
Dermal Filler								
Midface*	3.1	None: 0	Minimal: 1	Mild: 3	Moderate: 80	Significant: 16	Severe: 0	0
Nasolabial folds†	2.6	None: 0	Mild: 4	Moderate: 36	Severe: 59	Extreme: 1	–	0
Oral commissures‡	2.1	None: 0	Mild: 11	Moderate: 67	Severe: 21	–	–	1
Perioral lines§	1.6	None: 12	Mild: 24	Moderate: 52	Severe: 10	–	–	2
OnabotulinumtoxinA								
Glabellar lines at maximum frown‖	2.5	None: 0	Mild: 1	Moderate: 44	Severe: 52	–	–	3
Glabellar lines at rest‖	1.7	None: 1	Mild: 33	Moderate: 55	Severe: 8	–	–	3
Crow's feet lines at maximum smile‖	2.5	None: 0	Mild: 0	Moderate: 50	Severe: 47	–	–	3
Crow's feet lines at rest‖	1.9	None: 0	Mild: 26	Moderate: 52	Severe: 19	–	–	3

*Scores based on the Midface Volume Deficit Scale.
†Scores based on the Nasolabial Fold Severity 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.

anteromedial cheek was 1.2 (0.2–4.0) mL; 0.6 mL on each side (Table 4). About half of the 86 subjects who received filler in the anteromedial cheek were injected supraperiosteally (41 left, 43 right vs 37 on each side that were placed subcutaneously; Figure 2B). Investigators used small bolus injections, generally about 0.10 mL per injection, up to 0.20 mL. Notably, investigators expressed caution in treating anteromedial cheek, given the relationship to the angular artery medially and the infraorbital neurovascular bundle (Figure 5).

Only 52 subjects (54%) received initial treatment in the submalar (V4) area, and 24 subjects (25%) received touch-up treatments in this area at the day 14 visit (Table 4). The proportion of subjects injected at

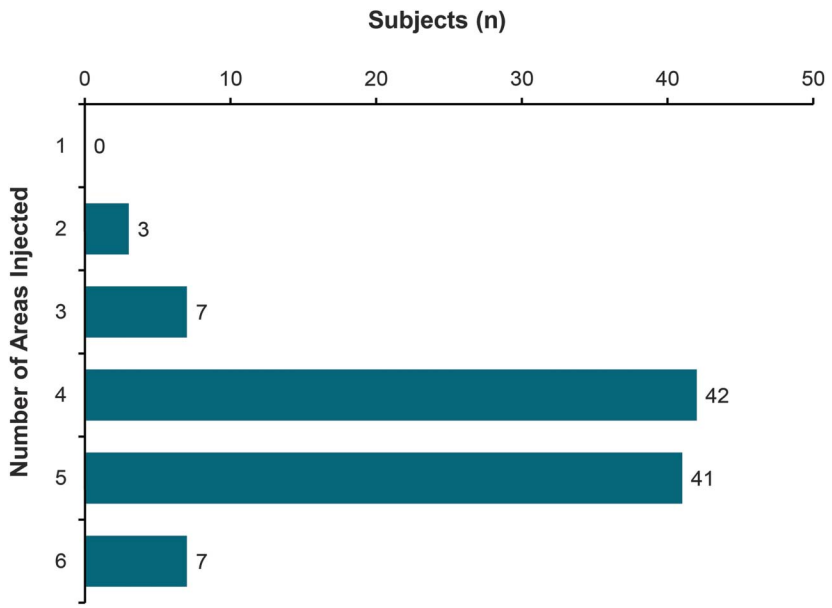

Figure 3. Distribution of the areas of the face injected, per subject.

TABLE 4. Mean Filler Volume Injected, by Facial Area

	Left		*Right*		*Total*	
Parameter	*n*	*Volume, mL*	*n*	*Volume, mL*	*n*	*Volume, mL*
Midface, overall						
VYC-20L						
Initial	96	1.2	96	1.2	96	2.4
Touch-up	54	0.6	51	0.6	55	1.2
Total	96	1.6	96	1.6	96	3.1
Zygomaticomalar						
Initial	92	0.6	91	0.6	92	1.2
Touch-up	36	0.4	33	0.4	38	0.7
Total	95	0.7	94	0.7	95	1.4
Anteromedial cheek						
Initial	84	0.5	86	0.5	86	1.0
Touch-up	39	0.4	39	0.3	42	0.6
Total	86	0.6	88	0.6	88	1.2
Submalar						
Initial	51	0.4	51	0.4	52	0.8
Touch-up	23	0.3	21	0.3	24	0.6
Total	53	0.5	52	0.5	54	1.0
Oral commissures						
Total filler injected	91	0.6	91	0.5	91	1.1
HYC-24L						
Initial	54	0.3	53	0.3	54	0.5
Touch-up	22	0.3	22	0.2	23	0.5
Total	58	0.3	57	0.3	58	0.7
HYC-24L+						
Initial	47	0.5	47	0.5	47	1.0
Touch-up	26	0.3	26	0.3	27	0.5
Total	55	0.5	55	0.6	55	1.1
Marionette lines						
Total filler injected	82	0.6	81	0.6	82	1.2
HYC-24L						
Initial	33	0.4	34	0.4	35	0.8
Touch-up	12	0.3	13	0.3	14	0.5
Total	41	0.4	42	0.4	43	0.8
HYC-24L+						
Initial	57	0.5	57	0.5	57	0.9
Touch-up	26	0.3	25	0.3	27	0.6
Total	60	0.6	60	0.6	60	1.1
Radial cheek lines						
Total filler injected	17	0.4	17	0.4	17	0.8
HYC-24L						
Initial	12	0.3	12	0.3	12	0.6
Touch-up	5	0.3	4	0.4	5	0.7
Total	15	0.4	15	0.4	15	0.7

TABLE 4. (Continued)

	Left		Right		Total	
Parameter	*n*	*Volume, mL*	*n*	*Volume, mL*	*n*	*Volume, mL*
HYC-24L+						
Initial	5	0.3	6	0.3	6	0.5
Touch-up	1	0.2	0	—	1	0.2
Total	5	0.3	6	0.3	6	0.5
Nasolabial folds						
Total filler injected	96	0.8	96	0.8	96	1.6
HYC-24L						
Initial	50	0.6	50	0.6	52	1.1
Touch-up	29	0.5	26	0.4	29	0.8
Total	58	0.7	55	0.7	59	1.4
HYC-24L+						
Initial	52	0.6	51	0.6	52	1.2
Touch-up	23	0.4	19	0.3	23	0.6
Total	59	0.7	57	0.6	59	1.3

	Upper		Lower		Total	
Parameter	*n*	*Volume, mL*	*n*	*Volume, mL*	*n*	*Volume, mL*
Perioral lines						
Total filler injected	61	0.5	51	0.4	61	0.9
HYC-24L						
Initial	51	0.4	41	0.3	51	0.7
Touch-up	20	0.3	18	0.4	21	0.6
Total	58	0.5	48	0.4	58	0.8
HYC-24L+						
Initial	6	0.2	6	0.2	6	0.5
Touch-up	3	0.3	3	0.3	3	0.6
Total	7	0.3	7	0.3	7	0.6

submalar cheek and total volumes used were relatively low compared with the V1/V2 and V3 regions. The mean (range) total volume of filler injected in the submalar area was 1.0 (0.2–3.2) mL; 0.5 mL on each side.

Following the treatment of the midface, investigators progressed caudally in their treatment. By agreement of the investigators, the next treated area was most commonly the OC, followed by ML then POL. Many investigators chose to treat the NLF last in the treatment sequence.

Both HYC-24L and HYC-24L+ were used for treatment of the lower face. Most (>80%) subjects received treatment for OC, ML, and NLF, and approximately 60% received treatment for POL; few subjects received treatment for RCL (Table 4; Figure 6).

Oral Commissures

HYC-24L and HYC-24L+ were used in approximately the same number of subjects at both initial treatment and touch-up (Table 4). Approximately half of the subjects who received injections in the OC at initial treatment were also treated at touch-up. Investigators injecting OC used mean (range) total volumes of 0.7 (0.1–1.7) mL for HYC-24L and 1.1 (0.2–4.0) mL for HYC-24L+. Most subjects treated for OC with HYC-24L and HYC-24L+

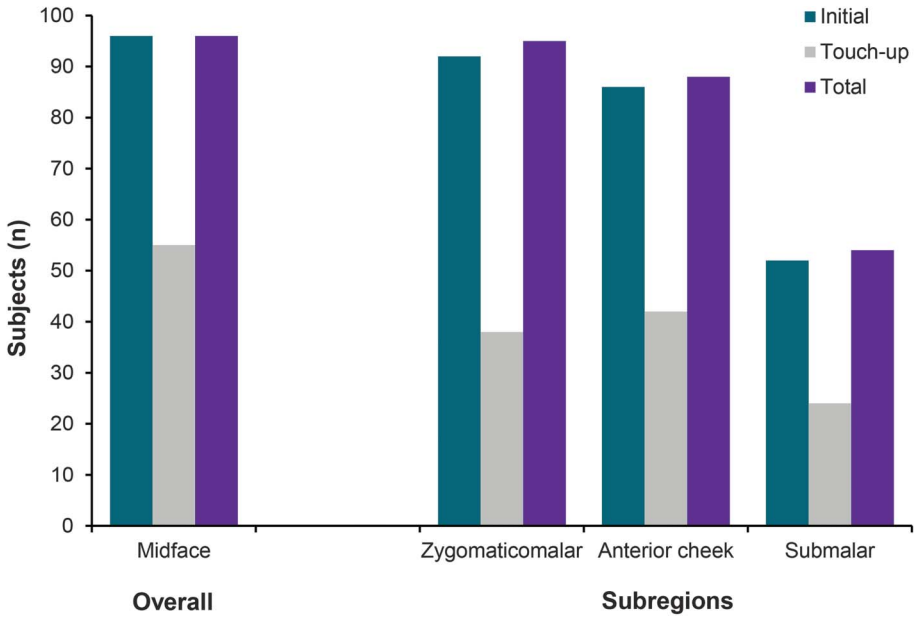

Figure 4. Subjects who received midface treatment with VYC-20L.

were rated with moderate severity at baseline (Table 5). The mean injection volumes of HYC-24L and HYC-24L+ were similar and were also similar for subjects with moderate or severe POL at baseline (Table 5). Linear threading was the most common technique investigators used during the

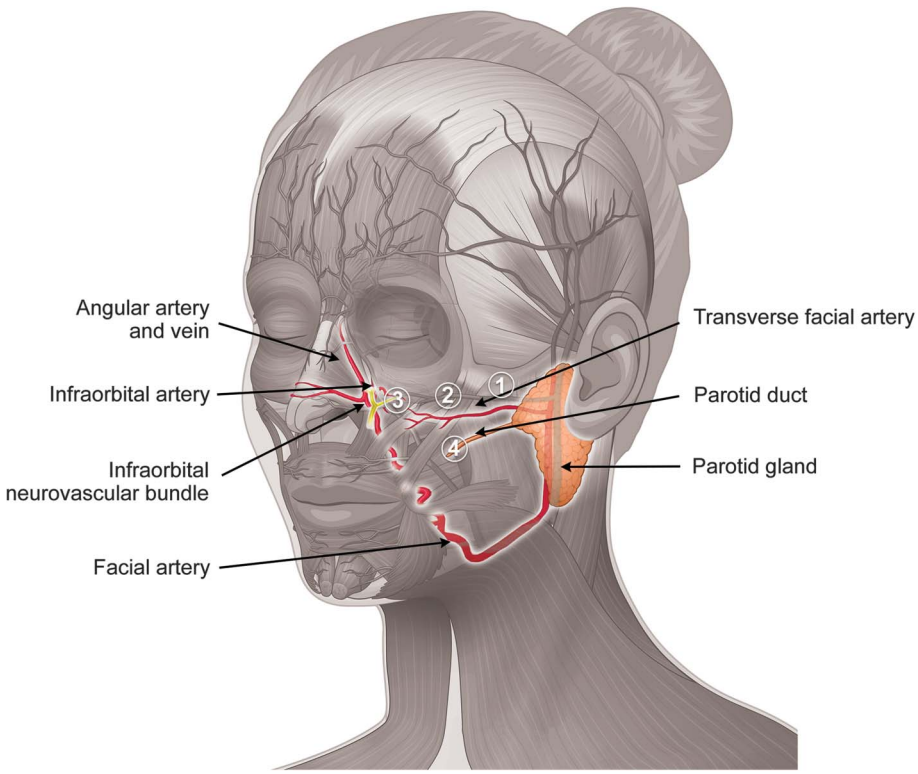

Figure 5. Superficial facial vascular and neural anatomic structures to be avoided during injection. Reprinted with permission from Allergan plc, Dublin, Ireland.

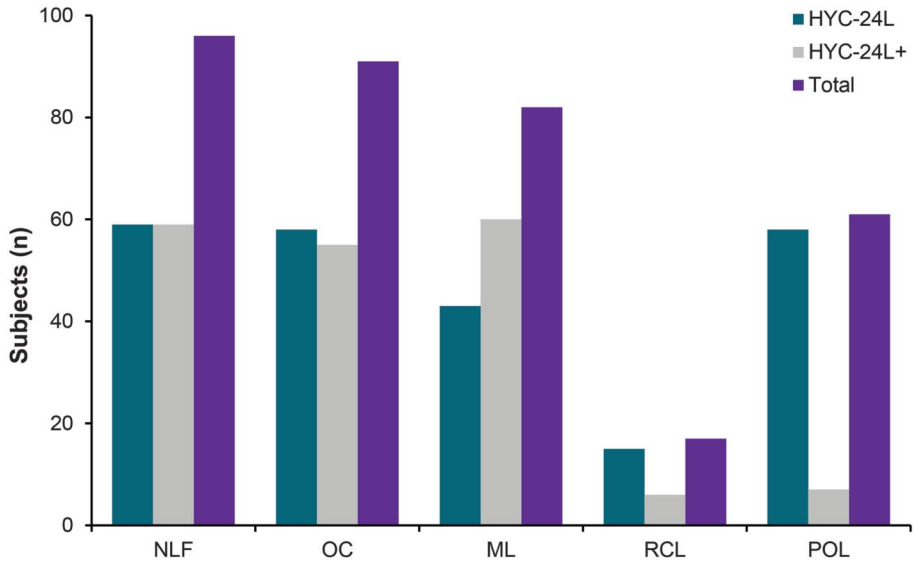

Figure 6. Subjects treated with HYC-24L or HYC-24L+ at nasolabial folds, oral commissures, marionette lines, perioral lines, and radial cheek lines. ML, marionette lines; NLF, nasolabial folds; OC, oral commissures; POL, perioral lines; RCL, radial cheek lines.

initial injection of HYC-24L in OC, followed closely by serial puncture, whereas serial puncture was more commonly used for follow-up injections. In contrast, HYC-24L+ was usually initially injected in the OC by serial puncture; linear threading was used in only 9 OC injections with HYC-24L+.

Perioral Lines

Investigators predominantly used HYC-24L for POL injections during both initial treatment and touch-up (Table 4). Few subjects received touch-up treatment of the POL, particularly with HYC-24L+. Investigators injecting POL used mean (range) total volumes of 0.8 (0.1–2.6) mL for HYC-24L and 0.6 (0.2–1.5) mL for HYC-24L+. Mean injection volumes of HYC-24L and HYC-24L+ were similar to each other and were slightly greater in the upper versus lower lip area (Table 4). Most subjects treated for POL were rated as moderate at baseline. Mean injection volumes of both HYC-24L and HYC-24L+ were slightly less for subjects with moderate POL versus severe POL at baseline. In the POL, investigators injected HYC-24L mainly using linear threading, although serial puncture was used in 29% of HYC-24L injections in POL. For the few subjects who were injected with HYC-24L+, investigators more frequently used serial puncture or cross-hatch.

TABLE 5. Mean Total Filler Volume Injected per Facial Area, by Baseline Severity

	None/Mild/Moderate		*Severe/Significant/Extreme*	
Parameter	*n*	*Volume, mL*	*n*	*Volume, mL*
Oral commissures				
HYC-24L	41	0.3–0.7	17	0.7
HYC-24L+	45	0.4–1.1	10	1.3
Nasolabial folds				
HYC-24L	21	1.0–1.3	38	1.4
HYC-24L+	22	1.2	37	1.3
Perioral lines				
HYC-24L	51	0.8–0.9	7	1.3
HYC-24L+	4	0.5	3	0.8

Marionette Lines

For subjects receiving ML injections, approximately 40% received HYC-24L and 60% received HYC-24L+. About half of subjects treated received additional treatment of ML at the touch-up visit. Investigators injecting ML used mean (range) total volumes of 0.8 (0.1–2.7) mL for HYC-24L and 1.1 (0.3–2.6) mL for HYC-24L+ (Table 4).

The most common technique used for treating ML with HYC-24L was linear threading; fanning was used in 6 HYC-24L injections in ML. When investigators used HYC-24L+ in ML injections, they most often used "other" (typically a combination of linear threading, serial puncture, and fanning), whereas linear threading and serial puncture were used in 19% and 16% of subjects, respectively.

Radial Cheek Lines

Few (n = 17 [17%]) subjects received RCL treatment (Table 4), possibly in part because RCL treatment was not permitted if the submalar area was treated with VYC-20L. When investigators did treat RCL, they were more likely to use HYC-24L compared with HYC-24L+. Additional injection of either product at touch-up was rare. Mean (range) total volumes were 0.7 (0.1–2.6) mL for HYC-20L and 0.5 (0.1–0.8) mL for HYC-20L+ (Table 4). Investigators most frequently used linear threading or fanning for initial injection of HYC-20L in RCL and serial puncture for touch-up injections of HYC-20L. In contrast, cross-hatching was the most common method in the few subjects in whom HYC-20L+ was used.

Nasolabial Folds

Investigators used HYC-20L and HYC-20L+ with similar frequency when treating NLF (Table 4). About half of treated subjects received additional filler at touch-up. Mean (range) total volumes of filler injected were 1.4 (0.2–4.0) mL for HYC-20L and 1.3 (0.4–3.0) mL for HYC-20L+. Approximately equal numbers of subjects with moderate NLF at baseline received HYC-20L and HYC-20L+ (Table 5). Similarly, approximately equal numbers of subjects with severe NLF at baseline received HYC-20L and HYC-20L+. Injection volumes for both HYC-20L and HYC-20L+ were similar regardless of severity. For NLF, the investigators primarily used linear threading for both HYC-20L and HYC-20L+.

Discussion

The HARMONY study was the first facial aesthetic study to investigate the potential benefits of a rational, on-label, multimodal approach to aesthetic treatment. This study combined dermal fillers, onabotulinumtoxinA, and bimatoprost into one treatment plan to achieve a desired aesthetic outcome.

The progression of treated facial areas generally moved from cranial to caudal. The opinion of the investigators was that treating the midface first may reduce the volume of filler required in other facial areas, such as NLF, allowing product to be used judiciously. Beneficial effects of deep midface filler injections have been demonstrated on neighboring facial areas, such as NLF, tear trough, and perioral lines around the upper lip.[28] Accordingly, a 2012 consensus statement on rejuvenation of the periocular area recommended that "volume restoration of the midface is the first essential step in the global approach" because treatment of the midface has the most substantial positive impact on facial appearance.[29] An additional benefit of following the sequence of midface to lower facial areas is the potential diffusion of lidocaine and its numbing effects from the midface injections to surrounding areas, such as the upper lip area and NLF.

VYC-20L was used for volumizing the midface, with the primary goal of restoring facial contour. Investigators generally chose to treat the lateral zygomatic area first (the V1 and V2 regions) with VYC-20L to provide lift and structure. This was followed by assessment and, if needed, treatment of the anteromedial (V3) and/or submalar areas. The overall mean injected volume of VYC-20L for midface regions in this study (3.1 mL) was approximately half that used in previous trials (6.65 mL and 5.1 mL, respectively).[8,30] In the current study, the mean injection volume in the zygomaticomalar area (V1/V2 region) was 1.4 mL total compared with 2.4 mL in the pivotal trial.[8] Similarly, in the current study, mean injection

volume in the anteromedial region (V3 region) was 1.2 mL compared with 2.1 mL in the pivotal trial. The most striking differences between the studies were seen with injection volumes in the submalar region (V4 region); in the current trial versus the pivotal trial, mean injection volume was 1.0 mL versus 2.4 mL, respectively.

The injection sequence that was ultimately applied for most subjects in the current study, beginning with the zygomaticomalar region, may allow for the efficient use of product. In the current study, 96% of subjects received injections in the zygomaticomalar area, 90% in the anteromedial area, and 54% in the submalar area. Conversely, in the pivotal trial, more than 92% of subjects received injections in each of the 3 areas.[8] In addition, touch-ups in the midface region were performed in approximately half of subjects in the current study, whereas 82% of subjects received touch-up treatment in the pivotal trial.[8] It is plausible that injections in the V1/V2 and V3 regions provided lift and support that extended to the submalar area and reduced the need for injections in the V4 region. However, it should be noted that the sequence generally followed in the current study (V1–V4) was optional and may not be appropriate for all patients.

Judicious use of VYC-20L in the V3 region, with injection into the deep medial fat pad, provides volume and lift. However, overfilling the V3 region or injection medial to the midpupillary line may result in undesirable lift below the eyes and raises safety concerns of unintended injection into important vessels. In particular, investigators pointed to variations in the paths of superficial vascular structures, such as the angular artery and the infraorbital neurovascular bundle. Indeed, physicians should approach the broad V3 to V2 area with caution to avoid unwanted injection into these vascular and neural structures. Figure 5 illustrates the most common location and tracts of these vessels, although the precise locations of these structures have shown variability between individual subjects.[31,32] Aspiration attempts by drawing back on the syringe once optimal needle placement is achieved is an essential precautionary measure to avoid injection into proximate arteries or veins. Older patients with thinner skin may require a deeper placement into the V3 region given that more superficial placement may not remain stable and may be more noticeable unless masked by support structures.

It is important to assess the results not just at rest, but with facial animation and at various angles while the patient is changing facial expressions as well, to ensure a natural-looking outcome. With greater tissue laxity and/or greater volume loss, injections on multiple planes may be necessary. Undesirable volume in the infraorbital region, resulting in excessive rounding and elevation of the upper cheek, can be avoided by careful control of the direction of product flow through injecting into the deep fat pad, aiming medially, and monitoring the direction of filler flow to avoid accumulation of product in undesirable areas and tissue planes.

With growing clinical experience with VYC-20L, investigators acknowledge that an understanding of the benefits of a conservative approach has emerged. In addition, investigators have been able to learn from their peers as well as through trial and error to better understand appropriate volumes and injection sites for optimal aesthetic outcomes with VYC-20L.

Lower facial areas, including POL, OC, ML, and RCL, were usually injected after the midface, with NLF injected last. In declining order, the proportions injected with filler were OC (91%), ML (82%), POL (61%), and RCL (17%). The investigators preferred to inject these areas around the mouth first because filler injection in POL and OC may decrease the volumes needed in the NLF area and also because subjects report that injections in these areas may be more painful than in other areas.

Virtually all subjects were injected with filler in the NLF (96%). Although subjects frequently focused attention on NLF and expected treatment in that area, optimal treatment in the midface and lower facial areas may have diminished the need for NLF treatment. In the current study, mean injection volume was 0.8 mL per side, whereas in a previous study of NLF treatment alone, in which only one NLF was injected with HA dermal filler, mean injection volume was

1.6 mL.[10] Filler was injected primarily in the cranial aspect of the NLF because filler injection in the facial areas around the mouth could obviate the need to treat the lower aspect of the NLF. Recent findings pointed to a close and significant relationship between perceived severity on midface volume deficit and severity of NLF.[33] The etiologic basis for NLF development is multifactorial and is related to the loss of deep medial fat, resulting in a lack of support for the nasolabial fat. As the deep fat layer decreases, the superficial layers collapse and descend, accentuating the NLF. Thus, replacing volume loss to the anteromedial cheek area may help to address the prominence of NLF, reducing the amount of volume replacement needed to correct NLF.

The selection of HYC-24L and the more robust HYC-24L+ was typically based on a balance of the versatility of these products in treating finer or deeper, more severe lines. Baseline severity did not appear to be a major determinant in the choice of which dermal filler was used to treat OC, POL, and NLF facial areas. For POL, a large majority of treated subjects were rated with moderate severity and were injected with the more lightly cross-linked HYC-24L. Similarly, most subjects treated for OC were rated with moderate severity; however, HYC-24L and HYC-24L+ were injected in a similar number of subjects. For subjects with NLF, most were rated as severe, but no preference for HYC-24L versus HYC-24L+ was seen. These observations reflect injector preference, investigator experience with regard to how to achieve optimal results, and the versatility of the products used. Perhaps surprisingly, injection volumes were not found to differ by product or by severity in individual facial areas.

Assessment of an individual subject's characteristics, needs, and desires should determine the location, volume, and sequence of injection of HA filler as well as choice of product. The panfacial approach to facial aesthetics considers each facial area and feature in relation to surrounding areas and in the context of overall facial appearance. This approach also resulted in the use of lower volumes of filler than previously reported in the pivotal studies. Recognition of the potential for adverse events contributes to the need for a judicious approach in applying optimal bolus volumes to achieve the desired effect.[34] The investigators emphasize the importance of not exceeding bolus volumes of 0.1–0.2 mL. Important factors, including slow and deliberate technique, smooth movement of the needle through the tissue, amount of filler injected, positions and plane of injection, and the overall experience and skill of the injecting physician, may impact safety and the incidence of complications that commonly occur with the use of all HA fillers. Although the on-label use of dermal fillers specifies the use of a syringe and needle for injection, the use of blunt microcannulas has been proposed as an appropriate and viable alternative.[29,35,36]

Conclusions

Dermal fillers have been used with onabotulinumtoxinA and bimatoprost for a combination approach to facial aesthetic treatment.[4,5] Although published reports describe clinical trial findings for the combined use of HA fillers and onabotulinumtoxinA for the treatment of specific facial areas,[12,37,38] this clinical trial utilized a unique combined treatment method with multiple modalities for a comprehensive, global, on-label approach. The perspectives and experience of the investigators with the injection pattern, sequencing, volume, and techniques in using VYC-20L, HYC-24L, HYC-24L+, and onabotulinumtoxinA provide a valuable guide to the use of these treatments in clinical practice. The investigators concur that this approach optimized multimodal treatments aimed at providing the type of results that patients seek: a natural, balanced, fresher, and more rested appearance.

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