

# A 12-Month Follow-up, Randomized Comparison of Effectiveness and Safety of Two Hyaluronic Acid Fillers for Treatment of Severe Nasolabial Folds

BENJAMIN ASCHER, MD,\* CHRISTIANE BAYERL, MD,<sup>†</sup> PHILIPPE KESTEMONT, MD,<sup>‡</sup>  
BERTHOLD RZANY, MD, ScM,<sup>§</sup> CAROLINA EDWARTZ, PhD,<sup>||</sup> AND MAURIZIO PODDA, MD<sup>¶</sup>

**BACKGROUND** Hyaluronic acid (HA) filler injection is an increasingly popular aesthetic procedure.

**OBJECTIVE** To compare the effectiveness and safety of two HA fillers (HA<sub>ED</sub> and HA<sub>PER</sub>) for the treatment of severe nasolabial folds (NLFs).

**MATERIALS AND METHODS** This was an evaluator-blinded and subject-blinded split-face study. At baseline, HA<sub>ED</sub> or HA<sub>PER</sub> was randomly assigned to the left or right NLF. The follow-up period was 12 months. Effectiveness was assessed using the wrinkle severity rating scale (WSRS) and subject preference. Safety was assessed by adverse events and local tolerability symptoms recorded by subjects during 3 weeks after the treatment.

**RESULTS** At 6 months, HA<sub>ED</sub> was noninferior to HA<sub>PER</sub> (assessed by mean change from baseline in WSRS score). There was a significant difference in mean WSRS score change from baseline in favor of HA<sub>ED</sub> at 3 to 12 months, and a majority of subjects preferred HA<sub>ED</sub> over HA<sub>PER</sub> at 12 months. However, the overall responder rate was similar between products, and it remained high throughout the study. At 12 months, approximately 80% of subjects were still responders. Both products were well tolerated and associated with a few treatment-related adverse events.

**CONCLUSION** To conclude, HA<sub>ED</sub> was at least as effective and well tolerated for the treatment of severe NLFs as HA<sub>PER</sub>.

*Galderma provided B. Ascher, C. Bayerl, P. Kestemont, B. Rzany, and M. Podda with a camera for use in the study. Galderma also provided all authors (except C. Edwartz) with the investigational products used in the study, and reimbursed the costs for subject participation in the study. B. Rzany is an advisor for Merz pharma. C. Edwartz is employed by Galderma.*

Hyaluronic acid (HA) dermal fillers have been used for aesthetic purposes since the 1990s, and Restylane was the first stabilized HA filler of nonanimal origin approved for use in the European Union 1996 and in the United States 2003. Currently, HA fillers are used for different purposes and are available with varying gel characteristics such as firmness and particle size. Emervel (Galderma SA, Lausanne, Switzerland) HA gel dermal fillers (from

now on referred to as HA<sub>E</sub>) have been developed for use in facial tissue augmentation.<sup>1</sup> The products in the HA<sub>E</sub> range are all manufactured using the optimal balance technology and have a HA concentration of 20 mg/mL. However, to allow for adaptation to different injection depths, treatment sites, and tissue quality, the products differ in the degree of cross-linking and calibrated gel particle size. Effectiveness and safety data for the HA<sub>E</sub> products are available for

\*Clinique de Chirurgie Esthétique Iéna, Paris, France; <sup>†</sup>Department of Dermatology and Allergology, HELIOS HSK Wiesbaden, Lehrkrankenhaus der Universität Mainz, Wiesbaden, Germany; <sup>‡</sup>Clinique Esthétique St. George, Nice, France; <sup>§</sup>RZANY & HUND, Privatpraxis, Berlin, Germany; <sup>||</sup>Galderma A&C, Uppsala, Sweden; <sup>¶</sup>Department of Dermatology, Klinikum Darmstadt, Darmstadt, Germany

*This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.*

© 2016 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Society for Dermatologic Surgery, Inc. ISSN: 1076-0512 • Dermatol Surg 2017;43:389–395 • DOI: 10.1097/DSS.0000000000001031

several facial indications.<sup>2-6</sup> Emervel Deep (HA<sub>ED</sub>), which was used in the present study, is intended for injection into the deep dermis to correct moderate to deep facial wrinkles, such as nasolabial folds (NLFs).<sup>2</sup>

Interim results (6-month data) from this randomized, controlled, split-face study with HA<sub>ED</sub> and Restylane Perlane (HA<sub>PER</sub>; Q-Med AB, Uppsala, Sweden) for the treatment of severe NLFs have been published previously.<sup>7</sup> Here, the final effectiveness and safety outcomes up to 12 months after the baseline treatment were reported, thereby extending the published literature on product duration and safety for HA<sub>ED</sub> in comparison with a well-established HA filler (HA<sub>PER</sub>) that has a similar intended use. This is also the first long-term study of HA<sub>ED</sub>, and the first long-term comparison of these two products for the treatment of severe NLFs.

## Subjects and Methods

### Study Design

This was a randomized, controlled, subject-blinded and evaluator-blinded, split-face, multicenter study. To compare the effectiveness and safety of HA<sub>ED</sub> with HA<sub>PER</sub> for the treatment of severe NLFs, subjects were followed up for 12 months after the treatment. Randomization of treatment to each side of the face was done centrally (one list per study center). Allocation concealment was achieved using randomization envelopes. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by independent ethics committees. The study included an open-label part where the first three subjects per center received HA<sub>ED</sub> in both NLFs. The rationale for this was to give the investigators an opportunity to familiarize themselves with the injection technique because HA<sub>ED</sub> had recently been developed at the time of the study. However, only outcomes from the blinded split-face comparison of HA<sub>ED</sub> and HA<sub>PER</sub> are presented here.

### Subject Selection

Adult subjects ( $\geq 18$  years) who provided signed informed consent and had severe NLFs on both sides of the face (i.e., Score 4, rated using the 5-point wrinkle severity rating scale [WSRS]<sup>8</sup>) were eligible for inclusion

in the study. Main exclusion criteria were (1) active skin disease or inflammation near or in the NLFs; (2) other relevant medical history (e.g., sensitivity to HA, bleeding disorder, impaired coagulation, severe keloids, or hypertrophic scars); (3) soft tissue augmentation with HA or collagen in the NLFs in the previous 18 months or any other soft tissue augmentation in the NLFs; (4) any aesthetic or dermatologic treatment in the face in the previous 12 months and during the study (except botulinum toxin Type A injections, which were allowed in the upper third of the face up to 1 month prior to baseline and from 3 months after the last injection in the study); (5) and pregnancy, nursing, or planned pregnancy.

### Treatments

At baseline, injection treatment with HA<sub>ED</sub> or HA<sub>PER</sub> (both products without lidocaine) was randomly assigned to either the left or right NLF. The evaluating investigator was not allowed to be present at the injection or assist in the preparations for injection, and subjects were blindfolded prior to and during the injection in order to maintain the blinding. If the blinded evaluator judged it necessary, the unblinded investigator could administer a touch-up injection 3 weeks after the baseline treatment. Local and/or topical anesthetics and/or infraorbital nerve block could be applied at the discretion of the investigator.

Injections were to be placed in the mid dermis using a 27-gauge needle. The aim was to achieve complete correction of the NLFs (without overcorrection). The injection technique and volume was decided by the investigator, provided that no more than 2 mL per product was injected at baseline and no more than 1 mL per product at touch-up.

### Assessments

The 5-grade WSRS<sup>8</sup> was used separately by blinded evaluators and subjects to evaluate the severity of subjects' NLFs. Mean change in WSRS from baseline was the primary effectiveness parameter. The percentage of subjects with at least one-grade improvement in WSRS from baseline (defined here as responder rate) was a secondary effectiveness parameter. Subjects were offered to receive a final retreatment at the end of the study. Those who wished to

receive this retreatment were asked to indicate their preferred treatment side.

Safety assessments included the blinded evaluator's assessment of adverse events (AEs) at each study visit. In addition, subjects assessed local tolerability (bruising, edema/swelling, erythema, nodule formation, pain/tenderness, and pruritus) on a daily basis using a subject diary during 3 weeks after the baseline treatment, and if applicable, touch-up treatment.

### Statistical Analyses

Sample size was calculated based on the assumption that HA<sub>ED</sub> and HA<sub>PER</sub> were equally efficacious at 6 months, with a 90% power to demonstrate noninferiority. The safety and intention-to-treat (ITT) populations included all subjects who received all planned treatments. The per-protocol (PP) population included all randomized subjects with no major protocol deviations.

The primary effectiveness criterion was the mean change in the blinded evaluator's assessment of WSRS from baseline to 6 months after baseline. A Student *t*-test was used to calculate the 95% confidence interval (CI) of the mean between-treatment difference (HA<sub>PER</sub> – HA<sub>ED</sub>). If the CI was above the margin of –0.5 in both the ITT and PP populations, noninferiority was to be declared.

Responder rate data are presented descriptively. Imputation for any missing effectiveness data was done for the ITT population (last observation carried forward) but not for the PP population, for which analyses were based on observed cases. A two-sided McNemar test was used to analyze subject preference at the end of the study. Safety data were analyzed descriptively.

## Results

### Subject Disposition

A total of 89 subjects were screened at the 6 study centers. Of these, 68 were randomized to the comparative part of the study, and 67 completed the study (Table 1). The first subject was enrolled March 17, 2009, and the last subject completed the study June 10, 2010.

**TABLE 1. Subject Disposition**

Subject Disposition	n (%)
Randomized	68 (100.0%)
Completed	67 (98.5%)
Withdrawn	1 (1.5%)
Lost to follow-up	1 (1.5%)
ITT population	68 (100.0%)
Safety population	68 (100.0%)
PP population	64 (94.1%)*

\*Four subjects were excluded from the PP population due to major protocol deviations (prohibited previous cosmetic procedure [n = 2], 6-month visit not within the allowed time window [n = 1], and treatment assignment revealed in case report form by mistake [n = 1]).

ITT, intention-to-treat; PP, per-protocol.

### Demographics, Baseline Characteristics, and Injection Information

All subjects were white with severe NLFs and had a mean age of 53 years (Table 2). The total mean injection volume (including touch-up) was similar for HA<sub>ED</sub> and HA<sub>PER</sub> (1.3 mL for both; see Table 3, which also includes details on use of preinjection anesthesia).

### Assessment of Effectiveness

#### Mean Change From Baseline in Wrinkle Severity Rating Scale as Assessed by the Blinded Evaluator (Intention-To-Treat Population)

Similar to previously reported interim data,<sup>7</sup> HA<sub>ED</sub> was noninferior to HA<sub>PER</sub> in terms of mean change

**TABLE 2. Demography and Baseline Characteristics**

Mean age (range), yr	52.7 (31–76)
Sex, n (%)	
Female	61 (89.7)
Male	7 (10.3)
Ethnicity, n (%)	
Caucasian	68 (100.0)
Fitzpatrick phototype, n (%)	
II	17 (25.0)
III	51 (75.0)
Evaluator's assessment of baseline WSRS, n (%)	
4: severe	68 (100.0)

WSRS, wrinkle severity rating scale.

**TABLE 3. Volume HA Gel Injected and Use of Preinjection Anesthesia**

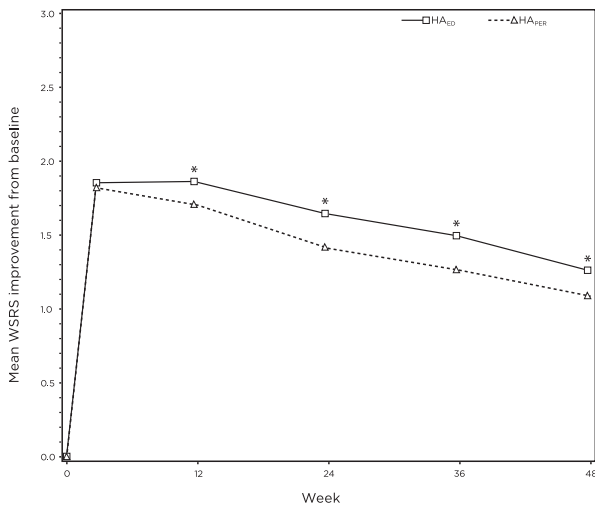
	<i>n</i>	<i>HA</i> <sub>ED</sub> , Mean Volume (Range), mL	<i>HA</i> <sub>PER</sub> , Mean Volume (Range), mL	Anesthesia, <i>n</i>
Baseline treatment	68	1.0 (0.6–2.0)	1.0 (0.5–2.0)	15*
Touch-up after baseline treatment	29†/31‡	0.6 (0.3–1.0)	0.7 (0.2–1.0)	14*
Total volume, baseline treatment	68	1.3 (0.6–2.8)	1.3 (0.5–3.0)	—

\*Topical anesthesia.  
 †*HA*<sub>ED</sub>.  
 ‡*HA*<sub>PER</sub>.  
 HA, hyaluronic acid.

from baseline in WSRS score at 6 months after the baseline treatment. At this time point, the mean between-treatment difference (*HA*<sub>PER</sub> – *HA*<sub>ED</sub>) was 0.24, and the 95% CI ranged between 0.10 and 0.37 (i.e., above the predetermined margin [–0.5]).

The statistical comparison of mean change from baseline in WSRS score favored *HA*<sub>ED</sub> over *HA*<sub>PER</sub> from 3 to 12 months after the treatment (Figure 1). However, the difference in mean change from baseline in WSRS score between the 2 products ( $\Delta$ *HA*<sub>ED</sub> – *HA*<sub>PER</sub>) was small, ranging from 0.17 to 0.24 during this period.

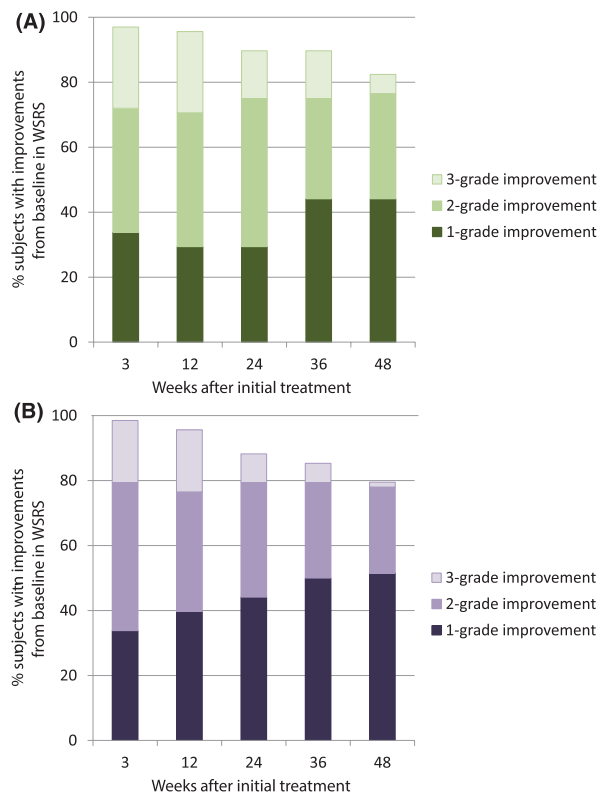
Corresponding comparisons for the PP population (data not shown) were similar to those for the ITT population. Furthermore, the subjects’ assessment of WSRS (data not shown) corroborated that of the blinded evaluator.



**Figure 1.** Mean improvement from baseline in WSRS over time as assessed by the blinded evaluator. \**HA*<sub>ED</sub> > *HA*<sub>PER</sub>, *p* < 0.01. WSRS, wrinkle severity rating scale.

*Responder Rate (Percentage of Subjects With At least One Grade Improvement in Wrinkle Severity Rating Scale) as Assessed by the Blinded Evaluator*  
 The overall responder rate was similar between *HA*<sub>ED</sub> and *HA*<sub>PER</sub> over time, ranging from 79% to 99% during the study (Figure 2).

The responder rate for the PP population (data not shown) was similar to that of the ITT population. Furthermore, the responder rate based on subjects’



**Figure 2.** Responder rate over time as assessed by the blinded evaluator. (A) *HA*<sub>ED</sub>. (B) *HA*<sub>PER</sub>.

assessment of WSRS (data not shown) corroborated that of the blinded evaluator.

### *Subjects' Preference*

At the end of the study (12 months after the baseline injection), 58 subjects wished to be retreated. The subject preference assessment favored HA<sub>ED</sub> over HA<sub>PER</sub> ( $p < 0.001$ ), with 42 subjects (72%) preferring the side that had been treated with HA<sub>ED</sub> at baseline, whereas the remaining 16 subjects (28%) preferred the side that had been treated with HA<sub>PER</sub> at baseline.

Figure 3 shows photographs of a representative subject.

### **Safety**

#### *Adverse Events*

Four treatment-related AEs occurred (Table 4); all were of mild intensity and anticipated reactions after HA filler injection. One subject had bilateral injection site pain, which started the day after the baseline treatment and resolved after 3 days after treatment with paracetamol (acetaminophen). Two subjects had telangiectasia (on the side treated with HA<sub>ED</sub>), but these events did not require intervention. All treatment-related AEs resolved, except one event of telangiectasia that was ongoing at the end of the study.

#### *Local Tolerability (Subject Diary Data)*

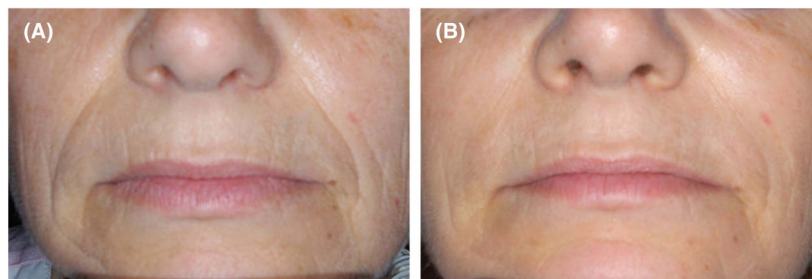
Both HA<sub>ED</sub> and HA<sub>PER</sub> were well tolerated. The local tolerability reactions (bruising, edema/swelling, erythema, nodule formation, pain/tenderness, and pruritus) recorded in this study were consistent with expected reactions after injection with an HA gel. The frequency of these reactions generally declined within 1 week, and a majority resolved within 2 weeks.

### **Discussion**

This study is the first comparison of HA<sub>ED</sub> and HA<sub>PER</sub>, with long-term follow-up extending 12 months. The results show that HA<sub>ED</sub> was noninferior to HA<sub>PER</sub> for the treatment of severe NLFs, assessed by mean change from baseline in WSRS score at 6 months. The effect lasted for at least 12 months in approximately 80% of subjects after 1 treatment. The final effectiveness results reported here are similar to the interim results reported previously.<sup>7</sup>

Analyses of secondary effectiveness parameters pointed toward that there was a statistically significant difference in the mean change from baseline in WSRS over time, favoring HA<sub>ED</sub> compared with HA<sub>PER</sub>. However, this difference was seemingly small (ranging between 0.17 and 0.24) and needs to be corroborated by results from further studies. Furthermore, the clinical relevance of this difference needs to be confirmed. However, the preference assessment at the end of the present study indicated that a majority of subjects preferred the side treated with HA<sub>ED</sub> over the side treated with HA<sub>PER</sub>. These results are in agreement with the comparison of difference in mean WSRS score improvement from baseline.

Carruthers and colleagues<sup>9</sup> previously reported that the 6-month responder rate was 75% for HA<sub>PER</sub>. This is somewhat lower than the corresponding data recorded in the present study (90% for HA<sub>ED</sub> and 88% for HA<sub>PER</sub>), although similar volumes of HA gel were injected. In fact, the 12-month results from the present study are similar to the 6-month results reported by Carruthers and colleagues.<sup>9</sup> It is possible that the difference in responder rates between studies is



**Figure 3.** Standardized photographs of a subject before (A) and 12 months after (B) treatment with HA<sub>ED</sub> and HA<sub>PER</sub> in the right and left nasolabial folds, respectively.



**TABLE 4. Treatment-Related AEs by Preferred Term**

	HA <sub>ED</sub> , n = 68 (%)	HA <sub>PER</sub> , n = 68 (%)
Injection-site pain	1 (1.5)	1 (1.5)
Telangiectasia	2 (2.9)	—
Total number of subjects with treatment-related AEs	3 (4.4)*	1 (1.5)*
Total number of treatment-related AEs	3	1

\*One subject had a treatment-related AE (injection-site pain) in both the side treated with HA<sub>ED</sub> and the side treated with HA<sub>PER</sub>, that is, a total of 3 subjects (4.4%) had a treatment-related AE.  
AE, adverse event.

a reflection of differences in study populations and/or differences due to the subjective components of the outcome criteria.

In the present study, the effectiveness results (both in terms of mean improvement from baseline in WSRS and in terms of responder rate) showed a gradual decline over time after the baseline injection, which is expected as both HA<sub>ED</sub> and HA<sub>PER</sub> are biodegradable. A majority of subjects (>88%) were responders 6 months after the baseline injection, and approximately 80% of subjects were still responders 1 year after the baseline injection.

The HA fillers used in this study did not contain lidocaine, which was due to the fact the only the non-lidocaine version of HA<sub>ED</sub> was available at the time of the study; HA fillers that do not contain lidocaine have the advantage that they may be used in subjects for whom lidocaine is contraindicated or who are allergic to this class of local anesthetics. However, drawbacks relate to pain and reduced treatment comfort. Therefore, a lidocaine-containing version of HA<sub>ED</sub> is currently available.

Both fillers were well tolerated and associated with few treatment-related AEs. For both HA products, local tolerability reactions generally resolved within a week. The treatment-related AEs that occurred were of mild intensity, and all except one had resolved by the end of the study.

## Conclusions

Basically, HA<sub>ED</sub> was noninferior to HA<sub>PER</sub> as measured by the mean change from baseline in WSRS score at 6 months after the baseline treatment of severe NLFs. There was a statistically significant difference in mean change from baseline in WSRS score in favor of HA<sub>ED</sub> at 3 to 12 months after the treatment. However, this difference was small and needs to be corroborated by results from further studies. Furthermore, the clinical relevance of this difference is unclear. The overall responder rates were similar between HA<sub>ED</sub> and HA<sub>PER</sub> over time and remained high throughout the 12 months, ranging from 79% to 99%. The preference assessment at the end of the study indicated that a majority of subjects preferred the side treated with HA<sub>ED</sub> over the side treated with HA<sub>PER</sub>. However, neither product used contained lidocaine, so it is not known if these results would apply to the lidocaine-containing products.

Both HA gel products were well tolerated and were associated with a few treatment-related AEs, all of which were anticipated reactions to HA filler injection.

To summarize, the results of the present study show that HA<sub>ED</sub> was at least as effective and well tolerated for treatment of severe NLFs as HA<sub>PER</sub>.

**Acknowledgments** The authors acknowledge Patrick Brun, MD, Dermatology, Cannes Hospital, Cannes, France, for serving as one of the study investigators and thereby contributing towards the collection of study data.

## References

- Segura S, Anthonioz L, Fuchez F, Herbage B. A complete range of hyaluronic acid filler with distinctive physical properties specifically designed for optimal tissue adaptations. *J Drugs Dermatol* 2012;11(1 Suppl):s5–s8.
- Cartier H, Trevidic P, Rzany B, Sattler G, et al. Perioral rejuvenation with a range of customized hyaluronic acid fillers: efficacy and safety over six months with a specific focus on the lips. *J Drugs Dermatol* 2012;11(1 Suppl):s17–s26.
- Kestemont P, Cartier H, Trevidic P, Rzany B, et al. Sustained efficacy and high patient satisfaction after cheek enhancement with a new hyaluronic acid dermal filler. *J Drugs Dermatol* 2012;11(1 Suppl):s9–16.
- Rzany B, Cartier H, Kestemont P, Trevidic P, et al. Correction of tear troughs and periorbital lines with a range of customized hyaluronic acid fillers. *J Drugs Dermatol* 2012;11(1 Suppl):s27–s34.

5. Rzany B, Bayerl C, Bodokh I, Boineau D, et al. Efficacy and safety of a new hyaluronic acid dermal filler in the treatment of moderate nasolabial folds: 6-month interim results of a randomized, evaluator-blinded, intra-individual comparison study. *J Cosmet Laser Ther* 2011;13:107–12.
6. Rzany B, Cartier H, Kestemont P, Trevidic P, et al. Full-face rejuvenation using a range of hyaluronic acid fillers: efficacy, safety, and patient satisfaction over 6 months. *Dermatol Surg* 2012;38(7 Pt 2):1153–61.
7. Ascher B, Bayerl C, Brun P, Kestemont P, et al. Efficacy and safety of a new hyaluronic acid dermal filler in the treatment of severe nasolabial lines—6-month interim results of a randomized, evaluator-blinded, intra-individual comparison study. *J Cosmet Dermatol* 2011;10:94–8.
8. Day DJ, Littler CM, Swift RW, Gottlieb S. The wrinkle severity rating scale: a validation study. *Am J Clin Dermatol* 2004;5:49–52.
9. Carruthers A, Carey W, De LC, Remington K, et al. Randomized, double-blind comparison of the efficacy of two hyaluronic acid derivatives, Restylane perlane and hylaform, in the treatment of nasolabial folds. *Dermatol Surg* 2005;31(11 Pt 2):1591–8.

---

Address correspondence and reprint requests to: Benjamin Ascher, MD, Clinique de Chirurgie Esthétique Iéna, 11 Rue Fresnel, 75116 Paris, France, or e-mail: benjaminascher@wanadoo.fr