Efficacy and Durability of Two Hyaluronic Acid–Based Fillers in the Correction of Nasolabial Folds: Results of a Prospective, Randomized, Double-Blind, Actively Controlled Clinical Pilot Study

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BACKGROUND This pilot study compared a monophasic hyaluronic acid dermal filler with a biphasic filler for the correction of nasolabial folds.

METHODS Participant- and assessor-blinded, randomized clinical trial involving participants with moderate to severe nasolabial folds. Split-face design comparing a monophase hyaluronic acid (HA) filler (mono-HA) with a biphasic HA filler (bi-HA). Injection with touch-up after 1 month. Wrinkle improvement was measured before and after injection and after 1, 2, 4, and 7 months, using the Wrinkle Severity Rating Scale and the Global Aesthetic Improvement Scale as outcome criteria. An optional treatment was offered at the end of the study, with participants allowed to choose one of the products.

OBJECTIVE Evaluation of efficacy and safety of both products.

RESULTS Both products showed immediate, good results after injection and touch-up and demonstrated good durability over time. Participant preference for optional treatment at the end of the study favoured mono-HA. Both products were well tolerated, without serious adverse events.

CONCLUSION The effect after injection of mono-HA and bi-HA is generally comparable, although there was a trend in favor of mono-HA.

Materials and funding for this study were provided by Teoxane, Geneva, Switzerland.

Injectable fillers are one of the cornerstones of aesthetic medicine.[1] Over the last decade, the use of injectable fillers has increased continuously, with hyaluronic acid (HA) preparations being used most frequently. HA is a naturally occurring polysaccharide consisting of linear chains of alternating D-glucuronic acid and *N*-acetyl-D-glucosamine molecules that is structurally homogenous across species. HA is strongly hydrophilic. Because of its natural hydrating function within the dermis, it promotes skin suppleness. HA has rapid turnover, so if injected externally, the product must be modified to improve its durability. The chemical cross-linking of HA results in the formation of a viscoelastic polymer and ensures persistence.

There are several types of HA fillers. Two types were investigated in this study: a biphasic injectable filler (Restylane Perlane, Q-Medical, Uppsala, Sweden) based on individual particles (bi-HA) with a HA content of 20 mg/g and a mono-phasic injectable filler (Teosyal 27G Deep Lines, Teoxane, Geneva, Switzerland) based on a homogenous HA preparation with a HA content of 25 mg/g (mono-HA). Both are produced using bacterial fermentation and therefore are free of products of animal origin. In both products, the HA is cross-linked with butanediol diglycidyl ether. The cross-linking strategy yields two different viscoelastic polymer gels. The mono-HA is less elastic (lower G′) and more cohesive than the bi-HA. Differences in the structural and

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ISSN: 1076-0512 • Dermatol Surg 2011;37:768–775 • DOI: 10.1111/j.1524-4725.2011.01993.x

mechanical properties of the two implants led us to expect differences in filling properties and implant durability in vivo.

Restylane products were introduced in Europe in 1996 and have been used in more than 10 million people worldwide. The bi-HA used for this pilot study is specifically designed for the correction of facial wrinkles and is intended for injection into the deep layer of the dermis and the surface layer of the subcutis.

Teosyal products were introduced in Europe in 2004, and more than 1,500,000 injections have been completed so far. The filler has not been introduced to the market in the United States. The mono-HA used for this pilot study is recommended for filling deep facial wrinkles, such as nasolabial folds and marionette lines, and is intended for injection into the deep dermis. To our knowledge, no studies have been conducted that compare the efficacy and tolerability of these two products.

The objectives of this pilot study were to evaluate the study design and obtain data for power analysis for a future clinical trial that will compare the safety and efficacy of these two products. Because this was a pilot study, no primary or secondary outcome measures were defined. Multiple outcome measures were assessed.

Material and Methods

Material

The mono-HA and the bi-HA are colorless transparent gels consisting of stabilized HA. The concentration of HA is 25 mg/g in mono-HA and 20 mg/g in bi-HA, dispersed in physiological saline solution. Both products are injected using 27 G needles.

Participant Selection

People were eligible to participate in the study if they had clinical evidence of moderate or severe bilateral aging defects in the nasolabial area of both sides rated by a trained investigator as grade 3 or higher using the validated Wrinkle Severity Rating Scale (WSRS).[1] They had to agree to refrain from using other aesthetic procedures for the duration of the study. They were not included in the study if they had had treatment of the face with a biodegradable filler in the last 2 years, with nonbiodegradable filler at any time, or facial injections of botulinum toxin A for wrinkle reduction in the last 6 months.

Study Design

Randomization was done electronically using standard statistical software. Each participant received mono-HA in one nasolabial fold and bi-HA in the other. The assigned injection sides were concealed after the randomization in opaque envelopes that the investigator administering the injections opened just before the injections and then resealed afterwards. The investigator administering the injections could not be blinded because commercially available syringes were used. As a consequence, the investigator who administered the injections did not participate in any of the efficacy evaluations, and his documentation was kept separate from that of the assessors. During the injections, participants were blinded by a mask that covered the eyes. The physicians performing the efficacy assessment and the safety assessment on site were not aware of the injected product. An independent panel of three experts who, after a training session, made their assessment using photographs presented to them without further information on study design, medication, or time point at which the photographs were taken performed the additional efficacy evaluations. The response to the initial injection of mono-HA or bi-HA was evaluated after 4 weeks. If the blinded assessor determined the result to be unsatisfactory, and if the participant agreed, the investigator who originally did the injection administered a "touch-up" re-injection using the same product on the same side. The investigators who administered the injections had comparable experience with both

products. Evaluation by a blinded assessor directly after the injection did not show any difference in the efficacy of the correction. Therefore, a relevant bias is very unlikely.

A eutectic mixture of lidocaine 2.5% and prilocaine 2.5% (Emla, AstraZeneca, Germany) was applied at least 45 minutes before the injection using an occlusive dressing (Tegaderm, 3M, Austria). The cream was removed before the injection, and a routine nonalcoholic aseptic technique was used for disinfection. The material was injected into the deep dermis using the tunnel technique in combination with the serial puncture technique. The injection volume was selected at the discretion of the investigator administering the injection until full correction was achieved. The exact injection volume was documented. Differences in the filling volume of the mono-HA syringes used (only 0.9 mL in this lot) were systematically corrected.

Efficacy and Safety Assessment

The following six outcome parameters were used to evaluate efficacy: comparison of change in the WSRS score by the independent expert panel using standardized photographs, comparison of change in the WSRS by the blinded investigator, comparison of the change in the Global Aesthetic Improvement Scale (GAIS) by the blinded investigator, comparison of the change in the GAIS by the participants, a participant self-satisfaction assessment and assessment of implant texture, and the amount of HA re-injected at month 6 if correction was needed.

The assessment of wrinkles was performed using the 5-point WSRS (none (1), mild (2), moderate (3), severe (4), extreme (5)). The GAIS has a value range from very much improved (1), much improved (2), improved (3), no change (4), to worse (5). In addition, participants performed a participant self-satisfaction assessment, which has values from very satisfied (1), satisfied (2), moderate satisfied (3), dissatisfied (4), to very dissatisfied (5). Participants were followed for up to 7 months after the first injection. Efficacy evaluations using the WSRS were done at visit 1 (V1, before and after the first injection), visit 3 (V3, after 1 month—if touch-up treatment was done again, before and after injection), visit 5 (V5, 2 months after V1, $\pm$ 7 days), visit 6 (4 months after V1, $\pm$ 7 days), and visit 7 (V7, 7 months after V1, $\pm$ 7 days). Assessment of the GAIS was done at V3, V5, V6, and V7. The safety and tolerability of the implant material was also documented.

Statistical Analysis

Because the analysis was primarily exploratory, no sample size or power calculation was done. All data were summarized and analysed using SAS version 9.1. Demographic and baseline characteristics were summarized for all participants. Descriptive statistics were provided. Analysis was performed using the intention-to-treat population.

For the efficacy analysis, mono-HA and bi-HA were compared using a nonparametric test (Mann and Whitney) for which a global assessment value was generated. In the case that there was no total concordance, at least two values must have had the same value to be considered in the data matrix. In case of nonconsideration (all assessment scores were different), the data was taken as missing value in statistical analysis. To assess clinical safety, skin evaluations (injection site reactions), adverse events, vital sign measurements, and clinical laboratory information were summarized according to visit and study group. Injection site reactions and adverse experiences were also summarized according to severity.

The ethics committee of Charité - Universitätsmedizin Berlin approved the study. All the trial participants gave written, informed consent before entering into the study. The study was conducted in accordance with guidelines for good clinical practice and the Declaration of Helsinki.

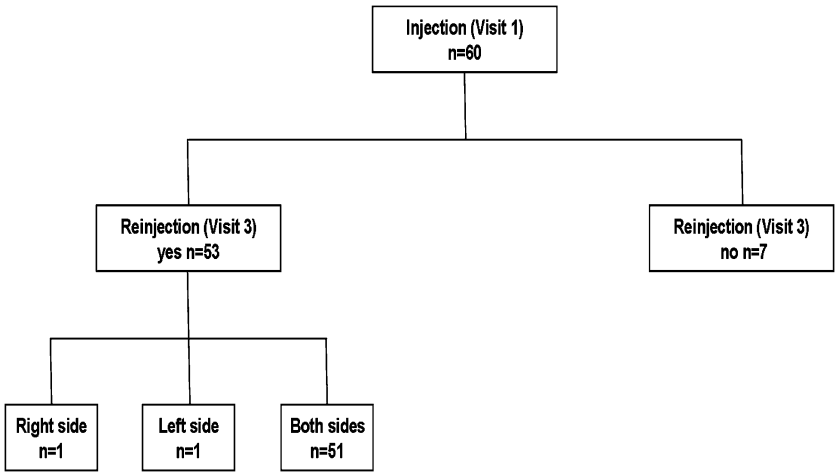

Figure 1. Flow chart of participants included in the study (intention to treat).

Results

Between March 16, 2007 (first date of informed consent) and March 25, 2008 (last date of V7), 60 participants were randomized. Fifty-two participants (86.7%) were female. The mean age of all participants was 54.8 ± 8.8. All but seven participants received a touch-up re-correction at V3 after a mean of 31 ± 4.45 days (Figure 1). Wrinkle severity before the injection as measured according to the WSRS was similar in both groups (mono-HA 3.17 ± 0.83; bi-HA 3.16 ± 0.79; $p = .94$).

Efficacy

Independent Expert Panel Assessment (Photographs)

Wrinkle Severity Rating Scale: The initial average WSRS score decreased from 3.17 (V1, before injection) to 1.98 (V1 after injection) for the mono-HA-treated side and from 3.16 (V1, before injection) to 1.89 (V1 after injection) for the bi-HA treated side.

After 1 month (V3), the average WSRS score on the side treated with mono-HA was 2.37 and for participants receiving a re-injection during that visit, decreasing to 1.62 after the injection. For the bi-HA

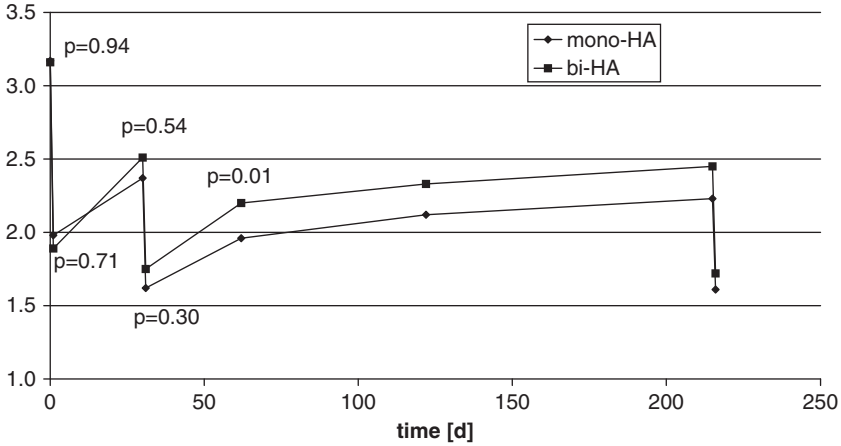

Figure 2. Average assessment of wrinkle severity of a monophase hyaluronic acid (mono-HA) filler and a biphasic hyaluronic acid (bi-HA) filler (assessment of photographs by three blinded assessors).

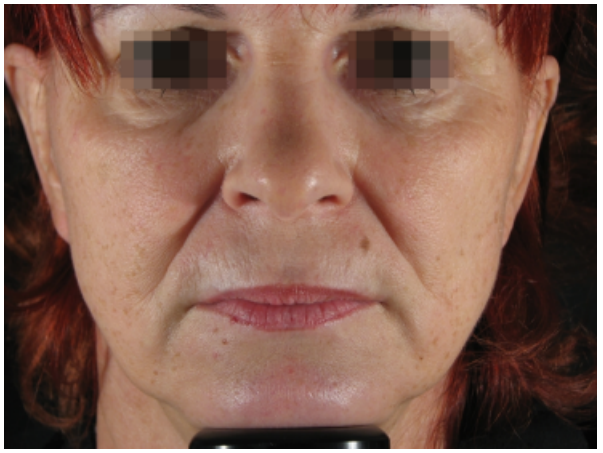

Figure 3. Participant 1 before injection.

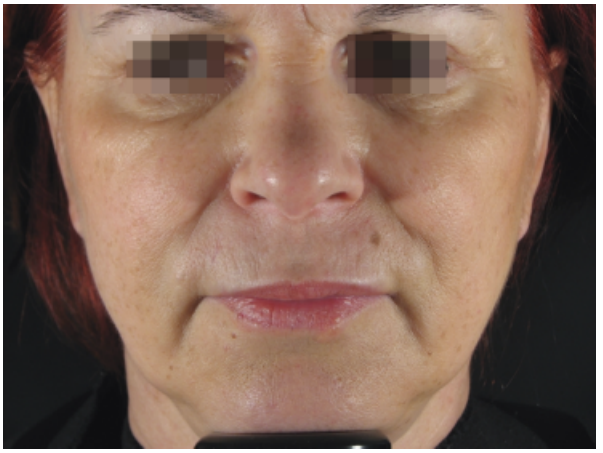

Figure 4. Participant 1, 6 months after injection.

treated side, the average WSRS score was 2.51, decreasing to 1.76 after re-injection. After 7 months (V7), the average WSRS score was 2.23 for the mono-HA side and 2.45 for the bi-HA treated side. A trend for superiority of mono-HA over bi-HA was observed throughout the study (Figure 2). Examples of clinical improvement are shown in Figures 3-6.

Blinded Investigator Assessment

Wrinkle Severity Rating Scale: The initial average WSRS score (V1) as judged by the blinded investigator was 3.67 for the side randomized to mono-HA and 3.72 for the side to be treated with bi-HA ($p = .71$). One month after the injection, the average WSRS score was 2.48 on the mono-HA-treated side and 2.53 for the bi-HA-treated side. After 7 months, the average WSRS score was 2.32 for the mono-HA-treated side and 2.67 for the side treated with bi-HA. A trend for the superiority of mono-HA over bi-HA was observed over time, which indicates better durability of mono-HA (Figure 7).

Global Aesthetic Improvement Scale: One month after the first injection (V3), the mean GAIS score was 2.15 for the mono-HA-treated side and 2.40 for the bi-HA-treated side. After 7 months (V7), the mean GAIS score was 1.87 for the mono-HA-treated side and 2.22 for the bi-HA-treated side ($p = .008$). A trend for the superiority of mono-HA over bi-HA

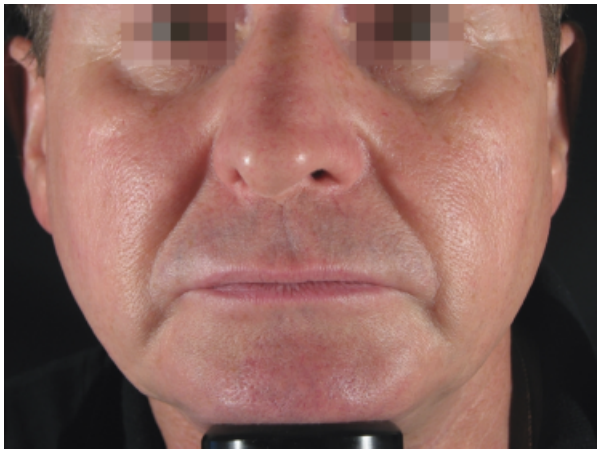

Figure 5. Participant 2 before injection.

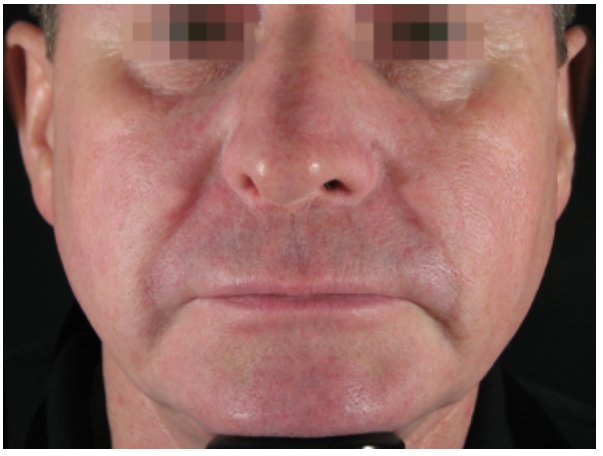

Figure 6. Participant 2, 6 months after injection.

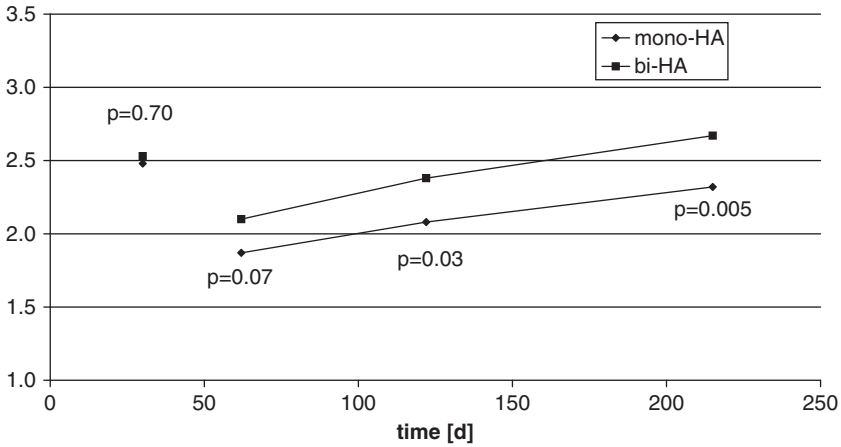

Figure 7. Assessment of wrinkle severity of a monophase hyaluronic acid (mono-HA) filler and a biphasic hyaluronic acid (bi-HA) filler (blinded investigators).

was observed over time, which indicates better persistence of mono-HA (Figures 7 and 8).

Participant Self-Assessment

Global Aesthetic Improvement Scale: One month after the first injection (V3), mean GAIS score was 2.18 for the mono-HA treated side and 2.40 for the bi-HA treated side. After 7 months (V7), mean GAIS score was 2.08 mono-HA and 2.28 for the bi-HA treated side. A trend for the superiority of mono-HA over bi-HA was observed over the whole study period in the participant self-assessment (Figure 9).

Participant Self-Satisfaction Assessment: Seven months after the injection (V7), 81.7% of the participants were very satisfied or satisfied with the treatment effect on the mono-HA-treated side, and 70% were very satisfied or satisfied with the result of the bi-HA-treated side, which indicates greater participant satisfaction with mono-HA.

Participant Preference for Optional Treatment After Clinical Study: At the end of the study, participants could choose one of the two study products for an optional treatment. If the participant did not have a preference, the treating physician made the choice.

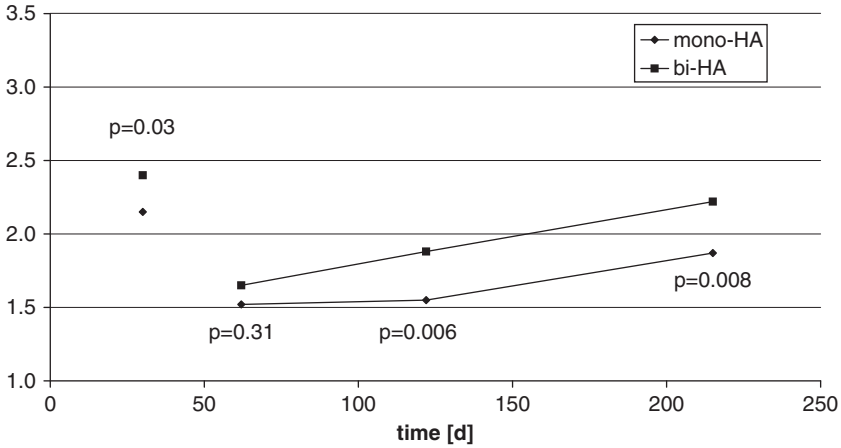

Figure 8. Global Aesthetic Improvement Scale for a monophase hyaluronic acid (mono-HA) filler and a biphasic hyaluronic acid (bi-HA) filler (blinded investigators).

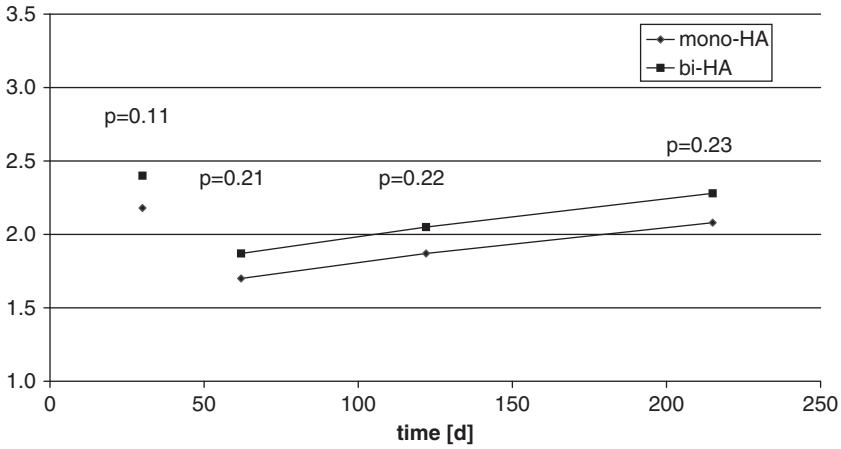

Figure 9. Global Aesthetic Improvement Scale for a monophase hyaluronic acid (mono-HA) filler and a biphasic hyaluronic acid (bi-HA) filler (participants).

There were 49 re-corrections (45 mono-HA, 4 bi-HA). Twenty-eight participants preferred mono-HA, three preferred bi-HA, and 15 did not have a preference.

Necessary Volume for Correction: The overall injection volume necessary to achieve optimal correction after V1 (first injection) and V3 (re-injection) was lower with mono-HA (1.36 $\pm$ 0.41 mL) than with bi-HA (1.64 $\pm$ 0.64 mL).

Safety

No severe adverse event occurred after the use of either product. Minor adverse events included erythema and edema. There was no edema at all in 56.7% of the participants, and 26.7% did not show erythema on either side after the first injection.

Discussion

This is the first study to compare an HA preparation of bacterial origin with another bacterial HA product for efficacy, durability, and safety. Nearly all previous studies used Zyplast, a bovine collagen, as a comparator.[2,3] It was appropriate to use bovine collagen[4,5] or avian HA (Hylaform)[5,6] as a comparator for the previous Q-Medical bi-HA studies because they were the criterion standards at that time. Because both comparators were less durable than the new product being evaluated, it was not difficult to show superiority of the new product. Now with bi-HA as a comparator it is much more difficult.

This pilot study showed good efficacy for both products (mono-HA and bi-HA) immediately after the first injection in terms of wrinkle severity improvement. Both products showed good and comparable efficacy after 6 months. For some of the efficacy criteria, mono-HA showed a trend toward better results than bi-HA. This needs to be confirmed in future studies. Further signs of a clinically relevant superiority may be drawn from participant preference. The majority of the participants preferred mono-HA at the end of the study for re-injection.

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