Safety and Effectiveness of Small and Large Gel-Particle Hyaluronic Acid in the Correction of Perioral Wrinkles

Fredric Brandt MD, a Benjamin Bassichis MD, b Michelle Bassichis MD, c Christopher O’Connell MD, a Xiaoming Lin d

aDermatology Research Institute, Coral Gables, FL
bAdvanced Facial Plastic Surgery Center, Dallas, TX
cCenter for Advanced Clinical Research, Dallas, TX
dMedicis Pharmaceutical Corporation, Scottsdale, AZ

ABSTRACT

Background: FDA-approved for the correction of moderate-to-severe facial wrinkles and folds, small gel-particle hyaluronic acid (SGP-HA, Restylane® Medicis Aesthetics, Inc., Scottsdale, AZ) and large gel-particle hyaluronic acid (LGP-HA, Perlane,® Medicis Aesthetics, Inc., Scottsdale, AZ) were studied to evaluate their safety for the correction of oral commissures, marionette lines, upper perioral rhytides and nasolabial folds (NLFs).

Objectives: The primary objective of this study was to investigate the safety of SGP-HA and LGP-HA in treating facial wrinkles and folds around the mouth; the secondary objective was to evaluate the effectiveness of these products.

Methods: This open-label, 4-week study at two US centers evaluated SGP-HA and LGP-HA in patients who intended to undergo intradermal injection for correction of perioral wrinkles and folds. At screening, a 5-grade Wrinkle Severity Rating Scale (WSRS) was used to evaluate the baseline appearance of bilateral NLFs, and a 6-grade Wrinkle Severity (WS) scale was used to evaluate the appearance of bilateral oral commissures, marionette lines and upper perioral rhytides. To qualify, each patient must have had moderate-to-severe wrinkles at one pair of marionette lines and upper perioral rhytides. Each wrinkle was treated to optimal correction with either SGP-HA or LGP-HA at the discretion of the treating investigator. All reported local and systemic adverse events (AEs) were recorded. At two weeks after treatment or touch-up, the treating investigator and the patient assessed appearance using the Global Aesthetic Improvement Scale (GAIS).

Results: Twenty patients with a mean age of 59.6 years (range 49 to 65 years) were treated with an average of 5.58±1.15 mL of HA for the entire perioral area. Treatment areas included NLFs, marionette lines, oral commissures and perioral rhytides. Eighteen of 20 patients received both SGP-HA and LGP-HA. Product was injected into the mid or deep dermis using primarily linear threading and multiple punctate pools. Patients experienced a total of 66 treatment-emergent AEs (TEAEs); each patient experienced at least one TEAE. The reported events in decreasing order of occurrence were bruising, tenderness, swelling, redness, headache and discomfort. Bruising was more common in the NLFs and marionette lines than in the oral commissures and perioral rhytides. Tenderness occurred more often in the perioral rhytides than in the other areas. The maximum intensity of all TEAEs was considered mild. Most TEAEs resolved within seven days, with an average duration of four days. No serious TEAEs occurred during the study. One hundred percent of GAIS evaluations by both investigators and patients indicated improvement, regardless of filler used or area treated.

Conclusion: Both SGP-HA and LGP-HA were found to be safe and effective for the correction of perioral wrinkles and folds, with few differences among treatment areas. Both investigator and patient GAIS evaluations indicated aesthetic improvement after SGP-HA and LGP-HA treatment in the perioral area.


INTRODUCTION

Aging decreases facial volume as fat atrophies and bone is lost, and it also leads to a decline in skin elasticity and muscle tone. In the lower face, aging manifests itself in perioral rhytides, marionette lines, downturned oral commissures and deep nasolabial folds (NLFs).1,2 Restorative procedures using hyaluronic acid (HA) have expanded with the introduction of different injection procedures. Patients are having more facial areas treated in procedures that involve larger volumes of HA and multiple HA products.3 Full correction of folds and wrinkles in one or two visits may delay or replace more invasive surgical options. Results normally last six to 12 months, but may persist up to 18 months with one retreatment.4

Naturally-occurring HA is a soluble biopolymer that may be crosslinked to create polymer gels with improved stability for use as aesthetic dermal fillers. By controlling the degree of crosslinking, particle gels of different sizes and properties
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are produced. Non-animal stabilized HA with small and large gel particles have an excellent safety record. They have been widely evaluated in clinical trials as well as in clinical practice, where more than one million aesthetic HA procedures are performed yearly. Immediate postprocedure adverse events (AEs) are typically localized and transient. Local AEs are typically related to the injection procedure rather than to the intrinsic properties of the HA. The incidence of treatment-emergent AEs (TEAEs) increases with increasing HA volume, rapid injection speed and flow rates, and fanlike needle use; however, no correlation with TEAEs has been seen for multiple punctures, injection depth, or gel-particle size. Common TEAEs typically include bruising, tenderness, edema and pain. Many variables contribute to successful outcomes with HA treatments, including product selection, the minimization of AEs, and technique. Technique encompasses injector experience, knowledge of facial anatomy, degree of correction and establishment of patient expectations. Often in well-controlled clinical trials, such variables are tightly regulated in order to minimize extraneous outcomes. In this study, the safety and effectiveness of two forms of HA were evaluated under conditions more closely resembling clinical practice than in previous studies.

Due to the rapid evolution of facial procedures involving HA, a study of HA use in the perioral region was conducted to evaluate the safety and effectiveness of small gel-particle HA and large gel-particle HA (SGP-HA, Restylane®; LGP-HA, Perlane®, Medicis Aesthetics, Inc., Scottsdale, AZ) in the lower face. Both products are approved by the US Food and Drug Administration for correction of moderate-to-severe facial wrinkles and folds (e.g., NLFs) with SGP-HA indicated for mid-to-deep dermal implantation and LGP-HA indicated for deep dermis to superficial subcutis implantation. The primary aim of the study was to examine the safety of these products in the treatment of perioral wrinkles and folds. Additionally, their effectiveness was assessed by both the treating investigator and the patient using the Global Aesthetic Improvement Scale (GAIS).

METHODS

Patients
Patients who intended to be treated with HA for perioral wrinkles and folds were recruited at two US centers to participate in an open-label study of SGP-HA and LGP-HA. Patient eligibility was determined by the treating investigator evaluating

three bilateral wrinkle pairs and upper perioral rhytides using two visual scales: A 5-grade Wrinkle Severity Rating Scale (WSRS) was used to evaluate bilateral NLFs, and a 6-grade Wrinkle Severity (WS) scale was used to evaluate bilateral oral commissures, bilateral marionette lines and upper perioral rhytides. Patients with bilateral marionette lines and upper perioral rhytides with moderate (3) or severe (4) WS scores were eligible for treatment; treatment of oral commissures and NLFs was optional. Screening was conducted within 14 days prior to treatment and included recording of medical history and obtaining informed consent. Patients were required to be 18 to 65 years of age; both men and nonpregnant, non-breast-feeding women could participate in the study. Patients with active or chronic skin disease and inflammation or related condition in the perioral area were excluded, along with patients who had undergone laser or chemical peels within six months prior to the study, who had received any facial tissue augmentation with nonpermanent filler or aesthetic facial surgical therapy within nine months prior to the study, or who had permanent implants in the perioral area.

Treatment

Wrinkles with WSRS/WS scores of 3 or 4 were eligible for treatment, with a maximum of three bilateral wrinkle pairs plus perioral rhytides treated per patient. Treatment was administered at baseline (day 0) to achieve optimal correction with either the SGP-HA or LGP-HA. Product selection and use was at the discretion of the treating investigator. A patient could receive both products but only one product per wrinkle; layering of products at a single site was not permitted. Touch-up of each wrinkle with the product received at baseline was provided at day 14±3 as needed to achieve optimal correction. If the patient received any touch-up injections, a third visit was scheduled two weeks after the touch-up treatment (day 28±3). The recommended maximum dose per patient was 6.0 mL per treatment session. Ice and lidocaine 4% cream were available for use at the discretion of the treating investigator for swelling prevention and prophylactic pain relief, respectively.

Assessment

The primary endpoint of safety was assessed by evaluating all local and systemic AEs at all visits. Event severity and relatedness of the event to the study device were determined by the treating investigator. Secondary endpoints of effectiveness were determined by assessing appearance on day 14 after treatment or touch-up relative to pretreatment using the 7-grade GAIS (3, very much improved; 2, much improved; 1, improved; 0, no change; -1, worse; -2, much worse; -3, very much worse). The treating investigator and the patient reviewed pretreatment photographs to aid in their GAIS assessments. Follow-up photographs were taken two weeks after the final injection. Improvements were defined as a
GAIS score of 1–3 (improved, much improved, or very much improved) for each treated site (i.e., marionette lines, upper perioral rhytides, oral commissures and NLFs).

**Statistical Methods**
Descriptive statistics were used to summarize TEAEs. TEAEs were reported as the overall incidence of at least one event and by body system; TEAEs were summarized by severity and by relationship to study product. Each patient contributed only once to each rate regardless of the number of occurrences experienced.

Descriptive statistics were used to evaluate treatment effectiveness by treating investigator assessment and patient assessment on the GAIS. No considerations were made for missing effectiveness data.

**RESULTS**

Demographics
This study evaluated 20 patients with a mean age of 59.6 years (range, 49 to 65 years). All patients were female and white; four were Hispanic or Latino.

Effectiveness
The treating investigators assessed all 20 patients as responders with at least a 2-grade improvement in GAIS; additionally, all 20 patients reported at least a 2-grade improvement in GAIS based on self-assessment (Table 1). The treating investigator mean post-treatment GAIS score was 2.90 (SD=0.31); the patient mean post-treatment GAIS score was 2.75 (SD=0.44).

Product Selection and Implantation
LGP-HA was frequently used to treat NLFs and marionette lines, whereas SGP-HA was almost exclusively selected to treat oral commissures and perioral rhytides (Figure 1). Most areas were treated using linear threading and multiple punctate pools, with injection depth ranging from mid to deep dermis to subcutaneous (Table 2). Patients received on average 2.94 mL (range, 1.5 mL to 5.3 mL) of SGP-HA and 2.93 mL (range, 1.0 mL to 5.6 mL) of LGP-HA to the entire face. Overall, the mean total amount of dermal filler (SGP-HA and LGP-HA) was 5.58 mL for the entire face. Slightly more than half of the patients (12/20) received

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**TABLE 1.**

<table>
<thead>
<tr>
<th>GAIS Evaluations</th>
<th>Very Much Improved (3 points)</th>
<th>Much Improved (2 points)</th>
<th>Improved (1 point)</th>
<th>No Change (0 points)</th>
<th>Worse (-1 point)</th>
<th>Much Worse (-2 points)</th>
<th>Very Much Worse (-3 points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Treating investigator</td>
<td>18 (90%)</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Patient</td>
<td>15 (75%)</td>
<td>5 (25%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Abbreviation: GAIS, Global Aesthetic Improvement Scale.

**FIGURE 1.** Number of patients receiving treatment by facial area and product type.

Abbreviations: LGP-HA, large gel-particle hyaluronic acid; NLF, nasolabial fold; SGP-HA, small gel-particle hyaluronic acid.

**TABLE 2.**

<table>
<thead>
<tr>
<th>Injection Techniques by Facial Area*</th>
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</thead>
<tbody>
<tr>
<td>Presentation</td>
</tr>
<tr>
<td>NLFs</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Marionette lines</td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Oral commissure</td>
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<td></td>
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<tr>
<td>Upper and lower perioral rhytides</td>
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<td></td>
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</tbody>
</table>

*Touch-up treatments were consistent with the method of initial treatment. Abbreviation: NLF, nasolabial fold.
TABLE 3.

<table>
<thead>
<tr>
<th>Injection Volumes</th>
<th>Statistic</th>
<th>SGP-HA (mL)</th>
<th>LGP-HA (mL)</th>
<th>Total (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location*</td>
<td>n</td>
<td>Mean (SD)</td>
<td>Median (min, max)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Entire face (initial + touch-up)</td>
<td>20</td>
<td>2.94 (1.09)</td>
<td>2.5 (1.5, 5.3)</td>
<td>5.58 (1.15)</td>
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<td>Initial treatment</td>
<td>20</td>
<td>2.44 (1.23)</td>
<td>2.0 (1.0, 4.0)</td>
<td>4.48 (0.87)</td>
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<td>Touch-up treatment</td>
<td>12</td>
<td>0.84 (0.26)</td>
<td>1.3 (0.6, 1.9)</td>
<td>2.2 (0.3)</td>
</tr>
<tr>
<td>NLFs (initial + touch-up)</td>
<td>6</td>
<td>1.67 (0.54)</td>
<td>1.3 (0.8, 3.0)</td>
<td>1.9 (0.69)</td>
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<tr>
<td>Marionette lines (initial + touch-up)</td>
<td>5</td>
<td>1.42 (0.59)</td>
<td>1.8 (0.7, 2.6)</td>
<td>1.6 (0.64)</td>
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<tr>
<td>Oral commissures (initial + touch-up)</td>
<td>18</td>
<td>1.65 (0.61)</td>
<td>1.9 (1.21)</td>
<td>1.77 (0.61)</td>
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<tr>
<td>Upper and lower perioral rhytides (initial + touch-up)</td>
<td>20</td>
<td>0.6 (0.39)</td>
<td>0.5 (0.2, 1.6)</td>
<td>0.6 (0.39)</td>
</tr>
</tbody>
</table>

*Patients may have received Restylane®, Perlane®, or both products, but each separate wrinkle could be treated with only one product. Abbreviations: LGP-HA, large gel-particle hyaluronic acid; NLF, nasolabial fold; SD, standard deviation; SGP-HA, small gel-particle hyaluronic acid

Safety

A total of 66 TEAEs were experienced by 20 patients (Table 4). Every patient experienced at least one TEAE, but all were characterized as mild. The most common TEAEs were bruising (n=19), tenderness (n=10), swelling (n=8) and redness (n=4). Two events of headache (3%) had an unknown relationship to the treatment. Eleven events of bruising, two events of swelling, and one event of discomfort were considered to be related to the study device, and all other events were not related to the study device. The average duration of the TEAEs was four days.

DISCUSSION

The frequency, severity and duration of TEAEs experienced by patients treated with HA fillers under conditions resembling clinical practice are consistent with those reported in previous clinical studies. The mild severity and transient nature of TEAEs experienced by patients in this study confirm the overall safety of SGP-HA and LGP-HA for correction of perioral wrinkles and folds. While the study sample size was not large enough to draw conclusions regarding the impact that specific injection techniques have on the incidence of TEAEs, a variety of injection methods using these products appear to be very well tolerated and consistent with other reports. Unexpected complications with HA fillers are uncommon, and none occurred in this study. The different injection techniques and the ability of the treating investigator to determine which product to use based on wrinkle severity produced successful outcomes as measured by patient and investigator GAIS assessments.

While the treating investigators employed different injection techniques and depths, both used similar volumes of products, experienced comparable rates of TEAEs and produced excellent outcomes. The treating investigators also were consistent in their choice of product by treatment area. Perioral rhytides were exclusively treated with SGP-HA, and the majority of the injections were into the mid dermis; oral commissures were similarly treated. More LGP-HA was used to treat marionette lines and NLFs, and injections to these areas tended to be deeper (Figure 1, Table 2).

The treatment goal was to obtain full correction of wrinkles in the perioral region in either one or two visits. Slightly more than
half of the patients received touch-up injections at their two-week return visit, with approximately 20% of the total product volume being used for the touch-up injections. From these results, it is apparent that many patients would benefit from follow-up visits. Follow-up visits also provide an additional opportunity for the monitoring of TEAEs.

In conclusion, SGP-HA and LGP-HA were shown to be safe and effective for correction of NLFs, marionette lines, oral commissures and perioral rhytides when variable injection methods were utilized. The methods used in this study followed the recommendations detailed in previous reports and exemplify the versatility of SGP-HA and LGP-HA as well as injector approach in achieving good aesthetic outcomes.¹,²

**DISCLOSURES**

[AUS: PLEASE PROVIDE ALL RELEVANT FINANCIAL DISCLOSURES, OR STATE IF NONE]
REFERENCES


4. Narins RS, Dayan SH, Brandt FS, Baldwin EK. Persistence and improvement of nasolabial fold correction with nonanimal-stabilized hyaluronic acid 100,000 gel particles/mL filler on two retreatment schedules: Results up to 18 months on two retreatment schedules. Dermatol Surg. 2008;34(suppl 1):S2-S8S.


