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JOURNAL OF DRUGS IN DERMATOLOGY

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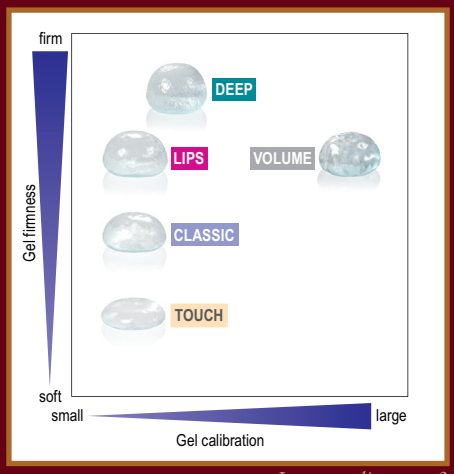

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Emervel®: Full-Face Rejuvenation With a Range of Customized Hyaluronic Acid Fillers

ISSN: 1545 9616

January 2012 • Volume 11 • Issue 1 (SUPPLEMENT)

JO0112

Disclosure of Commercial Support

This supplement to the Journal of Drugs in Dermatology *is supported by Galderma Research & Development.*

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JOURNAL OF DRUGS IN DERMATOLOGY

JANUARY 2012 VOLUME 11 ISSUE 1 (SUPPLEMENT)

EDITORIAL

ORIGINAL ARTICLES

COVER IMAGE

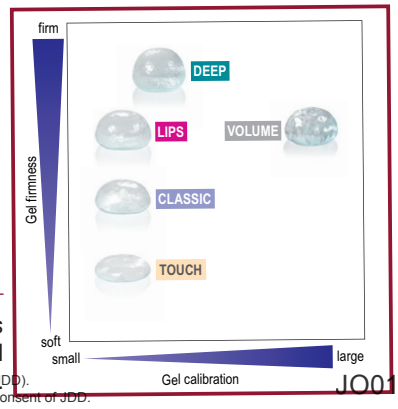

FIGURE 1. The five HA_E fillers have distinctive physical properties (page s6).

Emervel®: Full-Face Rejuvenation With a Range of Customized Hyaluronic Acid Fillers

Berthold Rzany MD ScM

Aesthetic enhancement of the face is more than the correction of nasolabial folds. A global approach with several indications treated simultaneously is increasingly used in order to achieve a natural, balanced look sought by patients. Patients with advanced signs of aging who have not received prior treatments present a specific challenge and benefit most from this approach. The global approach is also important from an anatomical perspective, as the facial indications do not exist alone, and treatment of some indications can lead to changes in other areas of close proximity. However, only a few studies evaluate the use of injectable fillers in a multiplicity of facial indications along with subject satisfaction. In this first supplement concerning facial rejuvenation using Emervel® dermal fillers, we highlight the key characteristics of this new range of hyaluronic acid fillers in terms of their physical properties and present results of a multi-center, comprehensive trial, in which up to eight indications could be treated simultaneously (including nasolabial folds, marionette lines, periorbital lines, upper lip lines, cheek folds, tear-troughs, lips and cheeks).

This open-label study reflects a real-life scenario, as dermatologists were allowed to choose the type of filler, the volume, and injection technique while taking into account the patient's expectations. Furthermore, this allowed the investigators to familiarize themselves with the new filler range, gathering valuable knowledge of how to customize each filler to suitable indications according to its distinctive physical properties, which is a unique aspect of Emervel® fillers.

In this supplement, the custom-tailored concept is described in the first article, in which the physical properties of the five fillers of the same range (Emervel® Touch, Emervel® Classic, Emervel® Lips, Emervel® Deep and Emervel® Volume) are reported. The next three articles are centered on essential areas of global aesthetic treatment: the cheeks, the perioral, and the periorbital areas. Results highlight the specificities of each filler, notably based on both subjective (investigators' and patients' evaluations) and objective assessments. Previously only used in studies with few subjects, three-dimensional imaging was employed in this rather large study (a total of 77 subjects) for documentation and particularly in defining volume variations.

Currently, physicians face a period where increasing longevity of the population and growing concern of patients for a youthful appearance without risks coincide to form a huge demand in the field. Non-invasive methods that are safe, durable and satisfactory to patients are the cornerstone to meeting this emerging need. This supplement will help us to better advise and treat our patients.

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A Complete Range of Hyaluronic Acid Filler With Distinctive Physical Properties Specifically Designed for Optimal Tissue Adaptations

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ABSTRACT

A new range of hyaluronic acid (HA) dermal fillers has been designed using Optimal Balance Technology™, which centers around three main parameters: the degree of cross-linking, the size of gel calibration and the HA concentration. The five different products in the range (HA_E Touch, HA_E Classic, HA_E Lips, HA_E Deep and HA_E Volume) have the same concentration of HA (20 mg/mL) and various degrees of cross-linking and gel calibration, in order to have distinctive physical properties adapted to their specific indications. HA_E Classic, HA_E Deep, HA_E Lips and HA_E Volume are available in two different formulations either with or without lidocaine. The efficacy, safety and patient satisfaction of the HA_E range in various indications have been assessed in several clinical studies. In this study, the rheological measurements of the HA_E fillers were performed, and the results showed that there are four different levels of gel firmness, with HA_E Touch being the softest and HA_E Deep being the firmest gel within the range. Addition of lidocaine did not change the rheological properties of the HA_E fillers. HA_E fillers have three different degrees of gel calibration, with HA_E Touch, HA_E Classic and HA_E Lips having the same smallest gel calibration and HA_E Volume having the largest gel calibration within the range. Injection of all HA_E fillers was smooth, regular, and required low extrusion force when using the Ultra Thin Wall (UTW) needle provided for each product. In summary, the HA_E fillers have distinctive physical properties in terms of gel firmness and gel calibration, which were designed to adapt to their specific indications.

J Drugs Dermatol. 2012;11(1)(suppl):s5-s8.

INTRODUCTION

Soft tissue augmentation with temporary fillers is a safe and effective aesthetic procedure for patients seeking to maintain a youthful appearance.[1] Hyaluronic acid (HA) fillers have been used extensively in recent years because of their low immunogenic potential and relatively long duration of effect.[2-4] HA is a naturally occurring polysaccharide in the skin and is a ubiquitous and essential component of the extracellular matrix of all adult animal tissues. When unmodified HA is injected into the skin, it is rapidly degraded by hyaluronidase and free radicals. However, the chemically cross-linked HA forms an extensive hydrogel matrix, which is resistant to degradation and leads to a prolonged residence time in the skin.[5]

Several HA fillers are commercially available, and the number keeps growing. Injection of HA fillers usually provides immediate results, with little recovery time and relatively long-lasting clinical effects.[2] However, not all HA fillers are the same. The currently available HA fillers differ substantially in their physical properties, which are related to the formulation, including the source of HA, concentration of HA, type of cross-linker, degree of cross-linking, and the manufacturing process.[5] Since the fillers' physical properties could influence their clinical performance and the injection experience, physicians should carefully select the products best adapted to individual needs of their patients.[6-7]

Emervel® (hereafter referred to as HA_E; Galderma S.A., Lausanne, Switzerland) is a range of HA dermal filler which received CE mark in Europe in 2008. It was designed using Optimal Balance Technology™, by keeping the same concentration of HA (20 mg/mL) and varying the degree of cross-linking and gel calibration (sizing) among the various fillers within the same range. The range includes five different products, HA_E Touch, HA_E Classic, HA_E Lips, HA_E Deep and HA_E Volume, each with a specific indication and thus different target tissues (Table 1). All HA_E fillers except HA_E Touch exist in two formulations either with or without 0.3% w/w lidocaine. Here, we report the key physical properties of HA_E and the rationale behind the design of this novel range.

TABLE 1.

Indication of Each HA_E Filler	
HA_E Touch	For injection into superficial dermis for the correction of superficial wrinkles
HA_E Classic	For injection into the mid-dermis for the correction of moderate to deep wrinkles
HA_E Lips	To restore and/or augment the volume of the lips
HA_E Deep	For injection into the deep dermis for the correction of moderate to deep wrinkles
HA_E Volume	For injection into the supraperiostic zone or subcutaneous fat tissue for the correction of facial volume

Degree of Cross-Linking and Rheological Measurements

The HA_E range employs the bi-functional cross-linker 1, 4-butanediol diglycidyl ether (BDDE). It can react at one end to one strand of HA and leave the other end pendant, or react at both ends to cross-link two different strands of HA.[5] A higher degree of cross-linking (but not pendant) leads to a more tightly packed network and thus a greater gel firmness.

The degree of cross-linking determines the gel firmness. Firmer gels can better resist deformation caused by facial movement and may have a longer duration of effect. On the other hand, gels which are too firm are usually more difficult to inject, easily palpable if injected too superficially into the skin, and are more likely to cause injection site reactions such as erythema and bruising.

Gel firmness can be assessed using rheological measurements. HA fillers are viscoelastic materials, which by definition have both elastic (solid-like) and viscous (liquid-like) components, characterized by the elastic modulus (G') and the viscous modulus (G"), respectively.[8] Tan δ is defined as the relative values of G" and G' (tan δ=G"/G')[8]; a lower tan δ corresponds to a firmer or more solid-like gel and a higher tan δ corresponds to a softer or more liquid-like gel.

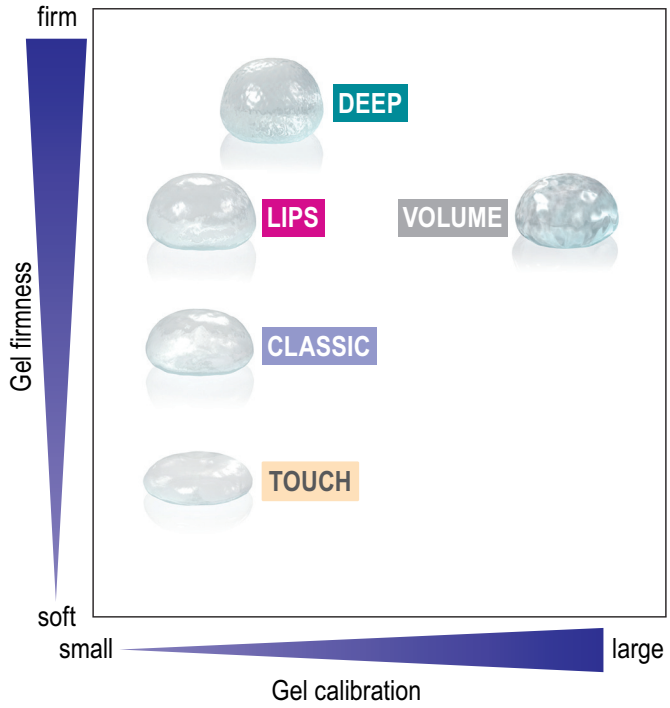
Gel Calibration and Extrusion Force

Sizing is an essential step in the manufacturing process of all HA fillers. Cross-linking reaction results in a gel block, which needs to be appropriately sized in order to be injected through fine-bore needles.[5] This process is referred to as "gel calibration" in the manufacturing of HA_E. Appropriately calibrated gels require low extrusion force and the flow of the filler is regular.

The degree of gel calibration affects the injection experience. Injection is smooth when gel calibration is adapted to the needle size, gel firmness and the target tissue. Firmer gels need to be sized into smaller pieces or to be injected through a larger gauge needle. Appropriate gel calibration also allows good tissue integration: while a filler with small gel calibration is more easily dispersible, avoiding lumps and bumps when injected into the denser superficial dermis or into lips, a filler with large gel calibration is less dispersible and more adapted to the loosely packed subcutaneous tissues.

There are three degrees of gel calibration for the HA_E range: HA_E Touch, Classic and Lips all have a small gel calibration; HA_E Deep has a medium calibration, while HA_E Volume has a large calibration (Figure 1).

FIGURE 1. The five HA_E fillers have distinctive physical properties.



MATERIALS & METHODS

Oscillation dynamic rheological measurements (G', G") were performed at 37 °C, using a Bohlin CVO Rheometer (Malvern Instruments Ltd, UK) equipped with a 40 mm/1° cone sensor. The frequency range was 0.1 to 2 Hz. The tan δ (G"/G') was calculated from the modulus data at the frequency of 2 Hz. Rheological measurements were carried out using a representative batch of HA_E fillers.

Extrusion force was measured using a dynamometer (Adamel Lhomargy DY30, Roissy-en-Brie, France) with a constant speed of 10 mm/min, and the "Ultra Thin Wall" (UTW) needle recommended for each HA_E filler. Extrusion force is defined as the force the injector needs to use to push the gel out of the needle, and this point is defined as "yield point."

RESULTS

The rheological data are summarized in Table 2. While the viscous modulus G″ was comparable among the products (18.6–23.3 Pa), the elastic modulus G′ varied substantially (34.5–213.8 Pa). In the HA_E range, HA_E Deep was the firmest gel with the lowest tan δ (0.11) and HA_E Touch was the softest gel with the highest tan δ (0.54). Addition of lidocaine did not affect the physical properties, and similar rheological data were obtained with HA_E fillers either with or without lidocaine.

Table 2 summarizes the extrusion force required for each HA_E filler. When injected using the respective recommended UTW needles, HA_E Deep and Touch required a very low extrusion force (8 and 9 N, respectively), while HA_E Volume required a slightly higher extrusion force (21 N). After reaching the respective yield point, injection was smooth and regular for all HA_E fillers, with no obvious peaks observed (Figure 2). Similar results were obtained with HA_E fillers without lidocaine compared to the formulations with lidocaine.

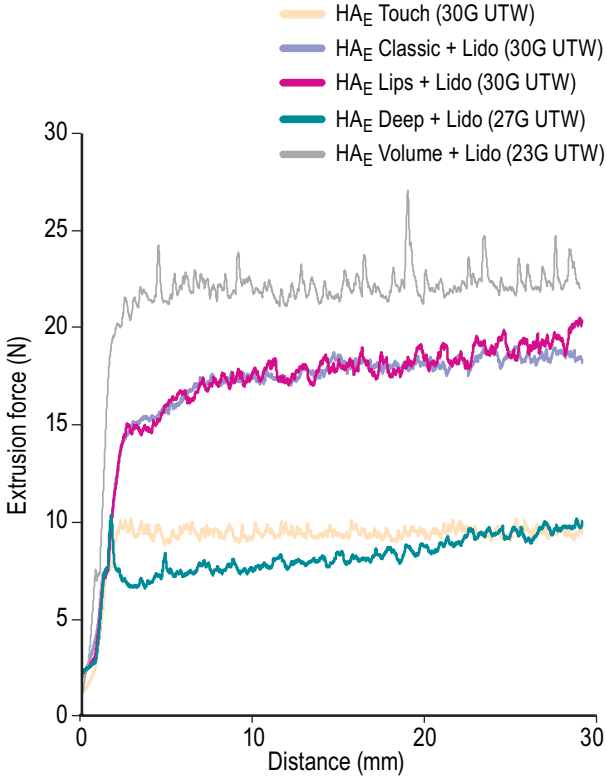
DISCUSSION

The HA_E filler range was designed using Optimal Balance Technology™, which includes three factors: concentration (of HA), cross-linking, and calibration. The fillers in the HA_E range have the same concentration of HA (20 mg/mL), but four degrees of cross-linking and three levels of gel calibration, resulting in five products with distinctive physical properties, each adapted to its specific indication (Figure 1).

HA_E Touch was designed for the correction of superficial wrinkles and should be injected into the superficial dermis. To this end, it must be soft and with a small calibration so that the results are smooth and natural-looking. HA_E Touch is easily injected with a 30 Gauge (G) x ½″ needle, which allows for maximum precision. The efficacy and safety of HA_E Touch on the correction of periorbital lines and upper lip lines were demonstrated in an open-label, six-month study.[12-13]

HA_E Classic has the same small calibration as HA_E Touch but is firmer. The injection was smooth and regular with a 30 G x ½″ UTW needle. The efficacy and safety of HA_E Classic in the treatment of nasolabial folds, marionette lines and tear troughs have been observed.[12-14] HA_E Classic is the most versatile filler of the range, with cheek folds, oral commissures and glabellar lines suggested to be additional suitable indications.[15]

FIGURE 2. Extrusion force and injection curve of HA_E fillers with the respective recommended needle.



HA_E Lips is firmer than both HA_E Touch and Classic, because fillers for lip enhancement need to resist deformation caused by strong and frequent movement of the lips. On the other hand, HA_E Lips has the same small calibration as Touch and Classic, for a smooth and natural enhancement. The small calibration also allows the filler to be injected through a 30 G x ½″ UTW needle for more treatment precision, which is essential for lip contouring. The efficacy and safety of HA_E Lips in lip augmentation were demonstrated in a six-month, open-label study.[13]

TABLE 2.

Key Physical Properties of the HA_E Range

	HA_E Touch	HA_E Classic + Lido	HA_E Lips + Lido	HA_E Deep + Lido	HA_E Volume + Lido
HA concentration (mg/ml)	20	20	20	20	20
G′ (Pa)	34.5	67.7	151.1	213.8	131.6
G″ (Pa)	18.6	20.3	19.9	23.3	20.3
Tan δ (G″/G′)	0.54	0.31	0.13	0.11	0.15
UTW Needle	30 G x ½″	30 G x ½″	30 G x ½″	27 G x ½″	23 G x 1″
Extrusion force (N)	9	18	18	8	21

Results were obtained with a representative lot of HA_E fillers. UTW=ultra thin wall.

HA_E Deep has the highest degree of cross-linking in the range, with a medium calibration. Despite its great firmness, the use of a UTW needle allows it to be injected with a low extrusion force. Since HA_E Deep is intended for deep injections into the dermis, it is not easily palpable despite its great firmness and medium gel calibration. HA_E Deep is efficacious and safe in the treatment of tear troughs, nasolabial folds and marionette lines.[12,13,16] It was also suggested to be suitable for cheek and chin volume enhancement.[15]

Because HA_E Volume was designed to be injected into the subcutaneous fat tissues for effective volume enhancement, it has the largest gel calibration of the range and also greater gel firmness compared to HA_E Touch and Classic. The large gel calibration makes HA_E Volume less dispersible and is adapted to the fibroblasts and adipose tissues. The moderately high gel firmness allows HA_E Volume to resist strong deformation, resulting in a long duration of volume enhancement. Extrusion force was acceptable when HA_E Volume was injected through the small, recommended 23 G x 1" UTW needle. HA_E Volume was safe and efficacious for cheek enhancement as demonstrated in a six-month, open-labeled study.[1]

In summary, selecting the appropriate filler adapted to the patient is challenging. Injectors largely rely on personal experience and expert opinion, because the scientific and clinical evidence is scant. This novel HA_E range was designed to obtain fillers with distinctive physical properties adapted to various indications. Results for both physical properties and clinical performance of this range are now available, which should help injectors to choose the filler that best matches their patients' needs.

DISCLOSURES

Authors Segura and Anthonioz are current employees of Galderma R&D. Authors Herbage and Fuchez are current employees of Symatese. This study was funded by Galderma R&D, Sophia Antipolis, France.

ACKNOWLEDGEMENTS

The authors wish to thank Y. May Ma PhD for editorial assistance.

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Sustained Efficacy and High Patient Satisfaction After Cheek Enhancement With a New Hyaluronic Acid Dermal Filler

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ABSTRACT

Background: Increasing volume is an important part of facial rejuvenation since volume loss is common and typically age-related. HA_E Volume is a moderately firm gel designed to be injected into the subcutaneous tissue for volume enhancement.
Objective: To assess the efficacy, patient satisfaction, and safety of HA_E Volume in patients with bilateral volume loss of the cheeks.
Materials and Methods: This was a multi-center, six-month, open-label study. Subjects received HA_E in the cheeks at baseline, and a touch-up injection was optional three weeks later. Global aesthetic improvement, cheek thickness (caliper measurements), changes in volume using three-dimensional (3-D) photo analysis, adverse events and injection site reactions were evaluated at each visit. Optimal correction was defined as results obtained three weeks after last injection. A subject satisfaction questionnaire was performed three weeks after the last injection.
Results: Investigators evaluated the great majority of subjects as much or very much improved in terms of aesthetic improvement of their cheeks at week 3 and at months 3 and 6 (89.3%, 90.9%, and 76.4%, respectively). After six months, 65.8 percent of the correction achieved at week 3 (optimal correction) was maintained in terms of cheek thickness (caliper assessments), confirmed by 67.7 percent of the volume maintained based on 3-D volume analyses. The majority of subjects (92.1%) were satisfied or very satisfied with their aesthetic outcome. A good tolerability profile was observed.
Conclusions: Treatment with HA_E Volume in cheeks led to good aesthetic improvement, sustained results confirmed by caliper and 3-D volume assessments, and high subject satisfaction.

J Drugs Dermatol. 2012;11(1)(suppl):s9-s16.

INTRODUCTION

Volume loss of deep medial cheek fat as well as of the malar fat pad is an important factor of midface aging.[1] The forces of gravity and age shift the subcutaneous tissues, bringing with it drooping of the cheeks and descent of the midface soft tissue prominences, which deepen the nasolabial crease.[2] Thus, increasing cheek volume and enhancing malar projection are important parts of facial rejuvenation.

Due to the present lack of scales for the assessment of cheek enhancement, three-dimensional (3-D) imaging may be helpful to assess volume changes as has been shown for the correction of nasolabial folds[3] and the tear trough area.[4] This tool provides objective quantifiable data, and is therefore complementary to the traditional aesthetic assessments of facial rejuvenation.

HA_E Volume (Emervel® Volume, Galderma S.A., Lausanne, Switzerland) is a hyaluronic acid (HA) filler designed to be injected into the subcutaneous tissue for volumizing effect. For this purpose, it has a moderately firm texture, and the largest gel calibration among the five products of the HA_E filler range.[5] This six-month study illustrates the use of HA_E Volume in cheek enhancement.

Practical Aspects of Injection and Outcomes

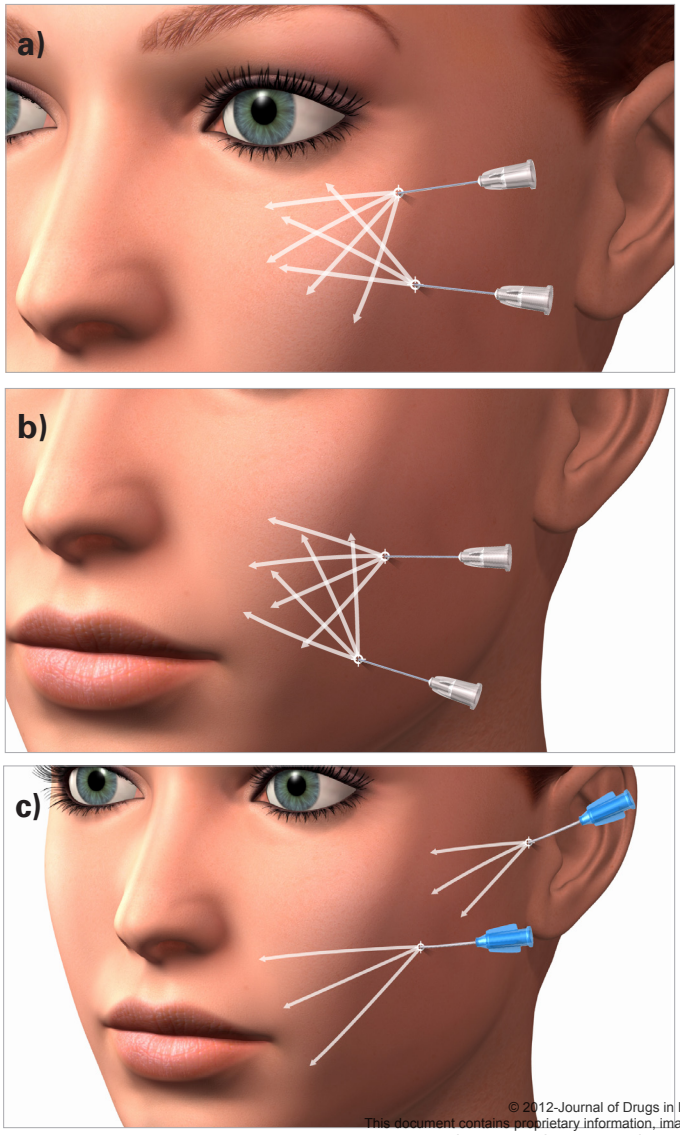
Visual analysis of patients in an upright position is important to establish proper markings in the cheek area.[6] Retrograde injection is usually used for a more uniform result, and fanning technique is suitable for the injection of large areas. To enhance the malar prominence, injection at multiple layers can be conducted, with

the needle first almost parallel to the skin, and then at a 30-45° angle for subcutaneous and muscular injections (Figure 1a). If needed, the needle can be inserted at a 90° angle until immediately above the periosteum for major projections of the malar area. For volume enhancement in the cheek among patients with moderate to severe fat reduction, similar fanning and retrograde techniques are usually used (Figure 1b). A cannula can also be used for the injection of both cheekbones and cheeks (Figure 1c). A soft massage in the area after injection will smooth surface irregularities and result in a more uniform and natural look.

MATERIALS & METHODS

This study was conducted in accordance with the ethical principles in the Declaration of Helsinki, the International Conference of Harmonization guidelines for Good Clinical Practices and in compliance with local regulatory requirements, and was both reviewed and approved by ethics committees. All subjects provided their written informed consent before entering the study.

FIGURE 1. Injection technique of **a)** cheekbone and **b)** cheek using a needle. **c)** Injection of both cheekbone and cheek can also be performed with a cannula.



This was a multi-center, six-month, open-label study in five centers located in France and Germany.[7] Subjects were of either sex, over 18 years old, seeking volume enhancement for their cheeks. At baseline, HA_E Volume was injected into the supraperiostic zone or subcutaneous fat tissue of the cheeks. Injection volume and technique were chosen by the investigator as appropriate. Based on the investigator's assessments and subject's expectations, touch-up injections could be performed at week 3 (on the same areas injected at baseline). Study visits took place at baseline, three weeks after baseline injection, three weeks after touch-up injection (if performed), and three and six months after the last injection (defined as baseline injection or touch-up if it was performed).

Efficacy measures included an investigator's assessment using the Global Aesthetic Improvement Scale[8] (from -1 (worse) to 3 (very much improved)), comparing the subject to baseline pre-injection photographs at each post-baseline visit. Also, cheek thickness assessments were performed by using a caliper (Skinfold Caliper, Chattanooga Group, Hixson, TN, USA) to measure the thickness of each injected cheek, and reported in millimeters at each visit. Volume assessments were performed using 3-D surface reconstruction and analysis software (LifeViz™, QuantifiCare S.A., Sophia Antipolis, France). At each visit, accurately calibrated and stereoscopic images of the face were acquired with a passive stereovision digital camera, and the images were then used for the reconstruction of a 3-D surface. The anatomical volume variations (in cm^3) of those 3-D images from baseline at each post-baseline visit were assessed in each treated area delineated at baseline. Optimal correction is defined as results obtained three weeks after last injection, and is used to calculate the maintained effect after six months (change from baseline to month 6 divided by change from baseline to week 3 (optimal correction)).

Investigator-assessed safety measures were the incidence of adverse events and injection site reaction scores (bruising, erythema, lump/bump, edema, pain and pruritus on a scale of 0 (none) to 3 (severe)) for cheeks at each visit. The same injection site reactions (except lump/bump) were evaluated by subjects using diaries for 14 days after injection. In addition, a subject satisfaction questionnaire was administered three weeks after the last injection.

Data were analyzed for the intent-to-treat population (ITT; the entire population enrolled) regarding efficacy and satisfaction, and on the safety population (APT (All Patients Treated); intent-to-treat population after exclusion of subjects who were not injected) for safety. No inferential statistics were performed. All variables were descriptively summarized on the ITT or APT population.

TABLE 1.

Baseline Demographic/Clinical Characteristics		
		Subjects (N=56)
Gender (%)	Male	3 (5.4%)
	Female	53 (94.6%)
Age (in years)	Mean±SD	54.3±8.5
	Median	54.0
	(Min,Max)	(38,71)
Phototype (%)	I	4 (7.1%)
	II	28 (50.0%)
	III	21 (37.5%)
	IV	3 (5.4%)
Race (%)	Caucasian	53 (94.6%)
	Hispanic	3 (5.4%)
Cheek thickness (mm) at baseline before initial injection (%)		
Number of sides		88
Mean±SD		12.33±3.83

TABLE 2.

Injection Information		
Injection technique*	N	56
	Multiple puncture	6 (10.7%)
	Retrograde linear threading	41 (73.2%)
	Fanning	23 (41.1%)
Needle*	N	56
	Provided needle	40 (71.4%)
	Cannula	9 (16.1%)
Type of anesthesia*	N	56
	Topical	10 (17.9%)
	Local	19 (33.8%)
	Nerve block	10 (17.9%)
	None	17 (30.4%)
Volume injected at baseline	N	56
	Mean±SD	2.6±1.2
Volume injected at touch-up	N	17
	Mean±SD	1.8±0.8
Total volume injected	N	56
	Mean±SD	3.1±1.7

*Baseline injection.

RESULTS

Subject Characteristics and Injection Details

A total of 56 subjects (112 sides) received injections of HA_E Volume for cheek enhancement. The great majority of subjects were female and Caucasian (both 94.6%), had phototypes II to III (87.5%), and the mean age was 54.3 years (Table 1). The mean cheek thickness before injection was 12.33±3.8 mm for the 44 subjects (88 sides) that had caliper assessments completed.

Technique and volume of injection are summarized in Table 2. About 30 percent (17/56) of subjects received a touch-up. The principal injection techniques were retrograde linear threading (73.2%) and fanning (41.1%), used either alone or in combination. On average, a total of 3.1±1.7 mL (2.6±1.2 mL at baseline, and 1.8±0.8 mL at touch-up) was injected per subject for both cheeks, with 44.6 percent of subjects receiving less than 2 mL.

Efficacy Evaluation and Subject Questionnaire

Figure 2 summarizes the results of aesthetic improvements in the cheeks as evaluated by the investigators. Three weeks after the last injection, 89.3 percent of subjects were judged as much or very much improved. This improvement was largely maintained at the end of the study, with 90.9 percent and 76.4 percent of subjects being much or very much improved at months 3 and 6, respectively. Three weeks after last injection of HA_E Volume, the mean cheek thickness measured by caliper increased by 3.45±2.80 mm from baseline. After six months, cheek thickness was still 2.27±4.08 mm greater, meaning that 65.8 percent of the effect was maintained compared to optimal correction (Figure 3). Data from the caliper assessment were confirmed by results of the 3-D volume assessment, another objective evaluation, as 67.7 percent of the volume was maintained at month 6 compared to optimal correction (Figure 3).

Figures 4 and 5 show the photos of two representative subjects at baseline, week 3 and month 6. Pseudo-color mappings illustrate the changes in volume compared to baseline in the cheek area.

Three weeks after injection, high levels of subject satisfaction were reached (Figure 6). The vast majority of subjects (92.1%) were satisfied or very satisfied with their aesthetic outcome, 76.9 percent of subjects would like to be retreated and 88.5 percent would recommend the treatment to friends and family. These high levels of subject satisfaction correspond to the results of the investigator's efficacy assessments, as a high proportion of subjects were improved.

Safety Evaluation

HA_E Volume was generally well-tolerated in cheek enhancement, despite the large quantity of volume injected (up to 8 mL in total). During the study, no serious or treatment-related

FIGURE 2. Global aesthetic improvement of cheeks at each visit (ITT).

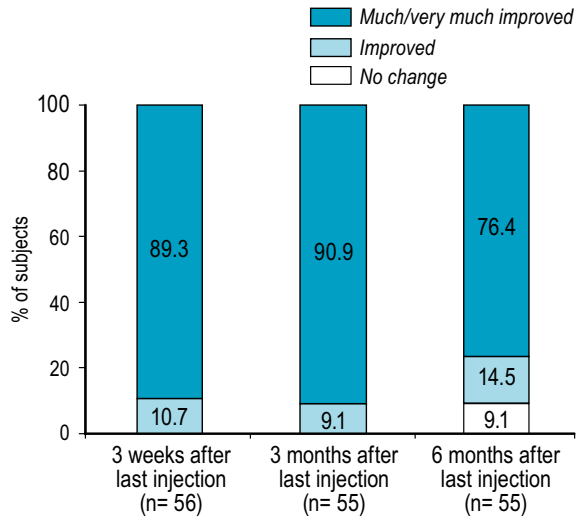


FIGURE 3. Mean change of cheek thickness and 3-D volume from baseline (ITT). The spheres at week 12 and week 24 represent the volume maintained compared to the volume at optimal correction (week 3).

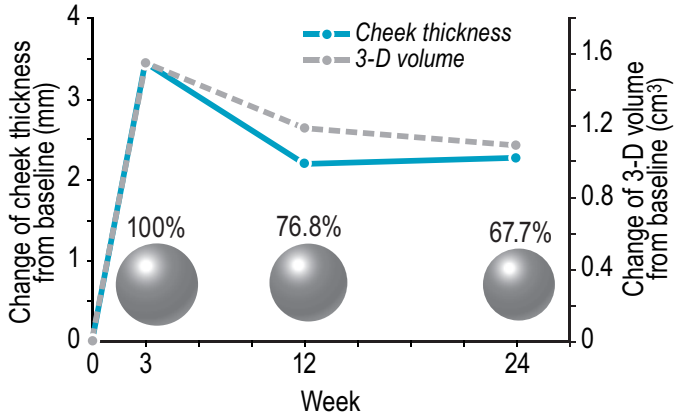


TABLE 3.

Mean Worst Scores (±SD) of Injection Site Reactions According to the Investigator's Assessment at Each Study Visit and Subject's Diary During the First 14 Days After Injection

	Investigator	Subject
Bruising	0.4±0.7	1.0±1.0
Erythema	0.9±0.9	0.7±0.9
Lump/bump	0.1±0.4	N/A
Edema	0.9±0.7	1.5±0.8
Pain	0.4±0.7	1.2±0.8
Pruritus	0.0±0.1	0.1±0.3

All injection site reactions were assessed using a 4-point severity scale (0=none; 3=severe).

AEs occurred in the cheek. There were no local tolerability issues except common injection site reactions. Worst scores for each injection site reaction are defined as the score of highest severity during the entire study (at all study visits for investigator assessments and during the first 14 days after baseline and touch-up injections for subject assessments). According to investigators, the mean worst scores were less than 1 (mild) for all parameters (Table 3). Edema and pain were the most frequent signs reported by subjects (HA_E Volume used in the study did not contain lidocaine). Mean worst scores based on subject assessments were higher than investigator assessments, likely due to the fact that reporting occurred soon after injection (Table 3). However, these signs were transient and disappeared without additional treatment, with a maximum duration of 5.6 days (edema). Based on evaluations of both investigators and subjects, touch-up injections did not induce more injection site reactions than baseline injections.

DISCUSSION

Cheeks need volume, particularly among older patients who present with clear signs of midface aging and who have not received previous treatments. This study provides information on the volume to be used and effects to be achieved with a filler specifically designed for volume augmentation. HA_E Volume was found to provide excellent correction and durability for cheek enhancement over a six-month period. The clinical evaluations were confirmed by two objective methods (3-D and cheek thickness measurements), which demonstrated similarly good improvement six months after injection compared to baseline. This is reflected by the patients' perspective, as they considered the treatment of their cheeks with HA_E Volume to be very satisfactory, with 92.1 percent being satisfied or very satisfied with their aesthetic outcome.

HA_E Volume was safe and well-tolerated, and the transient injection site reactions which were reported (such as edema and pain) and could be expected soon after injection of dermal fillers were mild to moderate in severity and self-limiting.[9-10] Analyses of other HA fillers indicate that injection site reactions may be related to the technique of injection.[11] This emphasizes the need for slow injection. In addition, the use of ice pack application and compresses may help reduce swelling and increase comfort.[12] It is of note that, despite the occurrence of injection site reactions, the majority of subjects were satisfied, would like to receive the same treatment again, and would recommend it to friends and family.

Though some practitioners may be apprehensive about injecting larger volumes of filler, this study showed a good tolerability profile with a mean total volume of 3.1 mL injected in the cheek/malar region, comparable to what has been reported.

FIGURE 4. Representative **A)** 2-D and **B-C)** 3-D photos of a subject receiving 1.8 mL HA_E Volume (1.0 mL at baseline and 0.8 mL at touch-up) on her right cheek. **C)** Pseudo-color mapping indicates the area of augmentation.

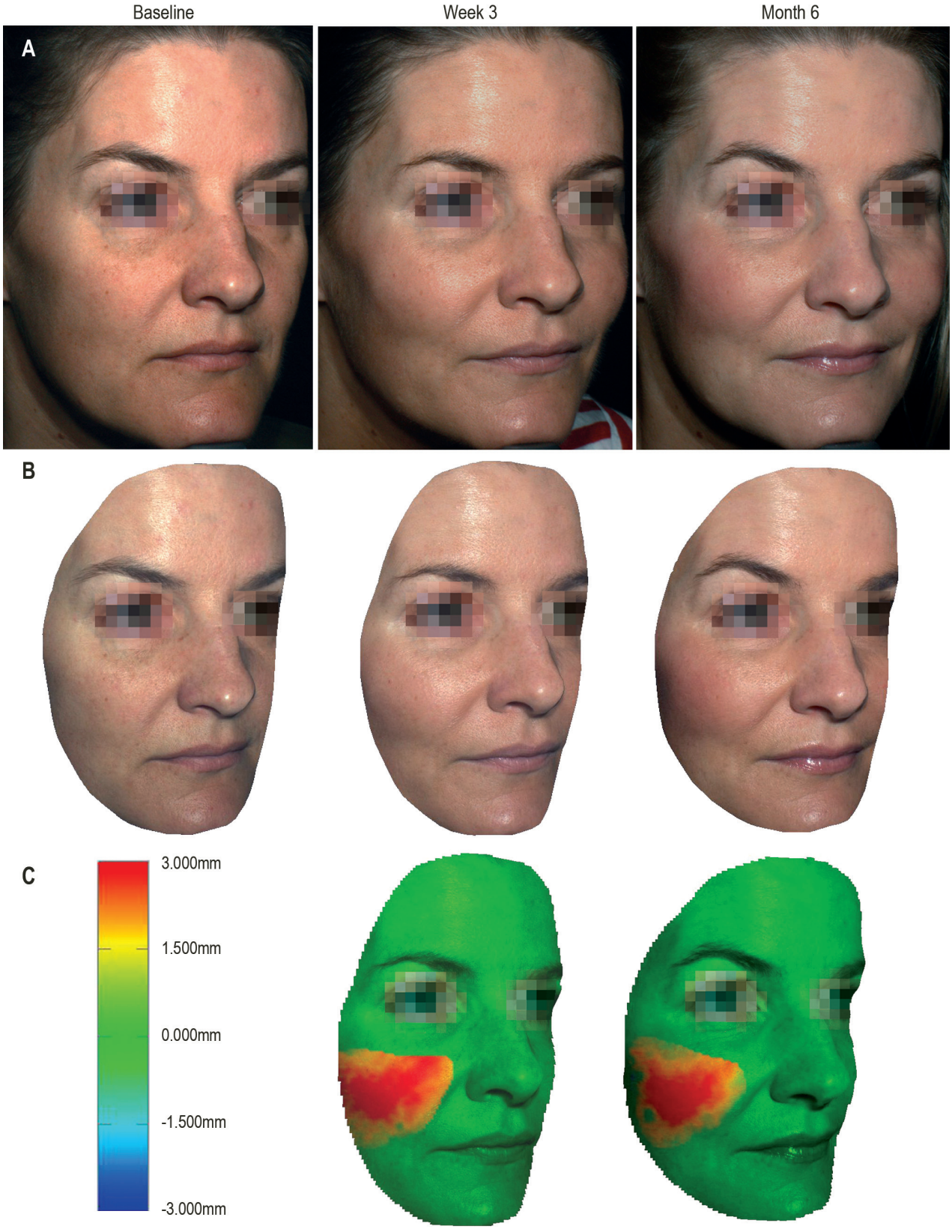


FIGURE 5. Representative **A)** 2-D and **B-C)** 3-D photos of a subject receiving 3.6 mL HA_E Volume (2.4 mL at baseline and 1.2 mL at touch-up) on her right cheek. **C)** Pseudo-color mappings indicate the area of augmentation.

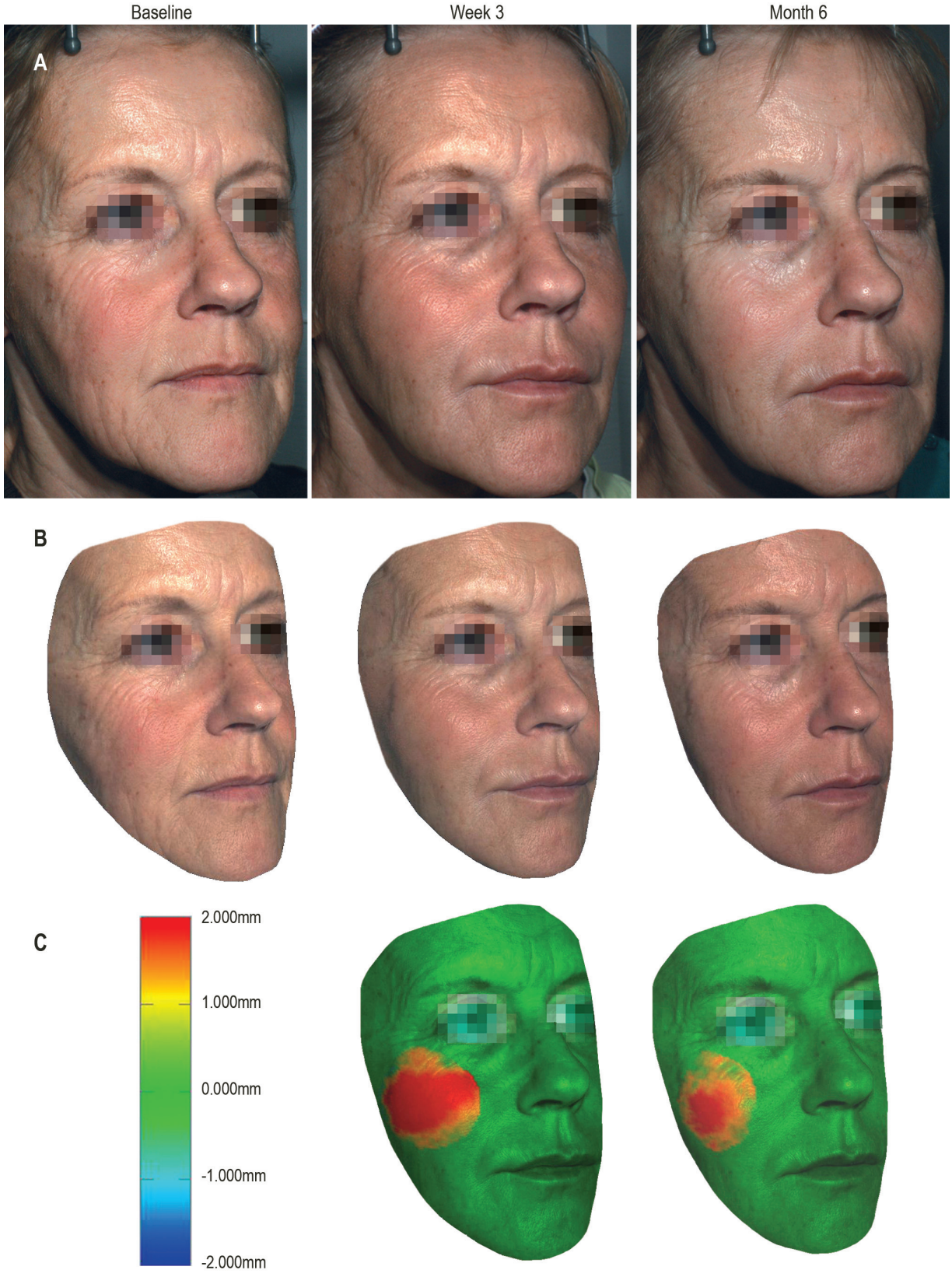
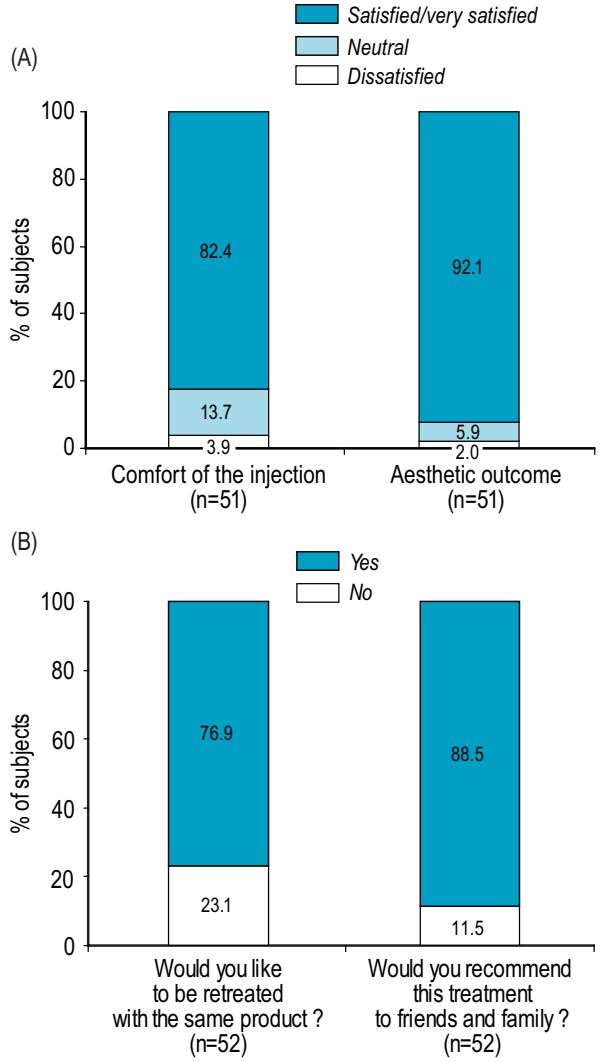


FIGURE 6. Results of subject satisfaction questionnaire three weeks after the last injection.



Indeed, another HA filler has been designed for deep-volume enhancement in areas such as the chin and cheeks, and in a recent study, the mean total volume used was 4.3 mL (including initial injection and touch-up four weeks later if needed; maximum 9.0 mL) and investigator-assessed aesthetic improvement was at least improved for 96 percent of subjects at six months.[13]

Few robust studies address dermal fillers specifically indicated for cheek volume enhancement and not only wrinkles and folds. Lowe and Grover found that a HA filler used in malar and mental augmentation was effective for up to 64 weeks.[14] Hoffmann reported that another HA filler can be used for the indication of facial volume loss, but the follow-up was brief (two weeks) and patient-reported outcomes were not assessed.[15] Therefore, our study, which shows the long-lasting efficacy of HA_E Volume, adds further evidence to this indication. The study results enable physicians to better communicate the volume needed, the best possible correction to be achieved, and the durability of this correction to their patients.

CONCLUSIONS

In conclusion, treatment with HA_E Volume in cheeks brought about high levels of long-lasting aesthetic improvement, confirmed in terms of cheek thickness and 3-D volume assessments. The good treatment tolerability and sustained improvement observed six months after the last injection were mirrored by a high patient satisfaction. This study adds further evidence to an important aesthetic indication for the benefit of patients and their physicians.

DISCLOSURES

The investigating authors received investigator fees for this clinical study. Two of the authors (Kerrouche and Dhuin) are employees of Galderma. This study was supported by Galderma R&D, Sophia Antipolis, France.

ACKNOWLEDGEMENTS

The authors wish to thank Galadriel Bonnel MSN for editorial assistance.

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Perioral Rejuvenation With a Range of Customized Hyaluronic Acid Fillers: Efficacy and Safety Over Six Months With a Specific Focus on the Lips

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ABSTRACT

Background: Injectable fillers are frequently used to restore volume and correct wrinkles in the perioral region. However, evidence for perioral indications is scarce.
Objective: Assess the efficacy, patient satisfaction, and safety of a new range of hyaluronic acid fillers (HA_E) in perioral enhancement.
Materials and Methods: This was a multi-center, six-month, open-label study. At baseline, subjects could receive HA_E Touch, HA_E Classic, HA_E Lips and HA_E Deep for the treatments of lips, upper lip lines, nasolabial folds and marionette lines, and a touch-up injection was optional three weeks later. Lip Fullness Grading Scale (for lips), wrinkle assessments (Lemperle Rating Scales for the remaining indications), adverse events, and local tolerance were evaluated at each visit, and 3-D volume analyses (for nasolabial folds and lips only) at each post-baseline visit. Optimal correction was defined as results obtained three weeks after last injection. A subject satisfaction questionnaire was performed three weeks after last injection.
Results: Overall, HA_E Lips was injected for lip enhancement, HA_E Touch and HA_E Classic for upper lip lines, and HA_E Classic and HA_E Deep for both nasolabial folds and marionette lines. After six months, around a 1-grade improvement persisted according to the lip fullness and wrinkle assessment scales. The long duration of effect was confirmed by 3-D analyses, with 62.7–71.4 percent of volumes obtained at week 3 (optimal correction) maintained after six months. The majority of subjects (from 80% for upper lip lines with HA_E Classic to 94.8% for nasolabial folds with HA_E Deep) were satisfied or very satisfied with their aesthetic outcome. All products were safe and well-tolerated.
Conclusions: Perioral enhancement with HA_E fillers led to sustained effect in terms of lip fullness, wrinkle and 3-D volume assessments, and high subject satisfaction.

J Drugs Dermatol. 2012;11(1)(suppl):s17-s26.

INTRODUCTION

Injectable fillers are often used in perioral rejuvenation.[1] Some biodegradable fillers such as polylactic acid and hydroxyapatite[2-3] are not suitable for lip augmentation because they do not add much volume and/or they increase the risk of nodule formation in this area. In contrast, hyaluronic acid (HA) preparations are the material of choice.

The perioral area is complex to treat, and clinicians must be knowledgeable of its anatomy. Besides being a major cosmetic feature of the lower face, the lips are essential for social interaction and of course for both solid and liquid intake.[4] Key landmarks include the philtrum, philtrum columns, cupid's bow and vermilion border. With aging, the lips become thin and flat, the upper lip lengthens and sags, vertical rhytides form, the oral commissures drop, and thinning of the vermilion, philtral columns and lower lip occurs.[5-7] Though most lip atrophy is age-related, hypoplastic lips can also occur in young patients.[8]

Lips do not exist alone. The surroundings of the lips must also be considered, particularly the nasolabial folds and labiomental folds (marionette lines). The nasolabial folds are located where the medial cheek septum separates the nasolabial fat from the medial cheek fat. Histology in this transition zone between nasolabial and medial cheek fat shows a dense fascial condensation separating these two compartments, and a direct insertion of this septum in the skin.[9] With age, ptosis of the superficial musculoaponeurotic system (SMAS) and skin elastosis contribute to the deepening of the nasolabial folds. As for marionette lines, with age, the depressor anguli oris and the platysma muscle pull down on the corners of the mouth,

while increased laxity of the SMAS and reduced skin elasticity allow the jowls to sag, thus deepening the marionette lines and contributing to an increased appearance of sadness.[4]

The HA_E range (Emervel®, Galderma S.A., Lausanne, Switzerland) includes five HA fillers with distinctive physical properties designed to match their specific indications.[10] This six-month study specifically addresses the use of HA_E in perioral enhancement, including the lips, upper lip lines, nasolabial folds and marionette lines.

Practical Aspects of Injection and Outcomes

For lips, using the correct injection technique can prevent nodules and promote patient comfort, while the characteristics of the HA filler influence the durability and long-term safety of the effect. The injection should be done slowly with the lip stretched, and a finger can be placed at the "Glogau-Klein point" (the slight elevation where the lip turns from glabrous skin to mucosa) to ensure flow within the channel.[6] The vermilion border can be better defined either by injecting along the border separating the red lip from the surrounding skin (Figure 1a), or by inserting the needle just superior to the upper lip (or inferior to the lower lip) and perpendicularly to the vermilion border for a series of injections close to each other (Figure 1b). For cutaneous upper lip and red lip enhancement, a deep transcutaneous injection following the dental arch can be done (Figure 1c). Injection can also be transmucosal (through the red lip), and a needle may be more adapted than a cannula. For upper lip rhytides, injection can be performed along the cutaneous lip for each rhytide. A series of injections close to each other can be performed on a third of the height of the cutaneous upper lip for very fine, short rhytides and for enhancement of the vermilion border (Figure 1d). It is important to not inject too much product in a single session in order to avoid a flat and unappealing lip. Injecting the philtrum (Figure 1e) projects the lip forward, enlarges the median area (particularly if the upper lip is overly loose), and also reduces upper lip rhytides.

FIGURE 1. Lip enhancement: Injection techniques for **a-b)** enhancing the vermillion border, **c)** upper lip and red lip, **d)** upper lip lines, and **e)** philtrum. Note: white lines illustrate superficial injections and black lines illustrate deep injections.

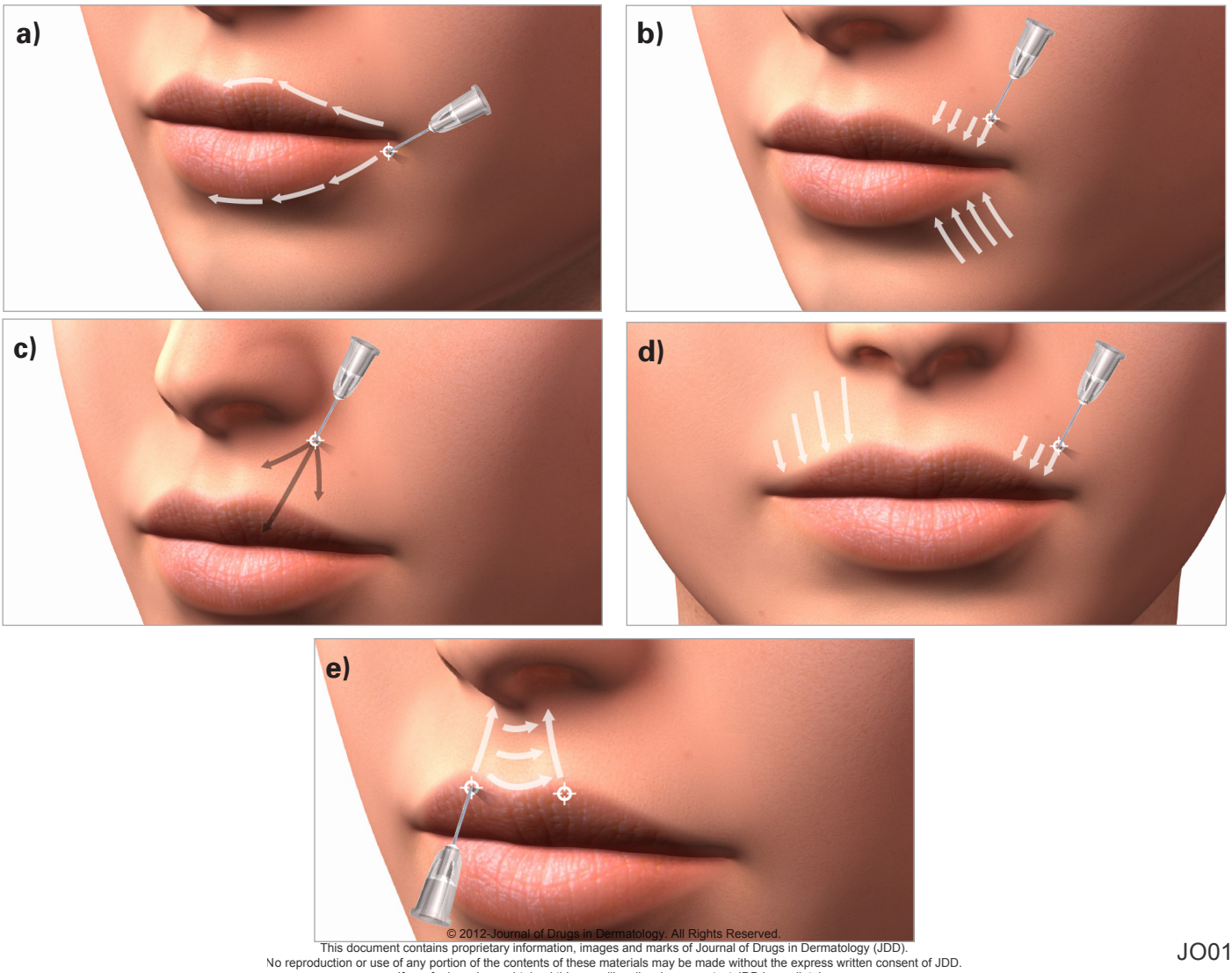


FIGURE 2. a-b) Injection technique for the treatment of nasolabial folds.

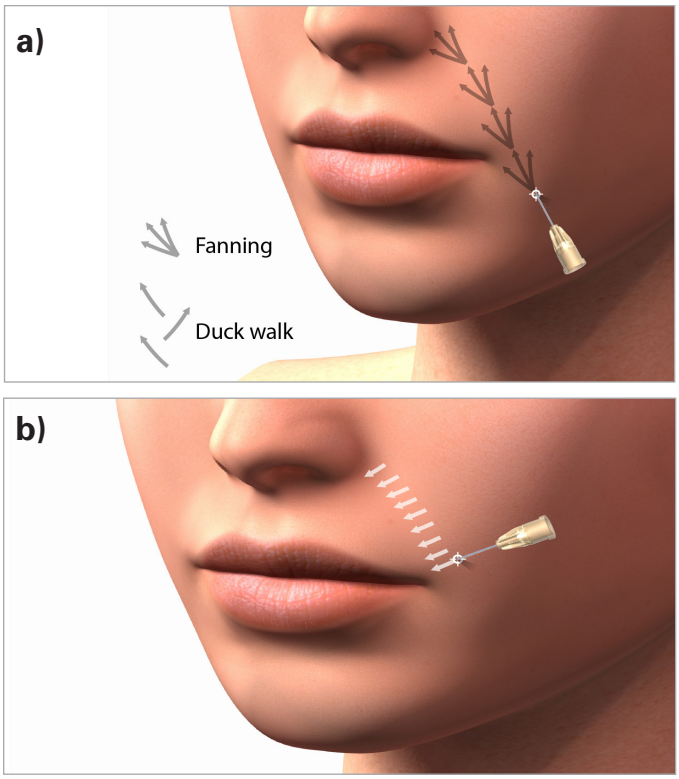


FIGURE 3. a-b) Injection technique for the treatment of marionette lines.

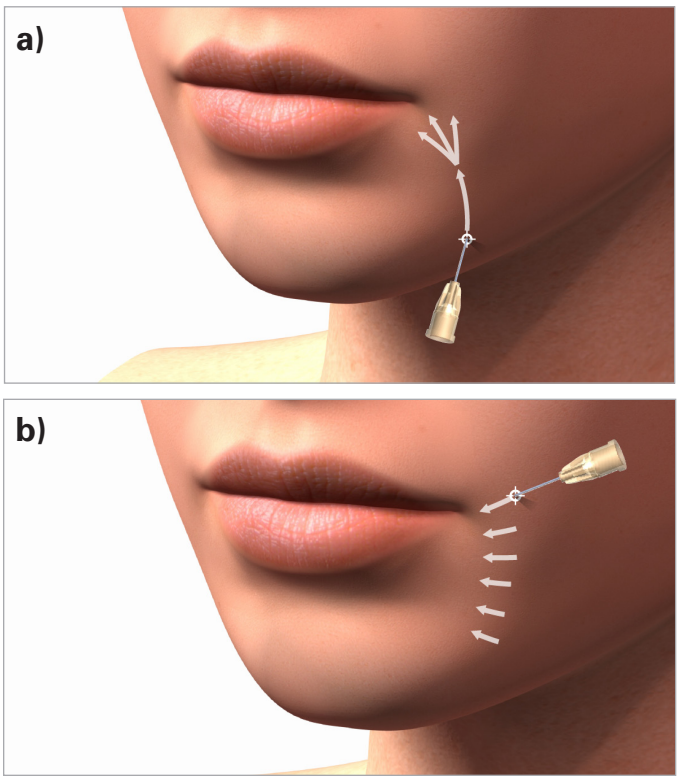
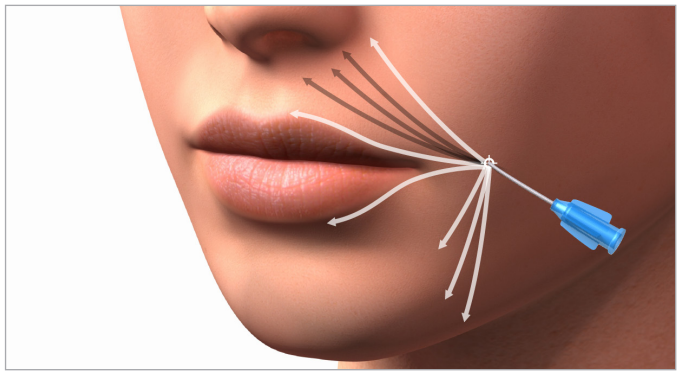


FIGURE 4. Treatment of nasolabial folds, vermilion border and marionette lines with a cannula.



When injecting the nasolabial fold, it is essential to think three-dimensionally, as the skin is lifted from deep under the fold toward the surface. No nasolabial fold is the same, and each must be approached with particular attention. Stretching the skin to visualize the fold and injecting medially to avoid deepening the treated folds is important.[4] With a deep injection, the fold can be lifted by injecting under the fold using the linear retrograde, duck-walk, or fanning technique (Figure 2a). With a superficial injection, smoothing the fold can be done with cross-injections along the fold to stretch the skin, and to create firm support against cheek ptosis (Figure 2b).

Marionette lines can be treated by injecting under the fold, with the linear retrograde and/or fanning technique, to anchor the commissure and the surrounding tissues in order to prevent drooping of the mouth corner (Figure 3a). A more superficial injection perpendicular to the marionette lines stretches the area and adds firm support to reduce cheek ptosis (Figure 3b).

Figure 4 illustrates the use of a cannula for a single injection of the nasolabial folds, vermilion border and marionette lines. Injection can be performed using anterograde or retrograde technique, either superficially or deeply with a blunt-end cannula.

MATERIALS & METHODS

This study was performed according to the ethical principles in the Declaration of Helsinki, the International Conference of Harmonization guidelines for Good Clinical Practices and in compliance with local regulatory requirements, and was both reviewed and approved by ethics committees. All subjects provided their written informed consent before beginning the study.

This was a multi-center, six-month, open-label study in five centers located in France and Germany.[11] Subjects were of either sex, over 18 years old, seeking tissue augmentation treatment of their lips, upper lip lines, nasolabial folds and/or marionette lines. As applicable, subjects presented with a score of at least 2 (shallow wrinkle) on the Lemperle Rating Scales[12] (LRS) for upper lip lines

or marionette lines, and a score of at least 3 (moderately deep wrinkle) or 4 (deep wrinkle) for nasolabial folds. For lips, subjects had to present with a score of 0 (very thin) to 2 (moderately thick) on the Lip Fullness Grading Scale[13] (LFGS) of the upper and/or lower lip. At baseline, fillers of the same HA_E range were used for the appropriate indication. HA_E Lips is indicated for lip volume augmentation, and HA_E Touch, HA_E Classic and HA_E Deep are designed for injection in the superficial, mid- and deep dermis, respectively.[10] Injection volume and technique were chosen by the investigator in order to provide a 100 percent correction. Based on investigator's assessments and subject's approval, touch-up injections could be performed at week 3 (on the same areas injected at baseline). Study visits took place at baseline, three weeks after baseline injection, three weeks after touch-up injection (if performed), and three and six months after the last injection (defined as baseline injection or touch-up if it was performed).

Efficacy measures included a lip enhancement assessment using the 5-point LFGS ranging from 0 (very thin) to 4 (full), on the injected upper and lower lips separately, at each visit. Wrinkle assessments were performed for nasolabial folds, marionette lines and upper lip lines, based on a LRS of 0 (no wrinkles) to 5 (very deep wrinkle, redundant fold), at each visit. Three-dimensional (3-D) surface reconstruction and analysis software (LifeViz™, QuantifiCare S.A., Sophia Antipolis, France) was used to analyze the photographs at each visit,[14] in order to assess the change in volume from baseline at each post-baseline visit for the nasolabial folds and lips.[13] Optimal correction is defined as results obtained three weeks after last injection, and is used to calculate the maintained effect after six months (change from baseline to month 6 divided by change from baseline to week 3 (optimal correction)).

Safety results are presented by indication taking into account all products used. Investigator-assessed safety measures were the incidence of adverse events and injection site reaction scores (bruising, erythema, lump/bump, edema/swelling, pain/tenderness and pruritus on a scale of 0 (none) to 3 (severe)) for each injected area at each visit. The same injection site reactions (except lump/bump) were evaluated by subjects using diaries for 14 days after injection. Also, specific functionality and sensation assessments on the injected lips (lip-touch sensation, paresthesia, frown, pucker, showing upper and lower teeth, smile and symmetry) were performed by the investigator and subject using a dichotomized response (normal/abnormal or yes/no), at each visit. In addition, a subject satisfaction questionnaire was administered three weeks after the last injection for each treated indication.

Data were analyzed for the intent-to-treat population (ITT; the entire population enrolled) regarding efficacy and satisfaction, and on the safety population (APT (All Patients Treated); intent-to-treat population after exclusion of subjects who were not injected) for safety. Inferential statistics were not performed. All variables were descriptively summarized on the ITT or APT population.

RESULTS

Subject Characteristics

At baseline, 44 subjects received lip enhancement (with 41 upper lips and 29 lower lips treated), 40 had upper lip lines treated, 72 received bilateral nasolabial fold treatment (total 144 sides), and 64 had bilateral marionette lines treated (total 128 sides). The majority of subjects were female Caucasians and about 55 years old on average (Table 1).

Baseline characteristics are summarized in Table 2. Before injection, 67.1 percent of the upper or lower lips were either thin or very thin. For the other three indications, some baseline severity differences were present. Upper lip lines treated with HA_E Touch were more severely affected (73.7% for HA_E Touch and 57.2% for HA_E Classic with moderately deep, deep or very deep wrinkles (grades 3 to 5)). HA_E Classic was used overall for less severe nasolabial folds than HA_E Deep (16.7% for HA_E Classic and 40.8% for HA_E Deep considered deep (grade 4)). Finally,

TABLE 1.

Baseline Demographics					
		Lips (N=44)	Upper lip lines (N=40)	Nasolabial folds (N=72)	Marionette lines (N=64)
Gender (%)	Male	2 (4.5%)	0	4 (5.6%)	2 (3.1%)
	Female	42 (95.5%)	40 (100.0%)	68 (94.4%)	62 (96.9%)
Age (in years)	Mean±SD	54.5±8.4	55.9±6.4	54.6±8.4	55.6±8.0
Phototype (%)	I	3 (6.8%)	2 (5.0%)	3 (4.2%)	4 (6.3%)
	II	18 (40.9%)	17 (42.5%)	34 (47.2%)	28 (43.8%)
	III	22 (50.0%)	17 (42.5%)	31 (43.1%)	28 (43.8%)
	IV	1 (2.3%)	4 (10.0%)	4 (5.6%)	4 (6.3%)
Race (%)	Caucasian	40 (90.9%)	38 (95.0%)	69 (95.8%)	62 (96.9%)
	Asian	1 (2.3%)	0	0	0
	Hispanic	3 (6.8%)	2 (5.0%)	3 (4.2%)	2 (3.1%)

TABLE 2.

Baseline Characteristics								
Indication		**Lips**	**Upper lip lines**		**Nasolabial folds**		**Marionette lines**	
Product		**HA_E Lips**	**HA_E Touch**	**HA_E Classic**	**HA_E Classic**	**HA_E Deep**	**HA_E Classic**	**HA_E Deep**
Lip fullness (LFGS)*	N (lips treated)	70						
	0: Very thin	10 (14.3%)						
	1: Thin	37 (52.8%)	N/A		N/A		N/A	
	2: Moderately thick	23 (32.9%)						
	Mean±SD	1.2±0.7						
Wrinkle severity (LRS)†	N (sides treated)	N/A	19	21	24	120	36	92
	2: Shallow wrinkles		5 (26.3%)	9 (42.8%)	0	0	14 (38.9%)	24 (26.1%)
	3: Moderately deep wrinkle		7 (36.8%)	5 (23.8%)	20 (83.3%)	71 (59.2%)	12 (33.3%)	38 (41.3%)
	4: Deep wrinkle, well-defined edges		4 (21.1%)	6 (28.6%)	4 (16.7%)	49 (40.8%)	6 (16.7%)	19 (20.7%)
	5: Very deep wrinkle, redundant fold		3 (15.8%)	1 (4.8%)	0	0	4 (11.1%)	11 (11.9%)
	Mean±SD		3.3±1.0	3.0±1.0	3.2±0.4	3.4±0.5	3.0±1.0	3.2±1.0

*If both upper and lower lips were injected, the subject was counted once, and the lowest fullness between the upper and lower lips was reported.
†If both left and right sides were injected, the subject was counted once, and the highest severity between both sides was reported.

a similar but less obvious trend was observed for marionette lines, with HA_E Classic used for less severe wrinkles than HA_E Deep (61.1% for HA_E Classic and 73.9% for HA_E Classic considered moderately deep, deep or very deep (grades 3 to 5)).

Injection Details

Injection information on all four perioral indications is summarized in Table 3. Regardless of the indication injected or product used, as the severity grade worsened, higher volumes of product were necessary, as can be expected. All 44 subjects who received lip enhancement were treated with HA_E Lips. The mean total volume of HA_E Lips injected in lips was 1.3±0.6 mL per subject (1.0±0.4 mL at baseline and 0.7±0.3 mL at touch-up). The mean total volume per upper and lower lip was 0.9±0.4 mL and 0.8±0.3 mL, respectively.

For those treated in the upper lip lines, 19 subjects were injected with HA_E Touch and 21 with HA_E Classic. The mean total volume injected in upper lip lines per subject was 0.9±0.5 mL for HA_E Touch and 0.7±0.3 mL for HA_E Classic. For nasolabial folds, 12 subjects were injected with HA_E Classic and 60 with HA_E Deep. The mean total volume injected in nasolabial folds per subject throughout the study was 1.3±0.6 mL for HA_E Classic and 1.5±0.7 mL for HA_E Deep. Regarding marionette lines, 18 subjects were treated with HA_E Classic and 46 with HA_E Deep. The mean total volume injected in marionette lines per subject throughout the study was 0.8±0.5 mL for HA_E Classic, and 1.1±0.5 mL for HA_E Deep.

Efficacy

Regarding lip enhancement using HA_E Lips, an average improvement of 1.1 (±0.7) grades three weeks after last injection followed by 0.8 (±0.7) grades after six months was reached (Figure 5), meaning that 72.7 percent of optimal correction was maintained at month 6. The vast majority of subjects (81.7%) showed an improvement in LFGS after three weeks, and after six months, 70.0 percent of subjects were still improved. The duration of effect was also confirmed by the 3-D volume analysis, which showed that 62.7 percent of the optimal correction of volume was maintained at month 6 in terms of volume measurement (Figure 5).

An average improvement in upper lip lines of 1.6 (±0.7) and 1.6 (±0.8) grades from baseline for HA_E Touch and Classic was attained three weeks after last injection, respectively, followed by 0.8 (±1.1) and 1.1 (±0.7) grades after six months, indicating that 50 percent and 68.8 percent of optimal correction was maintained at month 6 (Figure 6). Upper lip lines were improved in terms of LRS for 100 percent of subjects receiving HA_E Touch and in 90.5 percent of subjects receiving HA_E Classic after three weeks, and improvement was still observed in 52.6 percent and 80 percent of subjects, respectively, after six months.

For nasolabial folds, a mean reduction of 1.6 (±0.8) and 2.1 (±0.9) grades in LRS was achieved three weeks after last injection with HA_E Classic and Deep, respectively, followed by 1.1 (±0.8) and

FIGURE 5. Lips: mean change in LFGS from baseline and volume maintained after six months (by 3-D measurements). The spheres at week 24 represent the volume maintained compared to the volume obtained at optimal correction (week 3).

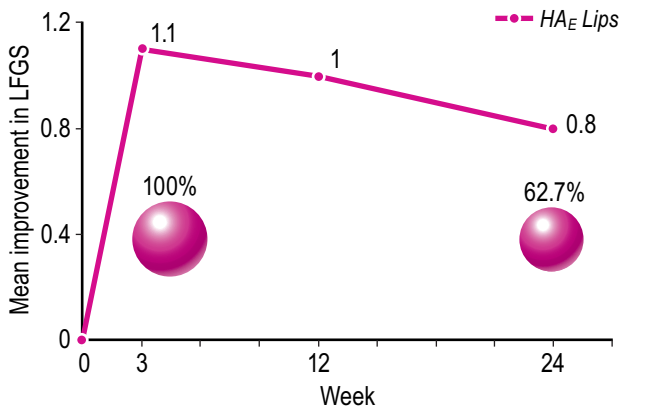


FIGURE 6. Upper lip lines: mean improvement in LRS from baseline.

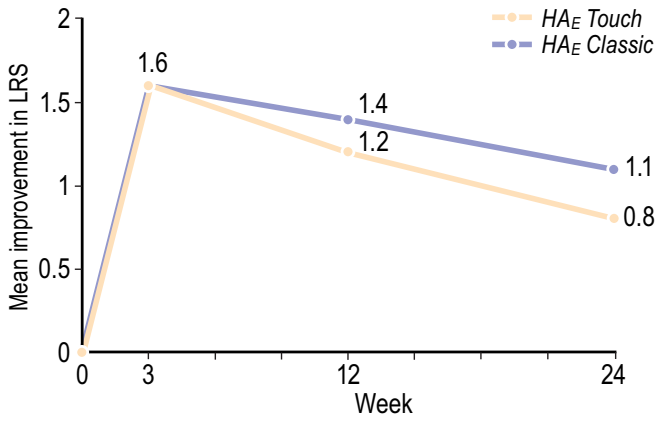


FIGURE 7. Nasolabial folds: mean improvement in LRS from baseline and volume maintained after six months (by 3-D measurements). The spheres at week 24 represent the volume maintained compared to the volume obtained at optimal correction (week 3).

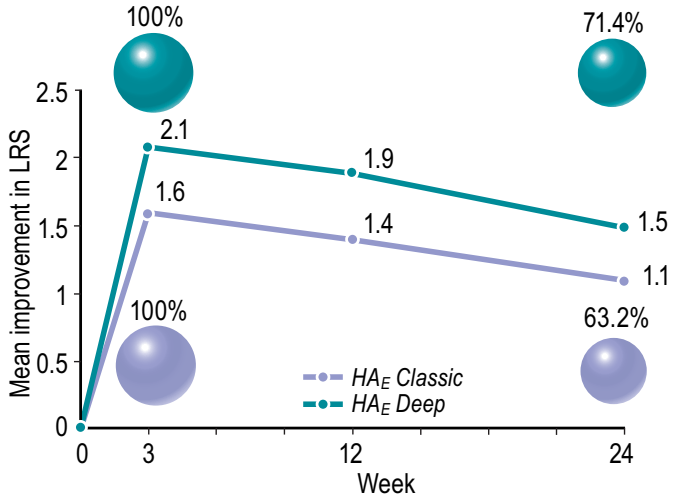
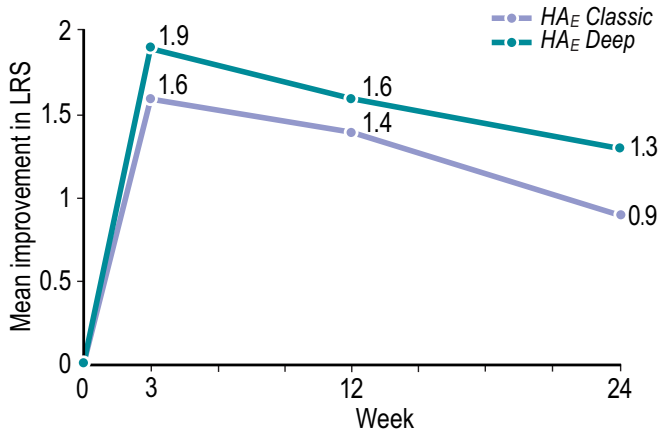


FIGURE 8. Marionette lines: mean improvement in LRS from baseline.



1.5 (±0.9) grades after six months (Figure 7), meaning that 68.8 percent and 71.4 percent of optimal correction was maintained at month 6. Improvement in terms of LRS was observed in 91.7 percent and 95.8 percent of subjects receiving HA_E Classic and Deep three weeks after last injection, respectively. After six months, improvement was still observed in 90.9 percent of subjects with HA_E Classic (including 31.8% with at least a 2-grade improvement) and 82.5 percent with HA_E Deep (including 52.5% with at least a 2-grade improvement). In addition, the duration of effect was confirmed by 3-D analysis for HA_E Classic and Deep, with 63.2 percent and 71.4 percent of the optimal correction maintained at month 6, respectively, in terms of volume measurement (Figure 7).

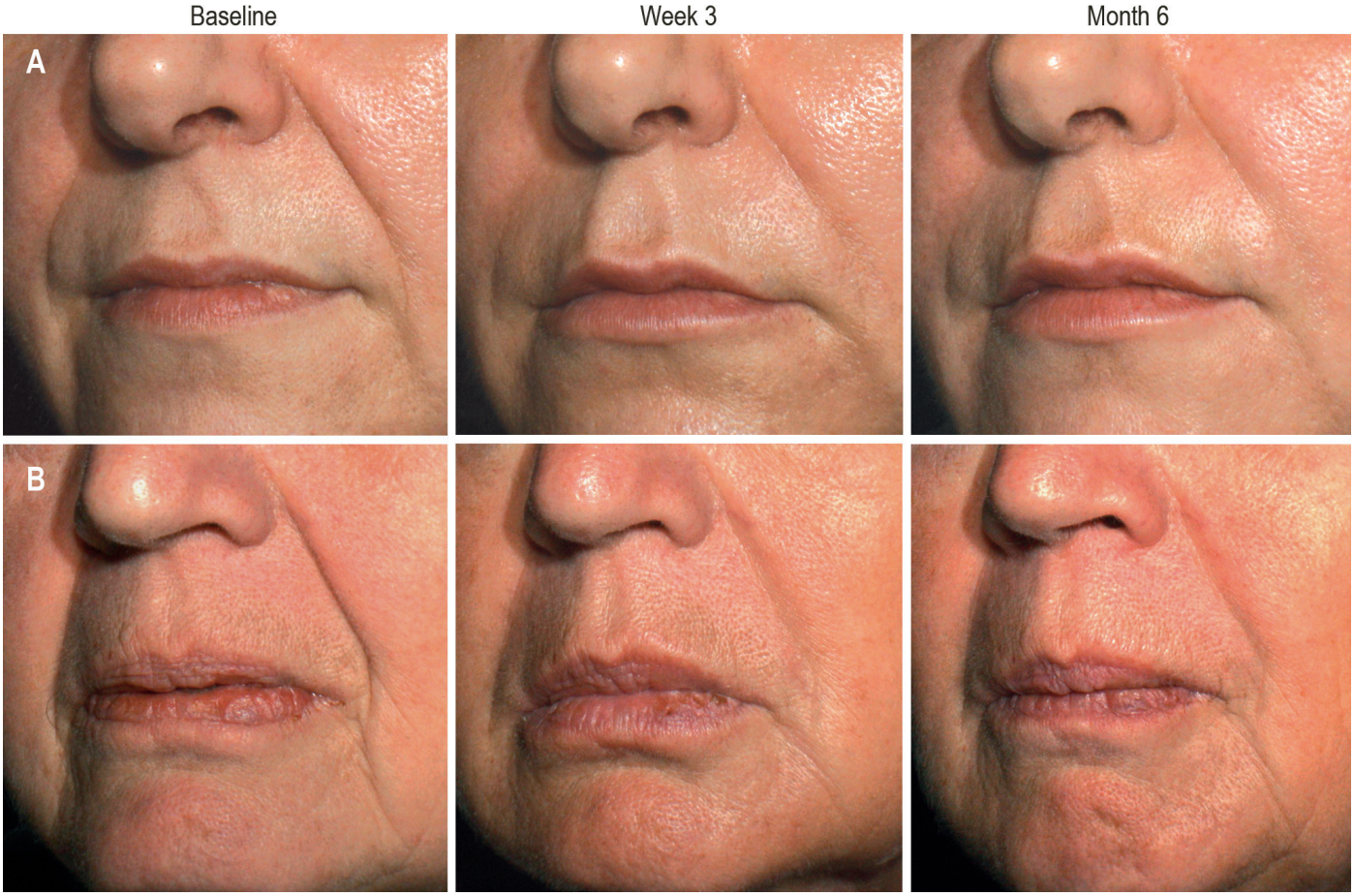
For marionette lines, an average reduction from baseline in LRS of 1.6 (±1.1) and 1.9 (±1.0) grades was reached three weeks after last injection with HA_E Classic and Deep, respectively, followed by 0.9 (±0.9) and 1.3 (±0.8) grades after six months, indicating that 56.3 percent and 68.4 percent of optimal correction was maintained at month 6 (Figure 8). Marionette lines were improved in terms of LRS for 88.8 percent of subjects receiving HA_E Classic and 96.7 percent of subjects receiving HA_E Deep three weeks after last injection, and after six months, improvement was still observed in 72.2 percent and 84.4 percent of subjects, respectively (including 22.2% of subjects treated with Classic and 36.7% with HA_E Deep having at least a 2-grade improvement).

Figure 9 shows the photos of representative subjects before, three weeks and six months after the perioral treatment with HA_E fillers.

Subject's Satisfaction Questionnaire

Three weeks after last injection, a high proportion of subjects were satisfied or very satisfied with their aesthetic outcome regardless of the indication (Table 4). For indications where two different products were used, satisfaction results were similarly high between products. Percentage of subjects who were satisfied or very satisfied ranged from 80.0 percent (treatment of upper lip lines with HA_E Classic) to 94.8 percent (treatment of nasolabial folds

FIGURE 9. Photos of representative subjects at baseline, three weeks, and six months after last injection: **A)** Upper lip: 1.1 mL HA_E Lips (0.6 mL at baseline and 0.5 at touch-up); Lower lip: 0.9 mL HA_E Lips (0.4 mL at baseline and 0.5 mL at touch-up); Left nasolabial fold: 0.8 mL HA_E Deep (0.5 mL at baseline and 0.3 mL at touch-up); Left marionette line: 0.3 mL HA_E Deep (0.2 mL at baseline and 0.1 mL at touch-up). **B)** Upper lip: 0.5 mL HA_E Lips at baseline; Lower lip: 0.5 mL HA_E Lips at baseline; Upper lip lines: 0.8 mL HA_E Touch at baseline; Left nasolabial fold: 1.2 mL HA_E Deep (1.0 mL at baseline and 0.2 mL at touch-up); Left marionette line: 1.2 mL HA_E Deep (1.0 mL at baseline and 0.2 mL at touch-up).



with HA_E Deep), and the majority would like to receive the same treatment again. These high levels of subject satisfaction reflect the positive results of the investigator's efficacy assessments in that the majority of subjects were at least improved.

Safety

There were no treatment-related adverse events (AEs) or serious AEs for the perioral area. Table 5 details injection site reactions and their corresponding mean worst score, which is defined as the score of highest severity during the entire study (at all study visits for investigator assessments and during the first 14 days after injections for subject assessments). Investigator-assessed worst scores remained less than 1 (mild) for all signs. For subjects, bruising and edema were the two most common signs reported with a slightly higher worst score (mild to moderate) than that observed by investigators, likely due to the fact that these signs and symptoms were reported soon after injection (within the first 14 days). However, these signs were transient, with a mean maximum duration of 5.4 days (bruising on the lips and upper lip lines). Based on both investigators' assessments and subjects' diaries, touch-up injections did not induce more local tolerability signs or symptoms than the initial injection.

Both investigators and subjects assessed lip-specific functionalities to be normal, except asymmetry and paresthesia for one subject immediately after the baseline injection which disappeared at the next visit and for the remainder of the study.

DISCUSSION

This is a comprehensive clinical study on the performance, safety and patient satisfaction of HA fillers specifically designed for lip enhancement and other indications of the perioral area, and our findings support the use of the HA_E filler range in enhancement of this region. In restoring a youthful appearance, simultaneous volume enhancement of the lips and correction of the other surrounding structures can lead to a harmonized

TABLE 3.

Injection Information								
Indication		**Lips**	**Upper lip lines**		**Nasolabial folds**		**Marionette lines**	
Product		**HA_E Lips**	**HA_E Touch**	**HA_E Classic**	**HA_E Classic**	**HA_E Deep**	**HA_E Classic**	**HA_E Deep**
Injection technique*	N	44	19	21	12	60	18	46
	Serial puncture	0	1 (5.3%)	1 (4.8%)	0	0	0	0
	Multiple puncture	1 (2.3%)	3 (15.8%)	1 (4.8%)	0	9 (15.0%)	2 (11.1%)	2 (4.3%)
	Retrograde linear threading	44 (100%)	19 (100%)	21 (100%)	12 (100%)	56 (93.3%)	18 (100%)	42 (91.3%)
	Fanning	0	7 (36.8%)	5 (23.8%)	4 (33.3%)	32 (53.3%)	10 (55.6%)	30 (65.2%)
Needle*	N	44	19	21	12	60	18	46
	Provided needle	37 (84.1%)	12 (63.2%)	16 (76.2%)	10 (83.3%)	48 (80.0%)	16 (88.9%)	34 (73.9%)
	Cannula	4 (9.1%)	7 (36.8%)	5 (23.8%)	2 (16.7%)	12 (20%)	2 (11.1%)	11 (23.9%)
Type of anesthesia*	N	44	19	21	12	60	18	46
	Topical	12 (27.3%)	5 (26.3%)	6 (28.6%)	1 (8.3%)	14 (23.3%)	2 (11.1%)	10 (21.7%)
	Local	1 (2.3%)	0	0	0	0	3 (16.7%)	9 (19.6%)
	Nerve block	26 (59.1%)	7 (36.8%)	9 (42.9%)	9 (75.0%)	22 (36.7%)	4 (22.2%)	9 (19.6%)
	None	5 (11.4%)	7 (36.8%)	6 (28.6%)	2 (16.7%)	24 (40.0%)	9 (50.0%)	18 (39.1%)
Volume injected at baseline	N	44	19	21	12	60	18	46
	Mean±SD	1.0±0.4	0.8±0.4	0.6±0.3	1.1±0.6	1.1±0.5	0.6±0.5	0.8±0.5
Volume injected at touch-up	N	17	3	7	2	32	7	25
	Mean±SD	0.7±0.3	0.5±0.2	0.4±0.2	0.7±0.4	0.7±0.4	0.5±0.3	0.5±0.2
Total volume injected	N	44	19	21	12	60	18	46
	Mean±SD	1.3±0.6	0.9±0.5	0.7±0.3	1.3±0.6	1.5±0.7	0.8±0.5	1.1±0.5

*Baseline injection.

TABLE 4.

Subject Satisfaction Three Weeks After Last Injection by Product and Indication							
Indication	**Lips**	**Upper lip lines**		**Nasolabial folds**		**Marionette lines**	
Product	**HA_E Lips**	**HA_E Touch**	**HA_E Classic**	**HA_E Classic**	**HA_E Deep**	**HA_E Classic**	**HA_E Deep**
Satisfied/very satisfied with aesthetic outcome - N (%)	35 (83.3%)	16 (88.9%)	16 (80%)	11 (91.7%)	55 (94.8%)	14 (82.4%)	38 (88.4%)
Would like to be injected with the same product again - N (%)	36 (85.7%)	16 (88.9%)	20 (100%)	11 (91.7%)	54 (93.1%)	15 (93.8%)	40 (93.0%)

and natural improvement of the lower face. The context of these results within a larger study of HA_E fillers used for multiple indications[11] emphasizes the need for a global approach when addressing facial rejuvenation.

A literature review on studies in the perioral region using HA fillers shows that in 1998, Olenius et al. published the first study with a HA filler, Restylane®, for various indications including lips, yet lip-specific results were not evaluated.[15] Duranti et al. found that the same filler was effective in treating nasolabial folds and lips, with 79.9 percent of moderate or marked lip improvement at eight months.[16] Similarly, Solish and Swift observed a sustained increase in lip fullness of at least one grade eight weeks after treatment with the product.[17] However, patient

TABLE 5.

Local Tolerance (Mean±SD) Throughout Study According to Investigators (Each Study Visit) and Subjects (Reported 14 Days After Injection)

	Lips		Upper lip lines		Nasolabial folds		Marionette lines	
	Investigator	Subject	Investigator	Subject	Investigator	Subject	Investigator	Subject
Bruising	0.2±0.6	1.7±1.1	0.1±0.3	1.5±1.1	0.3±0.7	1.3±1.1	0.3±0.6	1.3±1.1
Erythema	0.5±0.6	0.5±0.8	0.5±0.5	0.4±0.8	0.9±0.8	0.7±0.9	0.6±0.6	0.7±1.0
Lump/bump	0.2±0.4	N/A	0	N/A	0.2±0.4	N/A	0.1±0.4	N/A
Edema/swelling	0.8±0.6	1.5±0.9	0.5±0.6	1.4±1.0	0.7±0.7	1.3±0.8	0.5±0.6	1.1±0.8
Pain/tenderness	0.2±0.5	1.1±1.0	0.2±0.5	0.8±0.9	0.1±0.3	0.8±0.7	0.0±0.2	0.6±0.7
Pruritus	0	0.1±0.4	0	0.0±0.2	0.0±0.1	0.1±0.3	0	0.1±0.3

All injection site reactions were assessed using a 4-point severity scale (0=none; 3=severe).

satisfaction was not assessed in these studies. More recently, Lanigan et al. reported an improvement in lip appearance and patient satisfaction after injection with a lidocaine-incorporated HA filler, yet safety assessments were not reported.[18]

In another study on the treatment of the lower face, Carruthers et al. examined the effect of two HA fillers in combination with onabotulinumtoxinA, or either treatment alone, in treatment of the lips, oral commissures, marionette lines and chin.[19] Aesthetic outcomes were improved in both HA groups compared to the onabotulinumtoxinA-alone group. In addition, a median response duration (in terms of the time between the maximum effect and return to baseline) for the HA fillers was found to be about three months.

In the current study, in which four fillers of the same range were used for four indications of the perioral region (lips, upper lip lines, nasolabial folds and marionette lines), the fillers selected for each indication appear to be suitable, as around a 1-grade improvement persisted for all indications six months after injection. Regarding the indication of lip enhancement, treatment with HA_E Lips yielded high levels of sustained effect in terms of lip fullness. Treatment of upper lip lines with HA_E Touch and Classic also led to long-lasting effect regarding wrinkle severity, though results at month 6 were slightly better with HA_E Classic. Similarly, use of HA_E Classic and HA_E Deep for both nasolabial folds and marionette lines brought about long duration of efficacy regarding wrinkle severity reduction. It is of note that, in this study, HA_E Deep was used for nasolabial folds and marionette lines in a more severely affected population. Compared to HA_E Classic, HA_E Deep has a higher degree of cross-linking, resulting in a firmer gel texture suitable for injection into the deep dermis to correct severe wrinkles.[10] Furthermore, this study shows that for the correction of marionette lines, a rather high volume (similar to the volume for nasolabial folds) was used. This is an important finding, as it provides the quantity of filler necessary for obtaining optimal correction in patients with advanced signs of aging.

All products were safe and well-tolerated, and common injection site reactions including bruising and edema were transient. The mean total volume injected throughout the study ranged from 0.7 mL for HA_E Classic in upper lip lines to 1.5 mL for HA_E Deep in nasolabial folds. Though the lips remain a sensitive area to treat, the volume injected of HA_E Lips (mean total volume 1.3 mL) generally did not induce more frequent or severe injection site reactions than the other products used in the perioral area.

Patients were highly satisfied with the aesthetic outcome of all products used in this study. Since the perioral area, particularly the lips, are typically suggestive of youth, attractiveness, and sexuality,[8] perioral rejuvenation can presumably improve the well-being of the patient. As society progressively views normal aging as a medical and social problem, it is important to be attentive to the psychosocial issues of patients which may encompass anxiety and poor self-image, and to set realistic expectations of aesthetic treatment.[20] Further exploration of patients' aesthetic expectations along with their psychosocial needs could be performed in future studies. Specifically regarding lip enhancement, the patient's needs must be taken into account, along with goals of harmonizing with their unique appearance and avoiding hypercorrection.[21] Increasing a very thin lip to a full lip is rarely possible, and may be due to anatomical limitations. In general, paying careful attention to what the patient is seeking in lip enhancement, and not only to the improvement seen from the injector's perspective, is essential.

CONCLUSIONS

Different fillers of the HA_E range are adapted to the specific, complex needs encountered in perioral rejuvenation. When injected in patients with advanced signs of aging, the fillers maintained a clinically relevant effect after six months, and were safe and well-tolerated. This sustained improvement was mirrored by a high patient satisfaction of the aesthetic outcome, which is essential in meeting patients' expectations for a customized perioral region enhancement.

DISCLOSURES

The investigating authors received investigator fees for this clinical study. Two of the authors (Kerrouche and Dhuin) are employees of Galderma. This study was supported by Galderma R&D, Sophia Antipolis, France.

ACKNOWLEDGEMENTS

The authors wish to thank Galadriel Bonnel MSN for editorial assistance.

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Correction of Tear Troughs and Periorbital Lines With a Range of Customized Hyaluronic Acid Fillers

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ABSTRACT

Background: The periobital region is a challenging area for injectable fillers. Overcorrection and/or the use of unsuitable fillers may lead to unwanted results. As evidence for this region is limited, most physicians follow a trial and error approach.
Objective: Assess the efficacy, patient satisfaction, and safety of the HA_E filler range in periorbital rejuvenation.
Materials and Methods: This was a multi-center, six-month, open-label study. Subjects could receive HA_E Touch, HA_E Classic, and HA_E Deep for the treatment of tear troughs and periorbital lines at baseline, and an optional touch-up three weeks later. Global aesthetic improvement for both indications, periorbital wrinkle assessments (Lemperle Rating Scale), 3-D volume analysis (for tear troughs only), adverse events and injection site reactions were evaluated at each visit. A subject satisfaction questionnaire was performed three weeks after last injection.
Results: Overall, HA_E Classic and Deep were injected for tear troughs, and HA_E Touch for periorbital lines. Mean aesthetic improvement in tear troughs was 1.5–2 grades for both products at each post-baseline visit, and results of the clinical evaluation were confirmed by results of 3-D volume analysis. Improvements of periorbital lines in both aesthetic outcomes and wrinkle severity were around 1.5 grades at week 3, and close to 1 grade at month 6. The majority of subjects were satisfied or very satisfied with their aesthetic outcome. Treatments of both indications were safe and well-tolerated, with only mild and transient injection site reactions reported.
Conclusions: This HA_E filler range is suitable for rejuvenation of the periorbital region, which leads to safe results, long-lasting efficacy and high levels of patient satisfaction.

J Drugs Dermatol. 2012;11(1)(suppl):s27-s34.

INTRODUCTION

Hyaluronic acid (HA) fillers are traditionally used to correct moderate to deep facial wrinkles such as nasolabial folds and marionette lines. However, their indications have been considerably expanded recently. The importance of volume enhancement has been increasingly recognized and a global approach is starting to be widely adopted. In clinical practice, HA fillers are used in all areas of the face typically considered for aesthetic enhancement, including the periorbital region.[1] However, evidence for this area remains scant.[2-8]

The most challenging indication in the periorbital area is the tear trough.[9] The tear trough is usually defined as the nasojugal groove, the natural depression near the junction of the eyelid and cheek, which can extend inferolaterally from the inner canthus of the eye.[10-12] Sometimes, "tear trough" is used synonymously with infraorbital hollow. The infraorbital hollow is a delineation of the inferior orbital rim, which may give the face an unhealthy and tired appearance. It is usually observed together with tear trough deformity.

Periorbital lines include both dynamic lateral orbital wrinkles that appear when smiling, and static wrinkles caused by photoaging.[13] Injection of botulinum toxin type A (BoNT-A) blocks the release of the neurotransmitter acetylcholine, and is a very effective method for smoothing dynamic wrinkles in this region.[14] However, static wrinkles do not respond to BoNT-A treatment. Moreover, BoNT-A is only partially suitable for wrinkles extending to the cheek, since injection into the inferior region of the zygomaticus major muscle may lead to ptosis of the upper lip.[14]

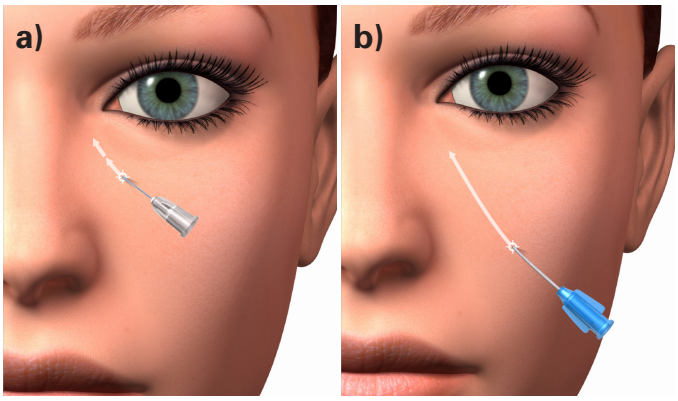
The objective of the present study is to assess the efficacy, safety and patient satisfaction of a customized HA filler range (hereafter referred to as HA_E; Emervel®, Galderma S.A., Lausanne, Switzerland) in the treatment of various facial indications. In this report, we focus on rejuvenation of the periorbital area, specifically tear troughs (may include infraorbital hollows) and periorbital lines.

Practical Aspects of Injection and Outcomes

For the treatment of tear trough deformity with HA fillers, physicians should first carefully examine the patient under a bright overhead light. The patient should be in a sitting position. Topical anesthetics are usually sufficient for this procedure. Injection should start at the deepest depression at the medial portion of the tear troughs, close to the orbital rim. The needle should be inserted immediately inferior to the orbital rim until it reaches the bone, so that the filler material is placed below the suborbicularis oculi muscle plane and just above the periosteum (Figure 1a). The depressed area above the nasojugal groove should be filled, and in patients with pronounced infraorbital hollows, the injections may follow the orbital rim if necessary. Deep injections are recommended. However, the infraorbital foramen should be avoided. If the fillers are placed too superficially, they may become visible as nodules or sausage-like structures. A cannula can also be used with a more distant entry point (Figure 1b). In this case, the retrograde linear threading method is commonly used. After injection, the area may be gently massaged in case irregularities are visible. To avoid overcorrection, a two-step approach may be recommended, with a touch-up session scheduled about one month after the baseline injection. It should be noted that correction of volume deficits in the tear trough area improves the shadowing below the eyes and above the nasojugal groove, but not the "dark circles" due to hyperpigmentation.

Combination of BoNT-A and a soft HA filler is usually used for the treatment of lateral periorbital wrinkles. Topical anesthesia can be used. The retrograde linear threading method may be applied along each rhytide. Due to the thin skin and rich subdermal vascular plexus in this area, a careful approach should be adopted to avoid bruising. Overcorrection, specifically in patients with thin skin, may create visible lumps/bumps and should be avoided. Laterally, injections of the fillers should be feathered out to avoid a "bean cushion" appearance.

FIGURE 1. Tear troughs: technique of injection with **a)** needle or **b)** cannula (note that for the treatment of the infraorbital hollows, other injection points might be necessary).



MATERIALS & METHODS

This six-month, open-label study[15] conducted at five centers in France and Germany was in accordance with the Declaration of Helsinki, Good Clinical Practices and local regulatory requirements, and was approved by ethics committees. All subjects provided their written informed consent prior to entering the study. Eligible subjects were of either sex, 18 years or older, seeking tissue augmentation treatments of their tear troughs and/or periorbital lines. Subjects could receive treatments on tear troughs (may include infraorbital hollows) based on their request. To be qualified to receive injections of periorbital lines, subjects had to have a score of at least 2 (shallow wrinkles) on the Lemperle Rating Scale (LRS). Exclusion criteria prohibited the enrollment of subjects who had received permanent fillers in the target zones of injection. Subjects with any facial aesthetic surgery in the preceding 12 months were also excluded, or botulinum toxin A (BoNT-A) injections or non-permanent dermal fillers in the face in the preceding six months.

At baseline, investigators chose the appropriate fillers from the HA_E range for each indication, based on their distinctive physical properties: HA_E Touch, Classic and Deep were designed for injection in the superficial, mid- and deep dermis, respectively.[16] The injection volume and technique were at the discretion of the investigator, aiming to provide an optimal correction. Based on the investigator's assessments and subject's approval, touch-ups could be performed at week 3 after baseline injection. Study visits occurred at baseline, three weeks after baseline injection, three weeks after touch-up injection (if touch-up was performed), and three and six months after the last injection (defined as baseline injection or touch-up if it was performed).

At each visit, investigators assessed the aesthetic improvement for each indication using the Global Aesthetic Improvement Scale (GAIS) (from -1 (worse) to 3 (very much improved)), and wrinkle severity of periorbital lines using LRS. Standardized photographs at each visit were analyzed using three-dimensional (3-D) surface reconstruction and analysis software (LifeViz™, Quantificare S.A, Sophia Antipolis, France) to assess the anatomical volume variations from baseline at each post-baseline visit in the tear troughs. Optimal correction is defined as results obtained three weeks after last injection, and is used to calculate the maintained effect after six months (change from baseline to month 6 divided by change from baseline to week 3 (optimal correction)).

Safety results are presented by indication taking into account all products used. Investigator-assessed safety measures were

TABLE 1.

Baseline Demographics and Wrinkle Severity			
		Tear troughs*	Periorbital lines
Gender (%)	N	24	25
	Male	0	2 (8.0)
	Female	24 (100)	23 (92.0)
Age (in years)	N	24	25
	Mean±SD	53.0±8.6	51.5±9.1
Phototype (%)	N	24	25
	I	3 (12.5)	3 (12.0)
	II	13 (54.2)	8 (32.0)
	III	8 (33.3)	14 (56.0)
Race (%)	N	24	25
	Caucasian	21 (87.5)	23 (92.0)
	Hispanic	3 (12.5)	2 (8.0)
Baseline wrinkle severity (LRS) (%)	N (sides treated)	N/A	50
	2: Shallow wrinkles		22 (44.0%)
	3: Moderately deep wrinkle		14 (28.0%)
	4: Deep wrinkle, well-defined edges		8 (16.0%)
	5: Very deep wrinkle, redundant fold		6 (12.0%)
	Mean±SD		3.0±1.0

*May include infraorbital hollows.

the incidence of adverse events and injection site reaction scores (bruising, erythema, lump/bump, edema/swelling, pain/tenderness and pruritus on a scale of 0 (none) to 3 (severe)) for each injected area at each visit. The same injection site reactions (except lump/bump) were evaluated by subjects using diaries for 14 days after injection. Subjects also completed a satisfaction questionnaire three weeks after the last injection for each indication.

The intent-to-treat (ITT) population included all subjects enrolled into the study, and the safety population included the ITT population, after exclusion of subjects who did not receive any HA_E filler injection. All variables were descriptively summarized on the ITT (for efficacy and subject satisfaction) or the safety (for adverse events and local tolerability) population.

RESULTS

Tear Troughs

At baseline, among the 77 subjects who had enrolled into the study, 27 received injections in both tear troughs. One subject discontinued from the study based on her request. Among the 27 subjects, nine had HA_E Classic, 15 had HA_E Deep and three had HA_E Touch. Only the efficacy data on HA_E Classic and Deep are presented here, due to the insufficient number of subjects who had received HA_E Touch. The majority of subjects were Caucasian females, with a mean age of 53 years (Table 1).

The injection information of tear troughs is summarized in Table 2. The mean total volume of injection (baseline and touch-up) per subject in the tear troughs was 0.4±0.1 mL for HA_E Classic and 0.7±0.4 mL for HA_E Deep. Retrograde linear threading was

FIGURE 2. Tear troughs: mean change in aesthetic improvements from baseline. The spheres at week 24 represent the volume maintained compared to the volume at optimal correction (week 3).

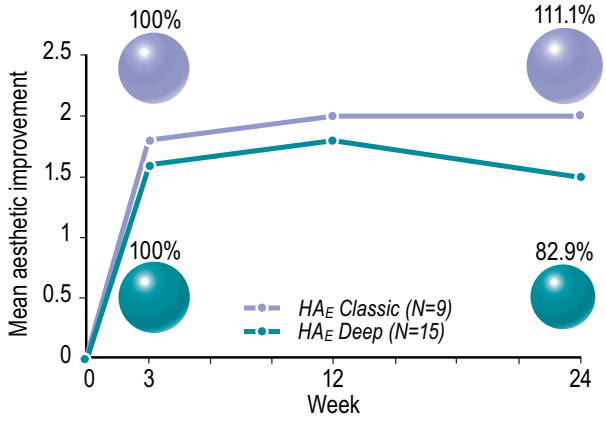


TABLE 2.

Injection Information				
		Tear troughs*		Periorbital lines
		HA_E Classic	HA_E Deep	HA_E Touch
Injection technique (%) **	N	9	15	25
	Anterograde linear threading	0	0	1 (4.0)
	Retrograde linear threading	9 (100)	13 (86.7)	24 (96.0)
	Fanning	0	2 (13.3)	1 (4.0)
Needle (%) **	N	9	15	25
	Provided needle	8 (88.9)	15 (100)	24 (96.0)
	Cannula	0	0	1 (4.0)
Type of anesthesia (%) **	N	9	15	25
	Topical	0	5 (33.3)	3 (12.0)
	Local	0	0	2 (8.0)
	Nerve block	0	3 (20.0)	0
	None	9 (100)	7 (46.7)	20 (80.0)
Volume injected at baseline	N	9	15	25
	Mean±SD	0.4±0.1	0.6±0.3	0.5±0.3
Volume injected at touch-up		3	5	11
	Mean±SD	0.2±0.1	0.2±0.1	0.5±0.4
Total volume injected		9	15	25
	Mean±SD	0.4±0.1	0.7±0.4	0.7±0.6

*May include infraorbital hollows.
**Baseline injection.

the most commonly used technique, and fanning was used in two subjects receiving HA_E Deep. During baseline injection, no anesthesia was used in the nine subjects who received HA_E Classic. Among the 15 subjects receiving HA_E Deep, seven (46.7%) had no anesthesia, five (33.3%) had topical anesthesia and three (20.0%) had nerve block.

Correction of tear troughs with HA_E fillers led to an improvement judged both subjectively and objectively as shown in Figure 2. For HA_E Classic and Deep, an average aesthetic improvement (as judged by the investigator) of 1.8±0.8 and 1.6±1.0 grades, respectively, was attained three weeks after last injection, followed by 2.0±0.7 and 1.5±1.0 grades after six months, meaning that 111.1 percent and 93.8 percent of optimal correction was maintained at month 6. Three weeks after the last injection, 100 percent of subjects receiving HA_E Classic and 93.3 percent of subjects receiving HA_E Deep were considered by the investigator as at least improved compared to baseline. Six months after the last injection, the percentage of subjects who had improvement remained high (100% of subjects receiving HA_E Classic and 73.3% of subjects receiving HA_E Deep). The results of the 3-D volume analysis were consistent with the results of aesthetic improvements for HA_E Classic and Deep, as 111.1 percent and 82.9 percent of the optimal correction of volume, respectively, was maintained at month 6. Figures 3a and b show photos of representative subjects before and six months after treatment of tear troughs with either HA_E Classic or Deep.

High levels of patient satisfaction were achieved with the treatment of tear troughs (Table 3). The vast majority of subjects were satisfied or very satisfied with the aesthetic outcome of the treatment (87.5% and 83.3% of subjects receiving HA_E Classic and Deep, respectively), reflecting the high proportion of subjects who had improved. In terms of comfort of injection (the HA_E products used in this study did not contain lidocaine), 77.8 percent of subjects receiving HA_E Classic and 91.7 percent of subjects receiving HA_E Deep were satisfied or very satisfied. This difference can most likely be explained by the use of anesthesia among subjects receiving HA_E Deep. All but two subjects receiving tear trough treatments would like to be injected with the same products again. Twenty out of the 21 subjects would recommend the treatment to their family and friends.

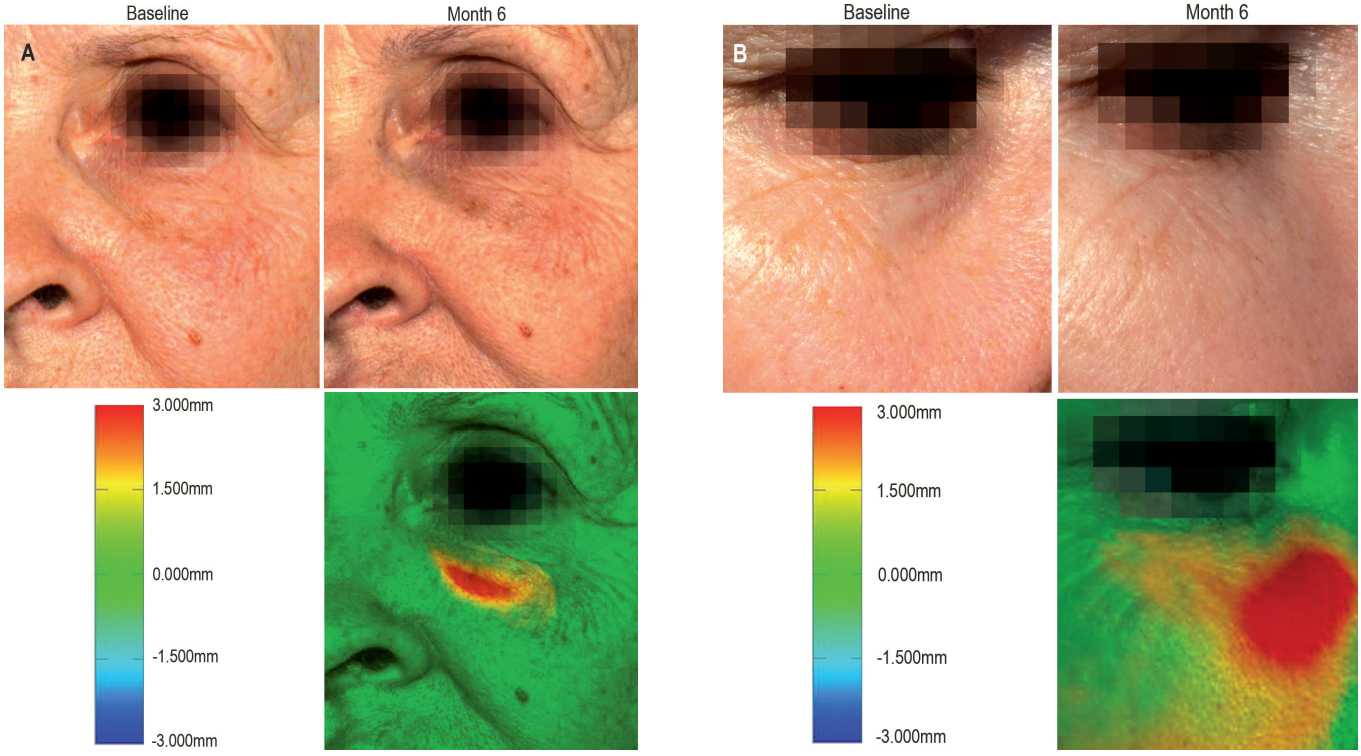
TABLE 3.

Subject Satisfaction Three Weeks After the Last Injection

		Tear troughs*		Periorbital lines
		HA_E Classic	HA_E Deep	HA_E Touch
How satisfied with aesthetic outcome?	N	8	12	23
	Satisfied/very satisfied – N (%)	7 (87.5)	10 (83.3)	19 (82.6)
How satisfied with comfort of injection?	N	9	12	23
	Satisfied/very satisfied – N (%)	7 (77.8)	11 (91.7)	19 (82.6)
Like to be injected with the same product again?	N	9	12	23
	Yes – N (%)	8 (88.9)	11 (91.7)	21 (91.3)

*May include infraorbital hollows.

FIGURE 3. Tear troughs: 2-D and 3-D photos of two representative subjects before and six months after the treatment. Pseudo-color mappings indicate the area of augmentation compared to baseline. **A)** 0.2 mL HA_E Classic at baseline in a 63-year-old female patient. **B)** 0.5 mL HA_E Deep at baseline and 0.3 mL HA_E Deep at touch-up in a 48-year-old female patient.



During the six-month study, one subject reported two AEs that were probably related to study treatment (moderate injection site indurations, after injecting 0.4 mL HA_E Deep in each tear trough), which resolved spontaneously without sequelae and did not lead to study discontinuation. Worst scores for each injection site reaction are defined as the score of highest severity during the entire study (at all study visits for investigator assessments and during the first 14 days after injection for subject assessments). Mean worst scores assessed by the investigators were less than 1 (mild) for all six parameters (Table 4). For subjects, bruising and edema were the two most frequent signs with mean worst scores slightly above 1, likely because they were recorded immediately after the injection. Nevertheless, these signs were transient and resolved without additional treatment, with a maximum duration of 5.2 days (bruising). Based on both investigators' assessments and subjects' diaries, touch-up injections did not induce more local tolerability signs or symptoms than the initial injection.

TABLE 4.

Mean Worst Scores (±SD) of Injection Site Reactions According to the Investigator's Assessment at Each Study Visit and Subject's Dairy During the First 14 Days After Injection

	Tear troughs*		Periorbital lines	
	Investigator	Subject	Investigator	Subject
Bruising	0.4±0.6	1.3±0.9	0.7±0.7	1.3±0.8
Erythema	0.6±0.8	0.6±0.7	0.5±0.6	0.5±0.7
Lump/bump	0.1±0.6	N/A	0.1±0.2	N/A
Edema/ swelling	0.4±0.6	1.2±0.7	0.4±0.5	0.9±0.8
Pain/ tenderness	0	0.6±0.8	0	0.5±0.6
Pruritus	0	0.1±0.5	0	0.0±0.2

*May include infraorbital hollows.

FIGURE 4. Periorbital lines: aesthetic improvements from baseline with HA_E Touch.

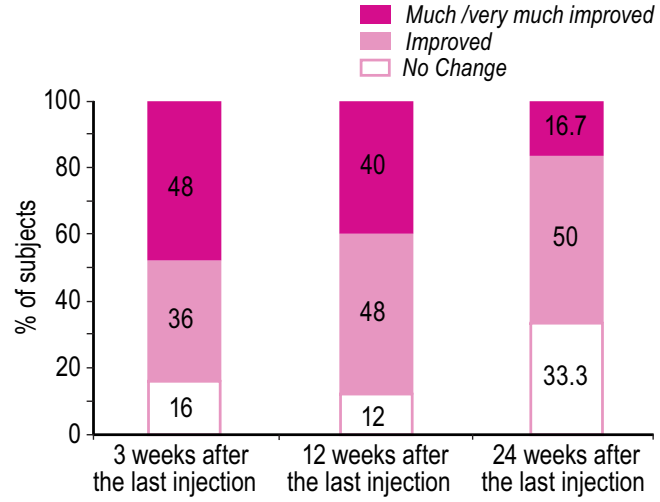


FIGURE 5. Periorbital lines: mean score of improvement in aesthetic outcome and wrinkle severity with HA_E Touch.

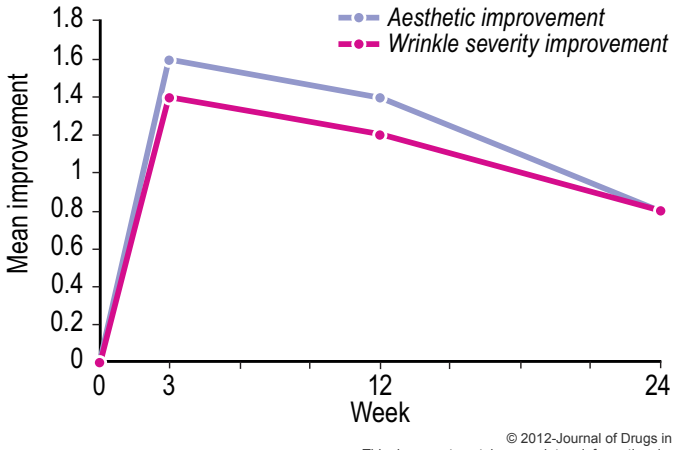
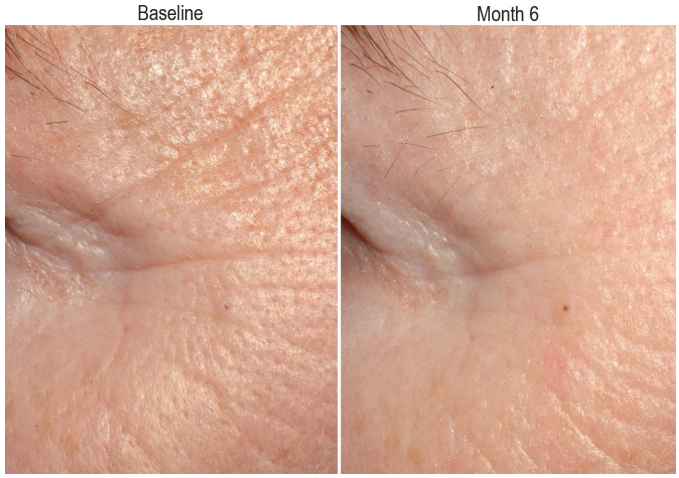


FIGURE 6. Periorbital lines: photos of a representative subject before and six months after treatment with 0.25 mL HA_E Touch at baseline and 0.3 mL HA_E Touch at touch-up.



Periorbital Lines

A total of 31 subjects were injected in periorbital lines on both sides, and all subjects completed the study. Among the 31 subjects, six had HA_E Classic, and 25 had HA_E Touch. Only the efficacy data on HA_E Touch are presented here, due to the insufficient number of subjects who had received HA_E Classic. The majority of subjects were female and Caucasian, with a mean age of 51.5 years (Table 1). On average, the subjects had moderately deep periorbital lines (mean score 3.0). The injection information for periorbital lines is summarized in Table 2. The mean total volume of injection (baseline and touch-up) per subject for the periorbital lines was 0.7±0.6 mL. During baseline injection, retrograde linear threading was the most frequently used technique, and the majority of subjects did not receive any anesthesia.

Improvements of aesthetic outcomes and periorbital line severity were observed following treatment with HA_E Touch. Three weeks after the last injection, 84.0 percent of subjects were considered by the investigator as at least improved compared to baseline (Figure 4). Six months after the last injection, 66.7 percent of subjects were still improved. An average of 1.6±1.1 grades was reached three weeks after last injection, followed by 0.8±0.7 after six months, meaning that 50 percent of the optimal correction was maintained at month 6. The results of wrinkle severity scores (LRS) were consistent with the results of aesthetic improvements (Figure 5): an average improvement of 1.4±0.8 grades three weeks after last injection was achieved, followed by 0.8±0.6 grades after six months, indicating that 57.1 percent of the optimal correction was maintained at month 6. An improvement in LRS was found in 92 percent of subjects three weeks after the last injection, and 66 percent of subjects were still improved after six months. Figure 6 shows photos of a representative subject before and six months after treatment

of periorbital lines with HA_E Touch. Consistently, a high level of subject satisfaction was observed three weeks after the last injection, with 82.6 percent of subjects being satisfied or very satisfied with the aesthetic outcome and comfort of injection (Table 3). All but two subjects would like to be injected with the same products again, and would recommend the treatment to their family and friends.

No AEs related to treatment of the periorbital lines were reported during the study. Mean worst scores of injection site reactions assessed by the investigators were less than 1 (mild) for all six parameters (Table 4). Mean worst scores assessed by the subjects were slightly higher, likely because they were recorded immediately after the injection. Nevertheless, the mean scores were overall below 1, except that of bruising with a mean maximum duration of 3.5 days. Based on both investigators' assessments and subjects' diaries, touch-up injections did not induce more local tolerability signs or symptoms than the initial injection.

DISCUSSION

HA-based fillers in the rejuvenation of the mid- and lower face have been widely used and frequently reported.[9] In contrast to common indications including nasolabial folds, marionette lines and lips, only a few individual observations and case series are available in the literature regarding the rejuvenation of the periorbital area.[2-8] Such treatment presents challenges to even the most experienced injectors: common side effects include bruising and lumps/bumps, likely due to inappropriate injection techniques, injected volume and/or filler. Therefore, a general approach in treating the periorbital region would be to use a small quantity of filler with appropriate physical properties, inject slowly, avoiding any visible blood vessel, and place the filler deeply in the tear trough/infraorbital hollow area. Physicians are encouraged to schedule a follow-up appointment after the first injection to assess the treatment outcome and to further correct the defect if needed.

The results of this analysis support the effective and safe use of the HA_E filler range in rejuvenation of the periorbital region. Treatment of tear troughs with HA_E Classic or Deep leads to long-lasting and stable results up to month 6. The results based on subjective evaluation of the physicians are consistent with data from objective 3-D analysis on the variation of volume between week 3 and month 6. Similar observations have been made with other HA fillers with effect extending beyond six months.[2,8] This long duration of effect after tear trough rejuvenation might depend on two factors: the consistency and durability of the filler used as well as the deep placement of the filler in an area where soft-tissue movement is limited (compared to other areas such as the lips).

In the present study, both HA_E Classic and Deep were used for the treatment of tear troughs, with comparably good results. It should be noted that, on average, a larger quantity of HA_E Deep than HA_E Classic was injected in the tear trough area. Therefore, it is possible that HA_E Deep was used more frequently for more severe cases of tear trough deformity. Considering the thin skin nature of the periorbital region particularly around the orbital rim, HA fillers suitable for this indication should have a relatively soft texture and small gel calibration, in order to avoid excessive swelling or formation of irregularities after injection.[16] Therefore, HA_E Classic is in theory more adapted than HA_E Deep in the treatment of mild tear troughs, specifically when targeting the upper medial part close to the orbital rim to correct the infraorbital hollows. However, when treating severe tear troughs above the nasojugal grove, HA_E Deep might be more appropriate due to its greater filling capacity. To avoid unsightly lumps and bumps requiring further treatment, this product must be injected deeply.[16]

For the treatment of periorbital lines, HA_E Touch is more suitable for this indication because of its soft texture and small gel calibration, which make it easily dispersible into the skin and result in a natural look after injection.[16] Improvements in aesthetic outcome and wrinkle severity were achieved in this study, with close to a 1-grade improvement six months after the last injection.

In summary, rejuvenation of the periorbital region with HA fillers is relatively new and challenging even for the most experienced physicians. A full understanding of both the physical properties of the filler and facial anatomy is essential to ensure satisfactory treatment outcomes. Treatment of tear trough deformities and periorbital lines with the HA_E filler range yielded effective, safe and satisfactory results. The methods of injection and choice of the HA_E filler provided here may serve as a reference for the treatment of the periorbital area.

DISCLOSURES

The investigating authors received investigator fees for this clinical study. Two of the authors (Kerrouche and Dhuin) are employees of Galderma. This study was supported by Galderma R&D, Sophia Antipolis, France.

ACKNOWLEDGEMENTS

The authors wish to thank Y. May Ma PhD for editorial assistance.

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