# A Multicenter Study of the Efficacy and Safety of Subcutaneous Nonanimal Stabilized Hyaluronic Acid in Aesthetic Facial Contouring: Interim Report

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BACKGROUND Nonanimal stabilized hyaluronic acid (NASHA) gel may offer longer-lasting cosmetic correction and lower antigenic risk than other soft-tissue augmentation agents.

OBJECTIVE To assess the efficacy and safety of the NASHA gel, Restylane® SubQ, in aesthetic facial contouring.

METHODS Fifty-seven adult patients seeking cheek and/or chin augmentation received subcutaneous and/or supraperiostal injections of Restylane® SubQ (20 mg/mL) at 114 treatment sites; 13 of these patients received ''touch-up'' injections at 20 sites. Efficacy was assessed subjectively using a 5-grade Global Aesthetic Improvement Scale (GAIS) at 1, 3, 6, 9, and 12 months after the initial treatment.

RESULTS At 3 months postbaseline, patients and investigators independently considered the treatment sites to be improved in 96.4% and 100% of cases, respectively. Patient- and investigator-assessed response rates (proportion of patients showing moderate or better improvement) were 84% and 95%, respectively. The majority of reported adverse events were treatment related (local injection-site reactions, implantation complications, skin tightness, and skin induration), but these were generally of mild intensity and short lived.

CONCLUSION Restylane® SubQ is well tolerated and maintains aesthetic correction of the cheeks and chin for at least 3 months after subcutaneous and/or supraperiostal treatment.

Q-Med AB provided the material used in this study. The authors were paid for their participation in this study.

An implant material used for soft-tissue augmentation should be capable of providing adequate and sustained aesthetic correction without migration, should be natural looking and nonpalpable, easy to administer and, if necessary, remove, non-immunogenic, and devoid of chronic inflammatory reactions.[1] As a soft-tissue augmentation material, hyaluronic acid (a naturally occurring polysaccharide) has low immunogenic potential, being chemically homogenous across all species and tissues.[2] Stabilization (or cross-linking) of the hyaluronic acid molecule improves its resistance to enzymatic degradation without compromising its biocompatibility, while the use of a nonanimal source reduces the likelihood of antigenic contamination and subsequent hypersensitivity reactions.[3]

Nonanimal stabilized hyaluronic acid (NASHA) is produced from a highly purified hyaluronic acid preparation obtained by bacterial fermentation. Various NASHA preparations of different particle sizes (Restylane®, Restylane® Touch, and Restylane®Perlane, Q-Med AB, Uppsala, Sweden) have been developed as dermal fillers for facial soft-tissue augmentation. Clinical studies indicate that these NASHA gels are

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effective in augmenting lips[4] and in correcting facial wrinkles and folds,[5–8] and that they offer a more durable aesthetic improvement than bovine collagen.[7] The extensive clinical experience gained from the intradermal use of NASHA gels in some 1.5 million facial cosmetic procedures confirms their safety.

Restylane® SubQ is a NASHA gel that is distinguished from the above-mentioned products by its appreciably larger gel particle size [~1,000 particles per mL, compared with 10,000 particles per mL (Restylane®Perlane) and 100,000–500,000 particles per mL (Restylane® and Restylane® Touch)] and its intended subcutaneous and/or supraperiostal site of implantation. The subcutis consists mainly of adipose tissue and is less dense and vascularized than the dermis, making it a more suitable matrix for implantation of Restylane® SubQ. These features lend its use to more extensive facial volume augmentation, such as facial contouring (e.g., accentuation of the cheeks and chin). Restylane® SubQ is currently approved in the European Union, Norway, and Switzerland, and is available to physicians trained in the techniques of subcutaneous soft-tissue augmentation of the face.

This long-term (12-month) open-label study was undertaken to ascertain the efficacy and safety of Restylane® SubQ in facial contouring and to gain practical insight into the optimal treatment procedure. The present report provides an interim analysis of the efficacy and safety findings after 3 months' follow-up.

## Materials and Methods

### *Materials*

Restylane® SubQ (Q-Med AB, Uppsala, Sweden) is a clear, colorless, viscoelastic gel consisting of NASHA (20 mg/mL) dispersed in physiological saline solution. The sterilized study material (2 mL) was supplied in a 3 mL glass syringe and was injected subcutaneously and/or supraperiostally using a sterilized 16-gauge Coleman™ infiltration cannula (7 or 9 cm in length) with a blunt tip (Byron Medical Inc., Tucson, AZ, USA) (Figure 1). Each study site was supplied with 5 types of cannula; for most administrations a Coleman™ COL-I7 infiltration cannula (7 cm, with a blunt, distally closed end and a single opening) was used.

### *Patient Selection and Study Design*

This prospective, open-label study, which was performed at 4 centers in Canada, recruited adult outpatients ($\geq$ 18 years of age) of either gender seeking cheek and/or chin augmentation therapy for aesthetic purposes. For study inclusion, patients were required to agree to abstain from other cosmetic procedures (e.g., further augmentation therapy, botulinum toxin injections, laser or chemical skin resurfacing, or face lift procedures) for the duration of the study. Patients who had undergone facial tissue augmentation therapy or laser/chemical peeling procedures within the previous 6 months or aesthetic facial surgery within the previous 12 months were excluded from the study. In addition, patients presenting with active skin disease or inflammation affecting the intended treat-

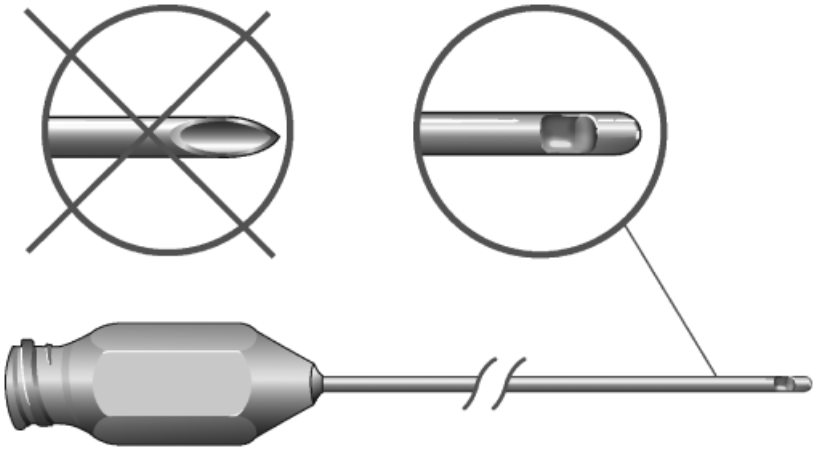

**Figure 1.** Schematic representation of the Coleman™ infiltration cannula. The conventional bevelled tip (left) is replaced with a blunt, distally closed tip (right).

ment area, those with known allergy/hypersensitivity to local anesthetics or previous adverse reactions to NASHA, and those currently taking anticoagulant or antiplatelet drugs were excluded from participation. The use of anticoagulants, aspirin, and nonsteroidal anti-inflammatory drugs was prohibited until the injection site had completely healed.

The study protocol was approved by the Canadian regulatory authorities (Therapeutic Program Directorate, Ottawa) and independent ethics committees at the study centers, and the study was performed in accordance with the principles of the Declaration of Helsinki, the International Conference of Harmonization guidelines for Good Clinical Practice, and local regulatory requirements. All patients provided their written informed consent before entry to the study.

### *Injection Technique*

The treatment area was cleaned with an antiseptic solution and, if local anesthesia was required, lidocaine (0.5% or 1.0%)/adrenaline solution was injected at the planned incision site. Additional anesthesia was provided, if required, by regional nerve block or subcutaneous injection of lidocaine/adrenaline at the proposed implantation site. A dermal incision 1–2 mm in length was made with a scalpel (11 blade) or sharp injection needle to facilitate transdermal insertion of a blunt-tipped cannula for administration of Restylane® SubQ into the subcutaneous adipose tissue or supraperiostal tissue. The NASHA gel was injected in small aliquots throughout the area requiring augmentation, rather than as a single bolus, by manipulating the cannula into a different tract after each injection, using a tunnelling technique. A maximum of 10 mL (5 syringes) of Restylane® SubQ could be administered at each treatment session to a maximum of 3 separate anatomical sites (chin and both cheeks). On completion of the injection, the treatment area was massaged to conform to the contour of the surrounding tissue and, if necessary, ice was applied briefly to reduce any swelling.

### *Evaluation*

After initial treatment with Restylane® SubQ, patients returned to the clinic 4 weeks later to determine whether repeat treatment ("touch-up") was necessary to correct for any asymmetry or unevenness in the initial aesthetic correction. Patient follow-up visits were scheduled for 4 weeks and 3, 6, 9, and 12 months after the initial treatment session (baseline) for evaluation of efficacy and safety. All efficacy and safety analyses were based on the intent-to-treat (ITT) population, comprising those patients who received the study material.

Clinical efficacy assessments were conducted independently by the Evaluating Investigator (one Evaluating Investigator was designated for each study center) and the patient. Clinical efficacy was assessed subjectively using a 5-grade Global Aesthetic Improvement Scale (GAIS). The Evaluating Investigator and patient independently graded the overall esthetic change ("worse, no change, somewhat improved, moderately improved, very much improved") by comparing the patient's visual appearance at follow-up against an archival photograph taken prior to treatment. In those cases where treatment was applied to more than one site, efficacy assessments were based on the overall esthetic impression (i.e., treatment sites were considered collectively for each patient). Patients were classified on the basis of the Evaluating Investigator's and patient's GAIS assessments as being either responders ("moderately or very much improved") or nonresponders ("worsened, no change or somewhat improved").

Safety assessments, based on directly observed and spontaneously reported adverse events, were performed at each treatment session and at each follow-up visit. Adverse events were assessed for seriousness (serious or nonserious), intensity (mild, moderate, or severe) and relationship (related or unrelated) to the study treatment. Any treatment-related adverse event that was present at the last clinical visit was followed up until it resolved or was classified as

"chronic" or "stable." Where medically indicated, clinical laboratory tests could be conducted at the discretion of the Evaluating Investigator.

### Statistics

Continuous variables were described using standard summary statistics (mean, median, maximum and minimum values, and standard deviation). Categorical variables (response rates, adverse event incidences) were summarized in frequency tables.

## Results

### Patient Demographic Characteristics

Of a total of 59 patients who were screened, 57 patients satisfied the study entry criteria and were treated with Restylane® SubQ (ITT population). This group comprised 55 women and 2 men, ranging in age from 23 to 76 (mean 52.7) years, and was predominantly Caucasian (96.5%); 38 patients (66.7%) had undergone a prior facial dermatologic procedure, most commonly plastic surgery (rhinoplasty, blepharoplasty, and face lifts), soft-tissue augmentation therapy and botulinum toxin injection. All but two of the 57 patients in the ITT population completed 3 months' follow-up assessment (the remaining two patients failed to attend the 3-month follow-up visit). A total of eight patients were classified as major protocol violators because of failure to attend the final follow-up visit within the stipulated time frame ($n = 7$) or recent lip augmentation therapy ($n = 1$).

### Extent of Exposure to Treatment

All 57 patients underwent initial treatment with Restylane® SubQ and received injections over a total of 114 sites (chin: 8 sites; both cheeks: 82 sites; chin and both cheeks: 24 sites). On initial treatment, the mean volumes of gel injected into each cheek and chin were 2.2 (SD = 1.0) and 2.1 (SD = 1.2) mL, respectively, while the mean total volume administered to each patient was 4.3 (SD = 2.2) mL. Thirteen patients subsequently received "touch-up" injections of Restylane® SubQ at a total of 20 sites (chin: 7 sites; cheeks: 13 sites). During "touch-up," the mean volumes of gel injected into each cheek and chin were 1.0 (SD = 0.7) and 1.0 (SD = 0.6) mL, respectively, while the mean total volume administered to each patient was 1.5 (SD = 1.2) mL. In accordance with the study protocol, Restylane® SubQ was injected into the subcutaneous adipose tissue, although in several cases injection was performed at deeper (submuscular/supraperiostal) levels, particularly at those anatomical sites (chin and upper cheeks) overlying bone. In all cases, local anesthetic was used at the initial treatment and at the "touch-up" treatment sessions.

### Efficacy

Independent GAIS assessments performed by the Evaluating Investigator (Figure 2) and patient (Figure 3) indicated high levels of satisfaction with the esthetic effect achieved with Restylane® SubQ. Thus, the patients considered the treatment sites to be improved in 100% of cases at 4 weeks postbaseline and in 96.4% of cases at 3 months postbaseline; corresponding figures for the

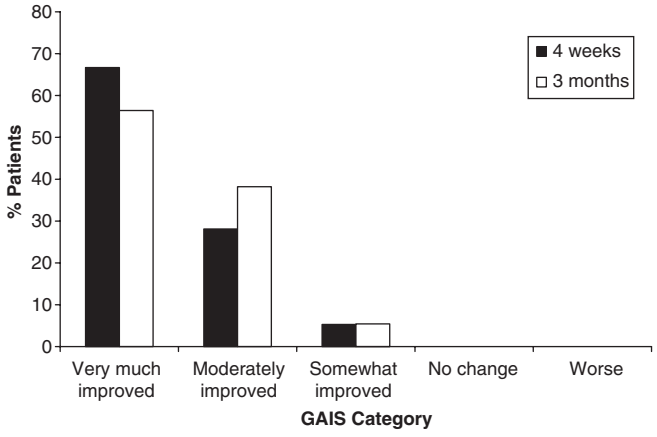


**Figure 2.** Categorical outcomes based on evaluating investigator-assessed Global Aesthetic Improvement Scale (GAIS) score at 4 weeks and 3 months post-treatment.

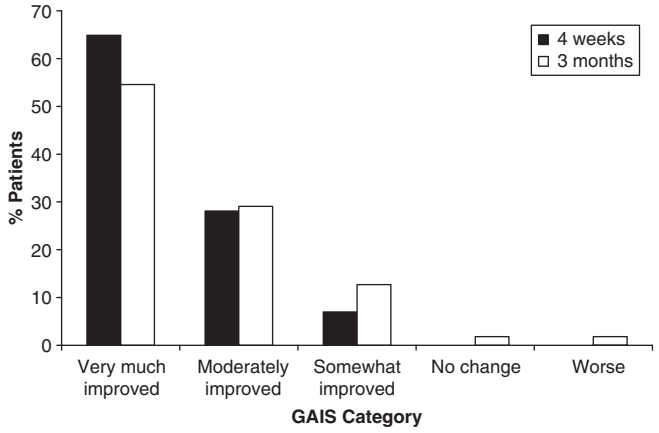


**Figure 3.** Categorical outcomes based on patient-assessed Global Aesthetic Improvement Scale (GAIS) score at 4 weeks and 3 months post-treatment.


**Figure 4.** Photographic images depicting the facial area of two representative patients (a) before treatment and (b) 3 months after treatment with Restylane® SubQ. Treatments were administered in variable volumes to the left and right cheeks of Patient 1 (3 and 5 mL, respectively) and Patient 2 (3.5 mL on each side).

Evaluating Investigator were 100% at both time points. Patient- and evaluator-assessed response rates (proportion of patients showing moderate or better improvement) were 93% (95% CI 86–100%) and 95% (95% CI 89–100%), respectively, at 4 weeks post-baseline and 84% (95% CI 74–93%) and 95% (95% CI 89–100%), respectively, at 3 months postbaseline. Serial photographic images of the face taken before and after treatment with Restylane® SubQ are presented in Figure 4.

### *Safety*

During the first 3 months of the study, treatment-related adverse events (local injection-site reactions, implantation complications, skin tightness, and induration) were reported by 52.6% of patients. The majority (83.8%) of these adverse events were of mild intensity. The most frequent types of reaction were injection site reactions (swelling, tenderness, and redness), injection-site bruising, skin induration ("nodules," "lumpiness," "clumping," and "hard mass") and implantation complications (local mobility of the implant) (Figure 5). Local injection-site reactions of bruising, swelling and tenderness typically lasted for approximately one week after injection and were of mild intensity. Injection-site pain was generally brief (2–7 days' duration) and mild, although 1 patient experienced severe facial

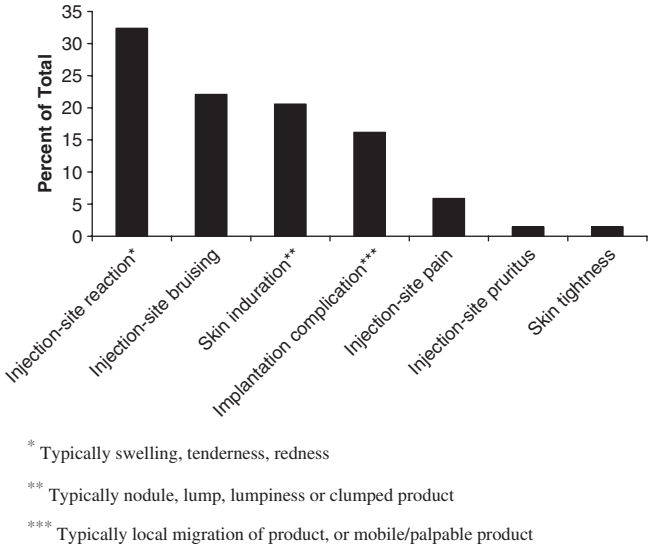


**Figure 5.** Pattern of treatment-related adverse events during the 3-month follow-up phase: numbers of each adverse event are expressed as a percentage of the total number of events ($n = 68$).

pain, possibly attributable to intramuscular injection of the gel.

Implantation complications (mobility of the study product) occurred in 8 patients, of whom 7 were treated in both cheeks and 1 in both cheeks and chin. (The majority of these complications were reported at one study center; this may be related to the tendency for use of larger injection volumes at this center than at the other study sites.) These complications, which typically commenced within 1 week of treatment and were of mild-to-moderate intensity, tended to be long lasting (median duration 1 month), and six of the nine events were still ongoing at the 3-month visit. Although refined guidelines regarding the site, depth and volume of injection of Restylane® SubQ remain to be formulated, it is likely that, as clinical experience in the use of Restylane® SubQ grows, the incidence of product mobility will decline.

No patient was withdrawn from the study because of adverse events, although 3 patients had their implants removed within the first 3 months because of skin induration associated with local mobility or clumping of the study product. In these patients, aspiration of the implanted gel led to resolution of these complaints. There were no signs of inflammation in conjunction with mobility or clumping of the implanted gel.

## Discussion

For the patient requiring large-volume facial soft-tissue augmentation, treatment options are limited. Lipo-sculpturing with autologous fat grafts offers good cosmetic results, but is a cumbersome and time-consuming surgical procedure that is often unappealing to potential patients; in addition, over-correction at the treatment site is required as the degree of fat resorption is frequently unpredictable.[9] The unpredictability of the treatment outcome necessitates several treatment sessions, each accompanied by extensive postoperative swelling. Moreover, to ensure graft survival, the fat has to be dispensed in small deposits over a large tissue area using a multichannel technique.[10] The results of the current study suggest that Restylane® SubQ offers an attractive alternative for facial contouring: the product is provided ready to use in a pre-filled syringe, is easy to administer, provides a predictable degree of tissue augmentation, and a clinically relevant esthetic correction that is sustained for at least 3 months post-treatment.

As experience in the use of Restylane® SubQ for facial contouring is presently limited, one of the aims of this study was to gather information regarding the preferred technique for administering the material at different anatomical sites. Although the study protocol specified that the gel was to be injected into the subcutaneous adipose tissue of the cheeks and chin, the depth and volume of injection and the pattern of distribution of the gel over the treatment area were largely left to the discretion of the

investigator. Variation between individual investigators and centers in the volume and depth of injection may partly account for the implantation complications (mobility of the gel) seen in 8 of 57 treated patients. These complications, which were largely confined to the cheeks, are possibly attributable to the use of an excessive amount of gel, since the mean injection volume in these patients (3.2 mL per cheek) was notably higher than that in patients for whom no gel mobility was reported (2.0 mL per cheek). Although a potential cause of lumpiness or unevenness of the skin surface, gel mobility is unlikely to be of major concern to the patient, since affected patients still experienced improvements in GAIS rating. Nevertheless, it would appear advisable to limit the volume of gel injected at each treatment session to no more than 2 mL per cheek or chin, and to spread the material diffusely in small aliquots.

Over the zygomatic bone, the orbicularis oculi muscle lies in close proximity to the dermis in the subcutaneous plane, and an implant placed superficial to this muscle is likely to cause lumpiness. Thus, in the upper cheek, it is advisable to inject Restylane® SubQ deep to the orbicularis oculi muscle and superficial to the periosteum; injection above the inferior orbital rim should be avoided. In the inferior cheek, deep subcutaneous injection at a level above the inferior margin of the zygomatic bone is recommended. Further refinement in the injection technique (specifically with regard to injection depth), based on consideration of the anatomical site, may be important in reducing the likelihood of local mobility of the implant and resulting problems of skin induration at the treatment site.

In summary, preliminary evidence indicates that Restylane® SubQ is safe and effective in creating and maintaining esthetic correction of the cheeks and/or chin for at least 3 months in the great majority of patients.

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