# Safety and Efficacy of Facial Rejuvenation with Small Gel Particle Hyaluronic Acid with Lidocaine and AbobotulinumtoxinA in Post-Chemotherapy Patients

## A Phase IV Investigator-initiated Study

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## ABSTRACT

**Background:** Due to advances in detection and treatment, approximately 70 percent of cancer patients are living more than five years after diagnosis. Research indicates that appearance worries are of great concern to cancer survivors impacting their quality of life. This is the first Phase IV investigator-initiated study to investigate the safety and efficacy of facial rejuvenation with small gel particle hyaluronic acid with lidocaine and abobotulinumtoxinA in post-chemotherapy patients. **Methods:** The safety and efficacy of facial rejuvenation with small gel particle hyaluronic acid with lidocaine and abobotulinumtoxinA was assessed in nine post-chemotherapy patients. Efficacy of small gel particle hyaluronic acid with lidocaine and abobotulinumtoxinA was measured at baseline, Week 2, and Week 8, using a wrinkle severity assessment score. Safety and tolerability of both products were assessed throughout the study by monitoring the occurrence of adverse events. **Results:** Patients received a mean total of 2.4mL of small gel particle hyaluronic acid with lidocaine in the nasolabial folds and 57.8 Units of abobotulinumtoxinA to glabellar lines at baseline. Additionally, at Week 2, a mean total 1.0mL of small gel particle hyaluronic acid with lidocaine was administered to four patients. The mean investigator's wrinkle severity assessment score at baseline was 2.22, indicating mild-to-moderate severity. At each of Weeks 2 and 8, there were significant improvements from baseline in wrinkle severity ($p$=0.004). Overall, small gel particle hyaluronic acid with lidocaine was well tolerated. Adverse events (i.e., bruising, redness, swelling, pain, tenderness, itching or other adverse events) were localized, self-limiting, and resolved within 1 to 2 days. The only adverse event attributed to abobotulinumtoxinA was soreness and slight tenderness at an injection site reported in one patient. **Conclusion:** Both study products were well tolerated in post-chemotherapy patients with no significant adverse events. There was a clinically meaningful and statistically significant improvement in wrinkle severity at Week 2 post-administration as compared to baseline. This improvement was maintained in all patients at Week 8.
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Because of advances in early detection and treatment, cancer has become a curable disease for some and a chronic illness for others.[1] The number of people living with cancer increased from three million (1.5% of the US population) in 1971 to 9.8 million (3.5%) in 2001. Approximately 70 percent of cancer patients are living more than five years after diagnosis. This growing number of people living with cancer poses challenges for researchers to understand the physical, psychosocial, and economic effects of surviving cancer and for healthcare practitioners to promote the health and wellbeing of cancer survivors.[1]

There is significant evidence that cancer treatments

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themselves may have long-term physical effects that can adversely influence quality of life, particularly the physical, emotional, social, and sexual wellbeing among cancer patients.[2–5] Rapid proliferation is not only a hallmark of the cancer disease process, it is also a property of the dermatological system.[6] Interfering with malignant cell growth may lead to alopecia, skin changes, and nail alterations. Although much research has been conducted to recognize and manage toxicities associated with chemotherapy, adverse events affecting the skin, hair, and nails have not attracted the same interest.[7] The introduction of newer chemotherapeutic agents that may induce dermatological toxicities in cosmetically sensitive areas has increased the importance of monitoring dermatological health in cancer patients. Minimization or avoidance of these side effects is critical to maintain quality of life (QoL) and consistent anticancer therapy and optimize clinical outcome.[7]

Long-term cancer survivors are concerned with some of the same issues as were salient at the time of diagnosis and treatment, but other issues emerge or are heightened, such as appearance and body-image concerns.[4] Research indicates that outside of their cancer returning, cancer survivors consider financial problems and appearance worries to be their greatest concerns.[2]

Facial rejuvenation procedures requiring the use of needle-based injections is progressively increasing due to their safe and effective results.[8] Of these injections, botulinum toxins and injectable hyaluronic acid dermal fillers are most often used either alone or in combination.[9,10]

Most cancer survivors have a post-treatment desire to improve their appearance in order to resume their lives looking at least as good as they did prior to chemotherapy. Interestingly, the age category of women with the highest incidence of breast cancer parallels the patient population that is the highest utilizer of aesthetic procedures. Facial rejuvenation with dermal fillers and botulinum toxin in the cancer survivor population is in demand both in the group that had previously received injectable treatment prior to their cancer diagnosis and in the group that were naïve.

Although the safety profiles of these injectable products used for facial rejuvenation have been extensively studied, there are no reports about the safety and efficacy in cancer survivors. The purpose of this study is to establish the safety and efficacy of a small gel particle hyaluronic acid with lidocaine dermal filler (SGP-HA-L) and abobotulinumtoxinA (BoNTA-ABO) used in combination in the post-chemotherapy patient.

## METHODS

This study was submitted and approved by the Investigational Review Board of Quorum Review. All patients enrolled were randomized and assigned a patient identification code.

Ten post-chemotherapy patients who have gone a minimum of six months post-chemotherapy treatment, were treated with small gel particle hyaluronic acid [Restylane-L™ (Medicis Aesthetics Inc, Scottsdale, Arizona)] in the nasolabial folds to full correction, and abobotulinumtoxinA [Dysport™ (Medicis Aesthetics Inc)] in the glabella. Safety and efficacy assessments were performed at baseline and at the two-week and eight-week post-treatment visits with the primary efficacy endpoint measured at eight weeks.

Male or female patients who met all of the following criteria were eligible for this study: eighteen years of age or older, post-chemotherapy treatment for equal to or greater than six months, negative urine pregnancy test result for female patients of childbearing potential, time and ability to complete the study and comply with instructions, subjects seeking augmentation in the nasolabial fold with a dermal filler, and subjects seeking correction of glabellar lines and wrinkles with botulinum toxin. Patients who met any of the following criteria were excluded from the study: a history of allergy or hypersensitivity to injectable hyaluronic acid gel, local topical or nerve-blocking agents, or botulinum toxin; the use of platelet inhibitors or anticoagulant agents within a clinically relevant period before study entry; a history of severe allergies or multiple allergies manifested by anaphylaxis; the presence of any condition, which in the opinion of the investigator, makes the subject unable to complete the study per protocol; concurrent therapy that, in the investigator's opinion, would interfere with the evaluation of the safety and tolerability of the treatment; active infection in the glabellar area or nasolabial folds; pregnant or nursing women; or current history of drug or alcohol abuse.

At the baseline visit, SGP-HA-L was administered to the nasolabial folds utilizing linear retrograde threading, linear antegrade threading, and serial puncture techniques. BoNTA-ABO was reconstituted with 0.9% sterile saline without preservatives and patients were injected with a 30g ½-inch needle into the glabellar area.

A touch-up session at two weeks post-treatment was optional based on investigator assessment to assure optimal correction. Optimal correction was defined as the best possible aesthetic result that could be obtained for an individual study participant as agreed upon by the physician and subject. Subjects were not required to receive unnecessary injections if optimal correction was achieved with the baseline visit. Patients were required to make an eight-week final visit.

The efficacy of SGP-HA-L and BoNTA-ABO in the post-chemotherapy patient was measured at baseline, Week 2, and Week 8, using a wrinkle severity assessment score indicating mild-to-moderate severity (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) for both the glabella and nasolabial folds.

The safety and tolerability of SGP-HA-L and BoNTA-ABO in the post-chemotherapy patient population were assessed throughout the study by monitoring the occurrence of adverse events. Safety evaluations included an interview with the subject at each visit by the investigator or coordinator to elicit information about any medical occurrence that may be considered an adverse event. Additionally, subjects were required to fill out a diary for seven days after baseline visit and for seven days after an

| TABLE 1. Patient demographics | |
|---|---|
| | N (%) |
| **AGE (YRS)** | |
| N | 10 |
| Mean (SD) | 52.0 (7.33) |
| Median | 51.0 |
| Interquartile range | 49–57 |
| Range | 39–63 |
| **RACE** | |
| Non-Hispanic | 10 (100.0) |
| **ETHNICITY** | |
| Caucasian | 10 (100.0) |
| **TYPE OF CANCER TREATED** | |
| Breast cancer | 9 (90) |
| Non-Hodgkin's Lymphomas | 1 (10) |

| TABLE 2. Drug administration | | | | |
|---|---|---|---|---|
| | BASELINE (N = 9) (%) | | WEEK 2[1] (N = 4) N | (%) |
| **TOTAL DOSE SGP-HA-L (mL)** | | | | |
| Mean (SD) | 2.4 | (0.50) | 1.0 | (0.06) |
| Median | 2.7 | | 1.0 | |
| Interquartile range | 2.0 | - 2.8 | 0.9 | - 1.0 |
| Range | 2 | - 3 | 1 | - 1 |
| **TOTAL DOSE BoNTA-ABO, GLABELLA (UNITS)** | | | | |
| Mean (SD) | 57.8 | (4.41) | 0 | |
| Median | 60.0 | | 0 | |
| Interquartile range | 60.0 | - 60.0 | 0 | |
| Range | 50 | - 60 | 0 | |

[1]Week 2 dosing not applicable for BoNTA-ABO

optional touch-up visit.

Photographs were taken at the baseline visit prior to injection with SGP-HA-L and BoNTA-ABO, and post-injection at the baseline, two-week, and eight-week visits. Diaries were collected at Week 2. All subjects received a follow-up call 24 hours post-injections.

**Statistical methods.** Descriptive statistics (mean, standard deviation, median, interquartile range, and range) were calculated for continuous variable (age); race, ethnicity, and childbearing potential were summarized as number (%) of patients enrolled. Descriptive statistics for the amount of drug administered were also calculated separately for SGP-HA-L (left, right, and total) and BoNTA-ABO at baseline and Week 2 (Restylane only).

Means, medians, and standard deviations were calculated for both observed wrinkle scores as well as for changes from baseline at each time point (baseline, Week 2, Week 8). The *p*-values for comparisons of mean wrinkle scores at Weeks 2 and 8 to those at baseline are from a mixed effects model with random subject effect. The *p*-values for comparisons of mean changes in wrinkle scores to zero at Weeks 2 and 8 are from the sign test. The proportions of patients with improvement of at least 1 point and at least 2 points were summarized at each time point (Week 2 and Week 8).

Adverse events (bruising, redness, swelling, pain, tenderness, itching, and other) were summarized; number (%) of patients with each event and mean (standard deviation) duration of each event in days were calculated. An inability to pull brows together (for Dysport) was summarized; percent of patients and mean (standard deviation) for time since enrollment were calculated. The SAS statistical analysis software (version 9.2) was utilized.

## RESULTS

Patient demographics are listed in Table 1. The mean standard deviation (SD) age of patients enrolled was 52.0 (7.3) years (range 39–63 years). All patients enrolled were Non-Hispanic, Caucasian women. The majority of patients had a history of breast cancer. Only one patient (10%) was of child-bearing potential. Enrolled patients reported taking the following medications at the time of the study: multivitamins, alendronate, anastrozole, buproprion, levothyroxine, tamoxifen, acetaminophen and hydrocodone (Vicodin™), alprazolam, calcium, vitamin D, and magnesium.

A total of nine patients completed the study. One patient dropped out due to inability to comply with multiple visits. At baseline, the mean total amount of SGP-HA-L used for treatment of both left and right nasolabial folds was 2.4mL (Table 2). Additionally, at Week 2, the mean of 1.0mL of SGP-HA-L was administered to four patients for touch-up. Patients were administered an average of 57.8 Units of

**TABLE 3. Mean observed and change from baseline in wrinkle assessment**

| WEEK | n | MEAN (SD)<br>MEDIAN (RANGE) |
|---|---|---|
| **BASELINE** | | |
| Observed | 9 | 2.22 (0.972) |
| | | 2.00 (1.0, 4.0) |
| **WEEK 2** | | |
| Observed | 9 | 0.89 (0.601) |
| | | 1.00 (0.0, 2.0) |
| Change | 9 | -1.33 (0.500) |
| | | -1.00 (-2.0, -1.0) |
| **WEEK 8** | | |
| Observed | 9 | 0.89 (0.601) |
| | | 1.00 (0.0, 2.0) |
| Change | 9 | -1.33 (0.500) |
| | | -1.00 (-2.0, -1.0) |

BoNTA-ABO in the glabellar at baseline. No further administration of BoNTA-ABO was performed.

**Efficacy.** The mean (SD) investigator's wrinkle severity assessment score at baseline was 2.22 (0.97), indicating mild-to-moderate severity. At each of Weeks 2 and 8, the mean improvement (SD) from baseline in wrinkle severity was 1.33 (0.5), $p$=0.004 (Table 3, Figure 1).

The mean (SD) wrinkle scores at Week 2 and Week 8 were 0.89 (0.6) for both weeks; the mean scores at both Week 2 and Week 8 were statistically significantly lower than those at baseline ($p$<0.0001 for both Week 2 and Week 8), (Figure 1).

At Week 2, improvement in wrinkle severity of at least one point was observed in all nine patients and was maintained at Week 8 for all nine patients (Table 4). At Week 2, the improvement in wrinkle severity of two points or more was observed in three (33.3%) patients. For all three patients, this improvement was maintained at Week 8.

The individual efficacy of SGP-HA-L was measured by assessment of nasolabial wrinkles. Mean nasolabial wrinkle scores were 2.44 (baseline), and 0.89 at Weeks 2 and 8. The individual efficacy of BoNTA-ABO was measured by assessment of glabella wrinkles. Mean glabella wrinkle scores were 2.22 (baseline) and 0.67 at Weeks 2 and 8. Each product improved its respective area equal to the others (i.e., improved by approximately one and a half points on the wrinkle-assessment scale). Wrinkles that were rated as mild to moderate at baseline were scored none to minimal by Week 2 and remained so through Week 8.

Discussions with the patients regarding quality of life and

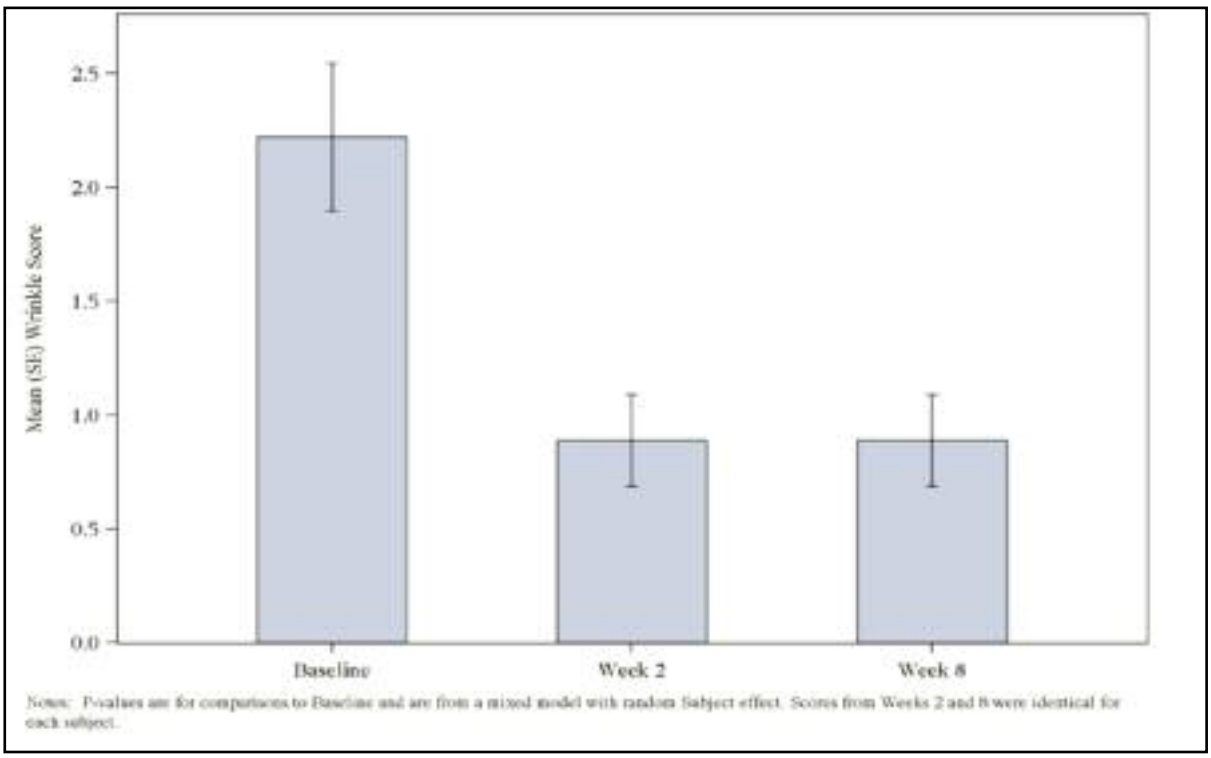


**Figure 1.** Wrinkle score by time since injection (N=9)

| TABLE 4. Wrinkle assessment levels of change by week | |
|---|---|
| | n (%) |
| Week 2 change from Baseline ≤ -1 | 9 (100.0) |
| Week 2 change from Baseline ≤ -2 | 3 (33.3) |
| Week 8 change from Baseline ≤ -1 | 9 (100.0) |
| Week 8 change from Baseline ≤ -2 | 3 (33.3) |

patient affect were documented at each visit. All subjects were satisfied with the results of their procedure and reported dramatic improvement of their appearance. Examples of patient quotes recorded in the subjects' source document include the following: "You have given me my femininity back and I feel so much better when I get dressed to go out. I am no longer ashamed of my appearance," and "I can really put the cancer behind me now," and "Now, I can look as well as I feel."

**Safety.** Safety evaluations were recorded based on patient interviews and diaries. A summary of adverse events is presented in Table 5. Overall, SGP-HA-L was well tolerated. The majority of patients experienced at least one short-term adverse event defined as lasting 1 to 2 days. These adverse events included bruising, redness, swelling, pain tenderness, and itching. The only report of adverse events with BoNTA-ABO was one patient who reported "sore and slight tenderness" at injection site. Adverse events were similar to those reported in non-chemotherapy patients.

Patients were assessed at Weeks 2 and 8 for any additional adverse events, such as long-term discoloration or any other epidermal changes. By reviewing baseline photographs at each visit, no subject demonstrated any additional adverse events.

| TABLE 5. SGP-HA-L adverse events | | | |
|---|---|---|---|
| | | Yes/No | Duration (days) |
| Adverse Event | N | n (%) | Mean (SD) |
| Bruising | 8 | 7 (87.5) | 1.5 (1.85) |
| Redness | 9 | 3 (33.3) | 0.3 (0.50) |
| Swelling | 8 | 4 (50.0) | 0.6 (0.74) |
| Pain | 9 | 3 (33.3) | 0.3 (0.50) |
| Tenderness | 8 | 6 (75.0) | 1.4 (1.60) |
| Itching | 9 | 3 (33.3) | 0.3 (0.50) |
| Other | 8 | 2 (25.0) | 0.3 (0.46) |

## DISCUSSION

Researchers and clinicians are increasingly aware of the importance of quality-of-life considerations among long-term cancer survivors.[3–5,11] Quality-of-life assessments can help identify long-term sequelae that clinicians should monitor and can identify areas where additional services or interventions may be needed. Although it is often assumed that medical variables during treatment are the key influences on long-term quality of life, this does not seem to be the case. In one study, concern about appearance was a key determinant of quality of life in cancer survivors.[2]

Research indicates that facial rejuvenation results in significantly better self-esteem and components of quality of life in non-cancer patients.[12] In addition, facial rejuvenation may contribute to improvements in physical health, mood, household activities, overall life satisfaction, body-appearance satisfaction, self-consciousness, perceived self-intellect, self-worth, appearance, comprehension, satisfaction with weight, attractiveness, a sense of doing well, appearance-related self-esteem, social-related self-esteem, and performance-related self-esteem.

Limitations of this study include small sample size and lack of control group.

In this study, patients received combination treatment with abotulinumtoxinA and small gel particle hyaluronic acid with lidocaine. There is currently an increased trend in the combined use of these products. It is suggested that combination treatment with botulinum toxin and dermal fillers may produce a more natural and refined outcome.[13] With dermal fillers, volume is restored, which may be lost due to the natural aging process and/or weight loss as a result of the cancer disease process or undergoing chemotherapy. Botulinum toxin decreases muscle movement. This dual-step approach may be effective in reshaping and contouring the face. By combining botulinum toxin and dermal fillers, both the dynamic and static components of rhytids may be corrected.

## CONCLUSION

The author's findings indicate that both study products were well tolerated in post-chemotherapy patients. There

was a clinically meaningful and statistically significant improvement in wrinkle severity at Week 2 post-administration as compared to baseline in both glabella and nasolabial folds. This improvement was maintained in all patients at Week 8.

To our knowledge, this is the first Phase IV investigator-initiated study that assessed the safety and efficacy of facial rejuvenation with SGP-HA-L and BoNTA-ABO in post-chemotherapy patients. Further studies should be conducted to determine the full benefit of this therapy in cancer survivors.

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