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FINAL REPORT

**A Double-blind, Randomized, Multi-center Evaluation of the Safety and Efficacy
of Hylaform[®] Viscoelastic Gel as Compared to Zyplast[®] Collagen Implant in
Patients Undergoing Cutaneous Correction of Nasolabial Folds**

Study Number: HYLA-001-01

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This study was designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in U.S. federal regulations as well as "Guidance for Good Clinical Practice," International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

2. SYNOPSIS

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<p>TITLE OF STUDY: A Double-blind, Randomized, Multi-center Evaluation of the Safety and Efficacy of Hylaform® Viscoelastic Gel as Compared to Zyplast® Collagen Implant in Patients Undergoing Cutaneous Correction of Nasolabial Folds (Protocol HYLA-001-01)</p>				
<p>INVESTIGATORS:</p> <table border="0"> <tr> <td data-bbox="384 861 938 1085"> <p>Site 1 [REDACTED]</p> <p>Site 2 [REDACTED]</p> <p>Site 3 [REDACTED]</p> <p>Site 4 [REDACTED]</p> <p>Site 5 [REDACTED]</p> </td> <td data-bbox="938 861 1452 1085"> <p>Site 6 [REDACTED]</p> <p>Site 7 [REDACTED]</p> <p>Site 8 [REDACTED]</p> <p>Site 9 [REDACTED]</p> <p>Site 10 [REDACTED]</p> </td> </tr> </table>			<p>Site 1 [REDACTED]</p> <p>Site 2 [REDACTED]</p> <p>Site 3 [REDACTED]</p> <p>Site 4 [REDACTED]</p> <p>Site 5 [REDACTED]</p>	<p>Site 6 [REDACTED]</p> <p>Site 7 [REDACTED]</p> <p>Site 8 [REDACTED]</p> <p>Site 9 [REDACTED]</p> <p>Site 10 [REDACTED]</p>
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<p>STUDY CENTER(S):</p> <table border="0"> <tr> <td data-bbox="384 1127 938 1681"> <p>Site 1 [REDACTED] Miami, FL 33125-1600</p> <p>Site 2 [REDACTED] New York, NY 10028</p> <p>Site 3 [REDACTED] San Francisco, CA 94117-3685</p> <p>Site 4 [REDACTED] Beverly Hills, CA 90210-5027</p> <p>Site 5 [REDACTED] Santa Monica, CA 90404-2115</p> </td> <td data-bbox="938 1127 1452 1681"> <p>Site 6 [REDACTED] San Francisco, CA 94102</p> <p>Site 7 [REDACTED] Dallas, TX 75320</p> <p>Site 8 [REDACTED] Birmingham, AL 35205</p> <p>Site 9 [REDACTED] Miami, FL 33156</p> <p>Site 10 [REDACTED] New York, NY 10016</p> </td> </tr> </table>			<p>Site 1 [REDACTED] Miami, FL 33125-1600</p> <p>Site 2 [REDACTED] New York, NY 10028</p> <p>Site 3 [REDACTED] San Francisco, CA 94117-3685</p> <p>Site 4 [REDACTED] Beverly Hills, CA 90210-5027</p> <p>Site 5 [REDACTED] Santa Monica, CA 90404-2115</p>	<p>Site 6 [REDACTED] San Francisco, CA 94102</p> <p>Site 7 [REDACTED] Dallas, TX 75320</p> <p>Site 8 [REDACTED] Birmingham, AL 35205</p> <p>Site 9 [REDACTED] Miami, FL 33156</p> <p>Site 10 [REDACTED] New York, NY 10016</p>
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<p>PUBLICATION (REFERENCE): None to date.</p>				
<p>STUDIED PERIOD: Initial Phase: 12 June 2002 (first patient enrolled) to 30 April 2003 (final 12-week visit) Repeat Treatment Phase: 2 April 2003 to 30 May 2003, the cutoff date for the last patient visit for the 4-week safety report. The 12-week repeat treatment phase is currently ongoing, and safety and efficacy data will be reported in a subsequent report.</p>				

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<p>PHASE OF DEVELOPMENT: Phase III, Pivotal Trial (US)</p>		
<p>OBJECTIVES:</p> <p>Initial Phase: The primary objectives were (1) to evaluate the efficacy (non-inferiority) of Hylaform viscoelastic gel for the correction of nasolabial folds as compared with Zyplast collagen implant, and (2) to evaluate the safety of Hylaform as compared with Zyplast. The secondary objective was to evaluate the clinical utility of Hylaform with respect to physician assessment and patient self-assessment.</p> <p>Repeat Treatment Phase: The primary objectives were (1) to evaluate the safety of repeat treatment with hylan B viscoelastic products*, and (2) to evaluate the efficacy (non-inferiority) of Hylaform Plus** versus Hylaform viscoelastic gel for the correction of nasolabial fold contour defects. The secondary objectives were (1) to determine safety through 12 weeks post treatment by the rates of adverse events associated with repeat treatment with Hylaform and Hylaform Plus and by the presence or absence of a potential immune response to hylan B gel as measured by the development of hylan B IgG antibody titers after repeat device implantation, and (2) to evaluate the clinical utility of Hylaform Plus and Hylaform with respect to physician assessment and patient self-assessment.</p> <p>*As proposed at a meeting with FDA on 5 March 2003, an interim safety summary for 4 weeks of repeat treatment is included in this report. Safety and efficacy results through 12 weeks will be provided in a separate report.</p> <p>**Hylaform and Hylaform Plus are composed of the same material but have slightly different median particle sizes (Hylaform ~ 500 microns; Hylaform Plus ~ 700 microns).</p>		
<p>METHODOLOGY:</p> <p>Initial Phase</p> <p>This was a double-blind, randomized, multicenter study involving patients receiving treatment for cutaneous correction of nasolabial folds. Eligible patients signed an IRB-approved informed consent form, underwent a physical examination and nasolabial fold assessment, had facial photographs taken, and had blood samples collected for hylan B IgG antibody titers and routine clinical laboratory testing. In addition, women of childbearing potential underwent a urine pregnancy test. During the 6-week screening period of the initial phase of the study, patients underwent double collagen skin testing and evaluation to screen for possible hypersensitivity to bovine collagen implants, eg, Zyplast, the control treatment. Eligible patients were randomly assigned to receive treatment with either Hylaform or Zyplast. Patients were blindfolded for treatment and remained blinded to study treatment throughout the study. Both nasolabial folds were corrected during the study procedure at Visit 3. Patients were observed for 30 minutes after implantation for any adverse events. Safety and efficacy assessments occurred at 3 days (Visit 4) and 2 weeks (Visit 5) after implantation and at 3 days after touch-up treatment (Visit 6). A touch-up, if required, was to occur at Visit 5. Adverse events and concomitant medications, patient's facial photographs, patient global assessment, investigator's global assessment (overall appearance of wrinkles), and investigator's live assessment using a 6-point grading scale occurred at 4 weeks (Visit 7), 8 weeks (Visit 9), and 12 weeks (Visit 11) after implantation for patients not receiving a touch-up and at 2 weeks (Visit 7), 4 weeks (Visit 8), 8 weeks (Visit 10), and 12 weeks (Visit 12) after the touch-up. A blinded independent panel of board-certified dermatologists reviewed, in random order, and scored the</p>		

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<p>patient photographs at the conclusion of the initial phase efficacy time period. Sunlight exposure and smoking history were collected prior to initial implantation and at the final visit. Clinical laboratory tests and serum antibody samples were collected at designated visits.</p> <p>Repeat Treatment Phase Patients receiving Hylaform during the initial phase of the study were eligible to enroll in the repeat treatment phase of the study. Eligible patients signed an IRB-approved informed consent form for the repeat treatment, underwent a physical examination and nasolabial fold assessment, had facial photographs taken, and had blood samples collected for hylan B IgG antibody titers and routine clinical laboratory testing. In addition, women of childbearing potential underwent a urine pregnancy test. Patients were randomly assigned (right/left randomization schedule) to receive Hylaform Plus in one nasolabial fold and Hylaform in the opposite nasolabial fold. A touch-up option was not offered in the repeat treatment phase; the investigator attempted to achieve optimal correction of each nasolabial fold in a single repeat treatment visit. As in the initial phase, the patient was blinded to study treatment throughout the repeat treatment phase. Patients were observed for 30 minutes after implantation and any adverse events were documented. Procedure-related events were documented at the repeat treatment visit and at 3 days after repeat treatment. Patients maintained a diary of their observations of the treatment site for 7 days following the treatment. Safety (adverse events, concomitant medications) data were collected at 3 days (Visit R2) and at 2, 4, 8, and 12 weeks (Visits R3 to R6) after the repeat treatment. Blood samples were collected prior to and at 4 and 12 weeks after repeat treatment to determine the presence or absence of hylan B IgG antibody titers and to assess hematology and chemistry values. Any unusual signs or symptoms were to be reported to the investigator throughout the study.</p> <p>Efficacy assessments, the same as those described for the initial phase, were also conducted through 12 weeks post repeat treatment. The repeat treatment phase of this trial will be reported in 2 parts. The first part will focus on the safety of repeat treatment with Hylaform products through 4 weeks; these results are reported in this report. The second part will include results of the efficacy of Hylaform Plus compared to Hylaform, and on safety of Hylaform Plus through 12 weeks. Those data will be reported separately at the completion of the repeat treatment phase of the study.</p>		
<p>NUMBER OF PATIENTS (PLANNED AND ANALYZED):</p> <p>Initial phase: 250 planned (125 in each group); 261 randomized and treated (133 in the Hylaform group and 128 in the Zyplast group)</p> <p>Repeat Treatment Phase: 133 planned; 96 randomized and treated</p>		
<p>DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:</p> <p>INCLUSION: Initial Phase Patients who met all of the following inclusion criteria were eligible to participate in the initial phase of the study:</p> <ul style="list-style-type: none"> • Men or women, 30 years or older but less than or equal to 55 years of age • Negative skin test to Collagen Test Implant • Two fixed facial sites, fully visible bilateral nasolabial folds, which were both 		

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<p>candidates for correction by the procedure described in the protocol</p> <ul style="list-style-type: none"> • Wrinkle severity score of 3 or 4 on the 6-point grading scale at the areas to be treated • If female and of childbearing potential, had a negative urine pregnancy test, agreed to use oral contraceptives for at least 1 month prior to treatment and for the duration of the study, or agreed to use 2 forms of contraception (eg, condoms plus spermicide), or was surgically sterile, or postmenopausal for at least 1 year • Ability to understand and comply with the requirements of the study • Willingness and ability to provide written informed consent prior to performance of any study-related procedures • Agreed to refrain from seeking other treatment for this condition without first notifying the investigator <p>EXCLUSION: Initial Phase Patients who met any of the following exclusion criteria were not eligible for participation in the initial phase of the study:</p> <ul style="list-style-type: none"> • Known, prior or present positive skin test to Collagen Test Implant • Personal or family history of collagen vascular disease • Wrinkle severity score of 0, 1, 2, or 5 on the 6-point grading scale at the areas to be treated • Women who are pregnant or lactating • Received prior therapy (eg, dermabrasion, facelift) within 6 months prior to entry into the study; patients restricted from undergoing such therapy throughout study duration • Previous tissue augmentation (bulking agents) for facial wrinkles and scars within 6 months at the proposed injection sites; patients restricted from undergoing tissue augmentation throughout study duration • Previous tissue augmentation with permanent implants (eg, Softform®, silicone); patients restricted from undergoing augmentation with permanent implants throughout study duration • Evidence of scar-related disease or delayed healing activity within the past 1 year; patients with scars were eligible for study entry but scars at the intended treatment sites were not treated • History of keloid formation • Any infection or wound of the face • Allergic history including anaphylaxis or multiple severe allergies, avian-sourced (eg, chicken products) or beef-sourced protein, natural rubber latex, bovine collagen-containing products, lidocaine • Planned relocation making follow-up visits impossible during the course of the study 		

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<ul style="list-style-type: none"> • Aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) within 1 week prior to treatment • Concomitant anticoagulant therapy, antiplatelet therapy, or history of bleeding disorders or connective tissue disease (eg, rheumatoid arthritis, juvenile rheumatoid arthritis, scleroderma, systemic lupus erythematosus) • Over-the-counter wrinkle products (eg, alpha-hydroxy acids) or prescription treatments (eg, Renova, Retin-A, microdermabrasion, chemical peels) within 4 weeks prior to study start; patients restricted from using over-the-counter wrinkle products or prescription treatments throughout study duration • Immunocompromised or immunosuppressed (eg, HIV-positive, transplant recipient, or presently receiving chemotherapy) • Clinically significant organic disease including clinically significant cardiovascular, hepatic, pulmonary, neurologic, or renal disease, or other medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the investigator, precluded participation in the trial or potentially decreased survival • Received any investigational product within 30 days prior to study enrollment; patient could not receive other investigational products throughout the course of the study • Clinically significant abnormal findings in baseline clinical laboratory parameters 		
<p>INCLUSION: Repeat Treatment Phase</p> <p>Patients who met all of the following inclusion criteria were eligible to participate in the repeat treatment phase of the study:</p> <ul style="list-style-type: none"> • Hylaform treatment during initial phase of the study • Completed 12-week (no touch-up required) or 14-week (touch-up required) follow-up visit for initial phase • If female and of childbearing potential, had a negative urine pregnancy test, agreed to use oral contraceptives for at least 1 month prior to treatment and for the duration of the study, or agreed to use 2 forms of contraception (eg, condoms plus spermicide), or was surgically sterile, or postmenopausal for at least 1 year • Ability to understand and comply with the requirements of the study • Willingness and ability to provide written informed consent prior to performance of any study-related procedures • Agreed to refrain from seeking other treatment for this condition without first notifying the investigator <p>EXCLUSION: Repeat Treatment Phase</p> <p>Patients who met any of the following exclusion criteria were not eligible for participation in the repeat treatment phase of the study:</p>		

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<ul style="list-style-type: none"> • Women who are pregnant or lactating • Received prior therapy (eg, dermabrasion, facelift) within 6 months prior to entry into the study; patients restricted from undergoing such therapy throughout study duration • Previous tissue augmentation (bulking agents) for facial wrinkles and scars (except Hylaform treatment during the initial phase of this study) within 6 months at the proposed injection sites; patients restricted from undergoing tissue augmentation throughout study duration • Previous tissue augmentation with permanent implants (eg, Softform®, silicone); patients restricted from undergoing augmentation with permanent implants throughout study duration • Evidence of scar-related disease or delayed healing activity within the past 1 year; patients with scars were eligible for study entry but scars at the intended treatment sites were not treated • History of keloid formation • Any infection or wound of the face • Allergic history including anaphylaxis or multiple severe allergies, avian-sourced protein (eg, chicken products), natural rubber latex, topical or subcutaneous anesthetic agents • Planned relocation making follow-up visits impossible during the course of the study • Aspirin or NSAIDs within 1 week prior to treatment • Concomitant anticoagulant therapy, antiplatelet therapy, or history of bleeding disorders • Over-the-counter wrinkle products (eg, alpha-hydroxy acids) or prescription treatments (eg, Renova, Retin-A, microdermabrasion, chemical peels in the nasolabial fold area) within 4 weeks prior to repeat treatment; patients restricted from using over-the-counter wrinkle products or prescription treatments throughout study duration • Immunocompromised or immunosuppressed (eg, HIV-positive, transplant recipient, or presently receiving chemotherapy) • Clinically significant organic disease including clinically significant cardiovascular, hepatic, pulmonary, neurologic, or renal disease, or other medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the investigator, precluded participation in the trial or potentially decreased survival • Received any investigational product within 30 days prior to enrollment in the repeat treatment phase of the study; patient could not receive other investigational products throughout the course of the study 		
TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; LOT NUMBER:		
Initial Phase: Hylaform was administered by intradermal injection to the nasolabial folds only.		

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<p>“Dosage” information for this medical device was collected as the volume of implant injected. The mean volume of implant used per nasolabial fold was approximately 1 full syringe, 0.8 mL (range 0.2 to 2.4 mL). A single lot was used (lot number T0128).</p> <p>Repeat Treatment Phase: For each patient, Hylaform was administered to one nasolabial fold and Hylaform Plus was administered to the opposite nasolabial fold by intradermal injection. “Dosage” information for these medical devices was collected as the volume of implant injected. The mean volumes of implant used per nasolabial fold were 1.1 mL (range 0.3 to 2.6 mL) for Hylaform and 1.1 mL (range 0.2 to 2.8 mL) for Hylaform Plus. Hylaform lots used were P0302, T0128, and X02022. Hylaform Plus lots used were N03061 and W02041.</p>		
<p>DURATION OF STUDY:</p> <p>Initial Phase: The patient enrollment was expected to be 2 to 4 months. Patient participation was to last up to 20 weeks: 6 weeks of screening and 12 to 14 weeks of follow-up. The study duration was expected to be approximately 9 months. Intradermal injection to both nasolabial folds occurred during Visit 3. At Visit 5, touch-up injections were allowed if the investigator assessed the degree of correction as less than 1-point improvement on the 6-point grading scale.</p> <p>Repeat Treatment Phase: Intradermal injections to each nasolabial fold occurred during a single repeat treatment visit (Visit R1). Patient participation was to last up to 12 weeks.</p>		
<p>REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION; LOT NUMBER:</p> <p>Zyplast, the control device, was administered by intradermal injections to nasolabial folds only during the initial phase of the study. Dosage was collected as the volume of implant injected. The mean volume of implant used per nasolabial fold was approximately 1 full syringe, 1.1 mL (range 0.3 to 2.6 mL). Zyplast lot numbers were 01E031D, 01I071D, 01L031A, 02A041A, and 07I077D.</p>		
<p>CRITERIA FOR EVALUATION:</p> <p>EFFICACY: The primary efficacy endpoint was assessed by the blinded independent panel review (IPR) median score of each nasolabial fold at 12 weeks after last study treatment (device implantation). Secondary efficacy endpoints were assessed by IPR median scores for each nasolabial fold at baseline (Visit 3), at 3 days, and at 2, 4, and 8 weeks after the last implantation of the device; patient global self-assessments; investigator global assessments; and investigator wrinkle assessments.</p> <p>SAFETY: Safety was evaluated by adverse events, antibody response, and clinical laboratory parameters.</p>		
<p>STATISTICAL METHODS:</p> <p>For the initial phase, primary efficacy and safety analyses were performed on the intent-to-treat (ITT) population. The ITT population was defined as all patients who were randomized and received study treatment. A secondary efficacy analysis was performed on the per-protocol population, defined as all patients in the ITT population who did not have a major protocol deviation that would affect the efficacy analysis.</p> <p>For the repeat treatment phase, safety analyses were performed on the ITT population. The ITT</p>		

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<p>population was defined as all patients who were randomized and received repeat treatment.</p> <p>EFFICACY:</p> <p>Initial Phase: Primary and secondary efficacy and duration of effect</p> <p>The primary efficacy analysis was an ITT analysis of the blinded IPR wrinkle assessment scores at 12 weeks after the last implantation of the device. These blinded IPR wrinkle assessment scores for a patient were the scores for the left and right nasolabial folds from the facial photograph of that patient. The analysis was a repeated measures analysis with the patient's scores for the left and right nasolabial folds at 12 weeks after the last implantation of the device as the repeated measures. The data were analyzed using a model including factors for treatment group, center, and wrinkle (within patient). No formal statistical test for the treatment group by center interaction was performed, but outcomes for each center were examined for each treatment group. The baseline score was included as a covariate. The outcomes were examined for subgroups of patients, based on the presence/absence of touch-up procedures.</p> <p>A lower-bounded 1-sided confidence interval ($\alpha [\alpha] = 0.025$) was constructed for the difference between the Zyplast group mean score and the Hylaform group mean score (ie, Zyplast mean score - Hylaform mean score). The non-inferiority of Hylaform treatment was demonstrated if the lower bound of the 97.5% confidence interval on the difference between the 2 means did not include the maximum tolerable difference for non-inferiority that was prespecified as -0.5.</p> <p>The superiority of Hylaform treatment would be demonstrated if the Hylaform group mean score was statistically significantly lower than the Zyplast group mean score at the $\alpha = 0.05$ (2-sided) level.</p> <p>A per-protocol (which included all patients in the ITT population who did not have major protocol deviations) analysis of the blinded IPR wrinkle assessment scores at 12 weeks after the last implantation of the device was presented as a secondary efficacy endpoint.</p> <p>The treatment response was examined for subgroups of patients based on smoking habit and sunlight exposure. No formal statistical testing was planned, but tabulations for subgroups are presented.</p> <p>The secondary endpoints of investigator global assessment and patient global self-assessment were summarized at each timepoint after the last implantation of the device for each treatment group. For categorical variables, frequencies and percentages are presented. Continuous variables were summarized by mean, median, standard deviation, minimum, and maximum.</p> <p>The proportion of patients who showed improvement of at least 1 point on the 6-point grading scale in both nasolabial folds at 12 weeks after last implantation of study device was estimated and the 95% confidence interval for the difference between treatment groups was constructed.</p> <p>Using the blinded IPR scores (the efficacy assessments from the blinded panel scoring of the photographs of patient nasolabial folds), the duration of effect for the Hylaform-treated group was summarized as the percent of all nasolabial folds that returned to the baseline value at 12 weeks after the last implantation of the device. The difference was computed for each nasolabial fold in the Hylaform-treated group, from the blinded IPR scores for baseline and 12 weeks after the last implantation of the device for that nasolabial fold. No comparisons were made to the control group, as the interest in duration of effect was for the Hylaform-treated wrinkles. No formal statistical analysis was performed on all nasolabial folds that returned to their baseline value.</p> <p>Repeat Treatment Phase:</p>		

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<p>Efficacy methods and results for the repeat treatment phase will be provided in a subsequent report.</p> <p>SAFETY: Initial Phase Adverse events were summarized by Primary System Organ Class and Preferred Term, giving the number of patients (incidence), the percentage of patients (incidence rate), and the total number of events reported. The 95% confidence intervals were calculated for the incidence rate in each treatment group and for the difference in incidence rates between treatments. Clinical laboratory data were summarized by visit (actual value and change from baseline) using descriptive statistics (mean, median, standard deviation, minimum, and maximum). Serum hylan B IgG antibody titers were summarized by treatment group and visit using descriptive statistics (minimum, first quartile, median [second quartile], third quartile, interquartile range, maximum). The number and percentage of patients with a positive hylan B IgG antibody titer were summarized.</p> <p>Repeat Treatment Phase Adverse events, clinical laboratory data, and serum antibody data were evaluated as described for the initial phase of the study through 4 weeks after repeat treatment. In addition, patients kept a diary to document signs and symptoms that occurred during the first 7 days following treatment. A subsequent report will provide a safety update through the 12 weeks of the repeat treatment phase.</p>		
<p>SUMMARY – CONCLUSIONS</p> <p>EFFICACY RESULTS: Initial Phase The mean IPR median score at 12 weeks after last treatment for Hylaform patients (2.3) was similar to Zyplast patients (2.2). Non-inferiority of Hylaform treatment was demonstrated based on the lower bound of the 1-sided confidence interval (-0.38), which was larger than the prespecified maximum tolerable difference of -0.5 points. While non-inferiority of Hylaform to Zyplast treatment was demonstrated, superiority was not.</p> <p>At 12 weeks after last treatment, 4.1% of Hylaform patients and 9.5% of Zyplast patients had at least a 1-point improvement. This difference was not statistically significant ($\alpha = 0.05$) based on the 95% confidence interval for the difference in proportions (-11.8%, 1.1%).</p> <p>Overall, results of the IPR nasolabial fold assessment at 12 weeks after last treatment were similar across study centers. Hylaform and Zyplast IPR median scores were similar for patient subgroups (with and without touch-up, smoking history, and sun exposure). In both treatment groups, improvement decreased over time. The mean IPR median scores returned to baseline levels at 12 weeks after the last treatment. In general, the more severe the nasolabial folds were at baseline, the more likely they were to maintain the treatment effect at 12 weeks. This trend was observed at each timepoint.</p> <p>Investigator live assessments showed similar patterns of improvement when compared to the blinded IPR—substantial improvement immediately after treatment, followed by improvement lessening over time for each treatment group. Live assessment scores resulted in higher scores (less favorable) at baseline (mean of 3.5 for Hylaform patients and 3.6 for Zyplast patients) than the blinded IPR</p>		

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<p>assessments at baseline (2.2 for Hylaform patients and 2.3 for Zyplast patients). Initial improvements (change from baseline scores at Day 3) were larger (more favorable) when assessed by the investigator (mean change of -2.1 for Hylaform patients and -2.3 for Zyplast patients) than when assessed by the blinded IPR (mean change of -0.5 for Hylaform patients and -0.8 for Zyplast patients). The investigator results support the general findings from the primary analysis.</p> <p>The global assessment scores assigned by patients and investigators were similar. Mean global assessment scores were similar for the treatment groups at each visit. Assessments 12 weeks after last treatment were 0.9 (investigator) and 0.8 (patient) for Hylaform, and 1.0 (investigator) and 0.9 (patient) for Zyplast (the larger the score, the more favorable the response to treatment).</p> <p>SAFETY RESULTS:</p> <p>Initial Phase</p> <p>No deaths were reported during the initial phase of the study. Two serious baseline adverse events (foot fracture, nephrolithiasis) were reported by 2 Zyplast patients and 1 treatment-emergent serious unrelated adverse event (hemorrhoids) was reported by 1 Hylaform patient. Two Zyplast patients discontinued the study due to adverse events (localized osteoarthritis and migraine); neither event was related to study device. Two Zyplast patients experienced injection site necrosis; 1 event resolved at Day 7 and 1 event was ongoing at the time of initial phase completion.</p> <p>A total of 117 (88%) of 133 Hylaform patients reported 342 treatment-emergent adverse events and 112 (88%) of 128 Zyplast patients reported 322 treatment-emergent adverse events. The 95% confidence intervals for the incidence rate of treatment-emergent adverse events were similar for Hylaform patients (81.2% to 93.0%) and Zyplast patients (80.5% to 92.7%). There was no evidence of a statistical difference in the incidence rates between treatment groups. Procedure-related adverse events were reported for 111 (84%) Hylaform patients and 109 (85%) Zyplast patients. No statistical difference in procedure-related adverse event incidence rates was identified between treatment groups.</p> <p>Adverse events not procedure-related were reported for 39 (29%) Hylaform patients and 43 (34%) Zyplast patients. Of these not procedure-related adverse events, anesthetic-related adverse events were reported by 1 (1%) Zyplast patient. Device-related adverse events were reported by 2 (2%) Hylaform patients and 9 (7%) Zyplast patients. Unrelated adverse events were reported by 29% of Hylaform patients and 27% of Zyplast patients.</p> <p>The majority of adverse events reported were mild or moderate in severity. Severe adverse events were reported by 3 (2%) Hylaform patients and 7 (6%) Zyplast patients. None of these severe events were device-related.</p> <p>Clinically significant laboratory values were reported as treatment-emergent adverse events for 3 Hylaform patients and 2 Zyplast patients. The investigators considered these events to be unrelated to study device.</p> <p>An increase greater than fourfold the baseline value was considered a positive hylan B IgG antibody titer response to treatment. One patient in the Hylaform group had a hylan B IgG antibody titer of 100 at Day 0 and 1600 at Weeks 4 and 12; the patient had no signs and symptoms of an allergic</p>		

<p>NAME OF COMPANY Genzyme Corporation One Kendall Square Cambridge, MA 02139 NAME OF FINISHED PRODUCT Hylaform® NAME OF ACTIVE INGREDIENT Hylan B gel</p>	<p>SUMMARY TABLE Referring to Part of the Dossier:</p> <p>Volume:</p> <p>Page:</p> <p>Reference:</p>	<p>FOR NATIONAL AUTHORITY USE ONLY:</p>
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response.

Repeat Treatment Phase

No deaths or discontinuations due to adverse events were reported through the data cutoff date of this interim safety report. Two serious treatment-emergent adverse events were reported by 1 patient (bilateral injection site abscesses).

Overall, 92 (96%) of the 96 repeat treatment phase patients (589 events) reported treatment-emergent adverse events. Eighty-seven (91%) patients reported 269 events on the Hylaform side, 92 (96%) patients reported 286 events on the Hylaform Plus side, and 21 (22%) patients experienced 34 events that developed at sites other than the nasolabial fold. The 95% confidence interval for the incidence rate of treatment-emergent adverse events was 83.0% to 95.6% for the Hylaform side and 89.7% to 98.9% for the Hylaform Plus side. There was a statistical difference in incidence rates between the 2 treatment sides favoring Hylaform. Hylaform Plus is delivered through a larger gauge needle (27G) than Hylaform (30G) which may account for increased procedure-related adverse events in the Hylaform Plus group.

Procedure-related adverse events were reported for 92 (96%) of the 96 patients. Three patients had adverse events that were possibly device-related: injection site abscess (both sides), involuntary muscle contractions (Hylaform Plus side), and dizziness (site other than the nasolabial fold area). All device-related adverse events were mild.

There were no clinically abnormal laboratory findings reported as treatment-emergent adverse events. No significant increase in hylan B IgG antibody titers was found in serum samples prior to and up to 4 weeks after repeat treatment before the data cutoff date for this interim safety report.

CONCLUSIONS:

Initial Phase

The efficacy of Hylaform in correcting nasolabial fold wrinkle severity was shown to be non-inferior to Zyplast at 12 weeks after treatment when assessed by an independent, blinded panel of dermatologists. In addition, assessment of improvement in wrinkle severity by the investigator and by the patient (via global assessments) was similar for Hylaform and Zyplast.

Technique-dependent variables that may influence the efficacy of dermal fillers include the volume of material injected. The mean volume of material injected into each nasolabial fold was 27% lower for Hylaform patients (0.8 mL) than for Zyplast patients (1.1 mL). This volume correlates with a higher percentage of Hylaform patients (16.5%) who required a touch-up compared to Zyplast patients (7.1%). In general, the more severe the nasolabial folds were at baseline, the more likely they were to maintain the treatment effect at 12 weeks.

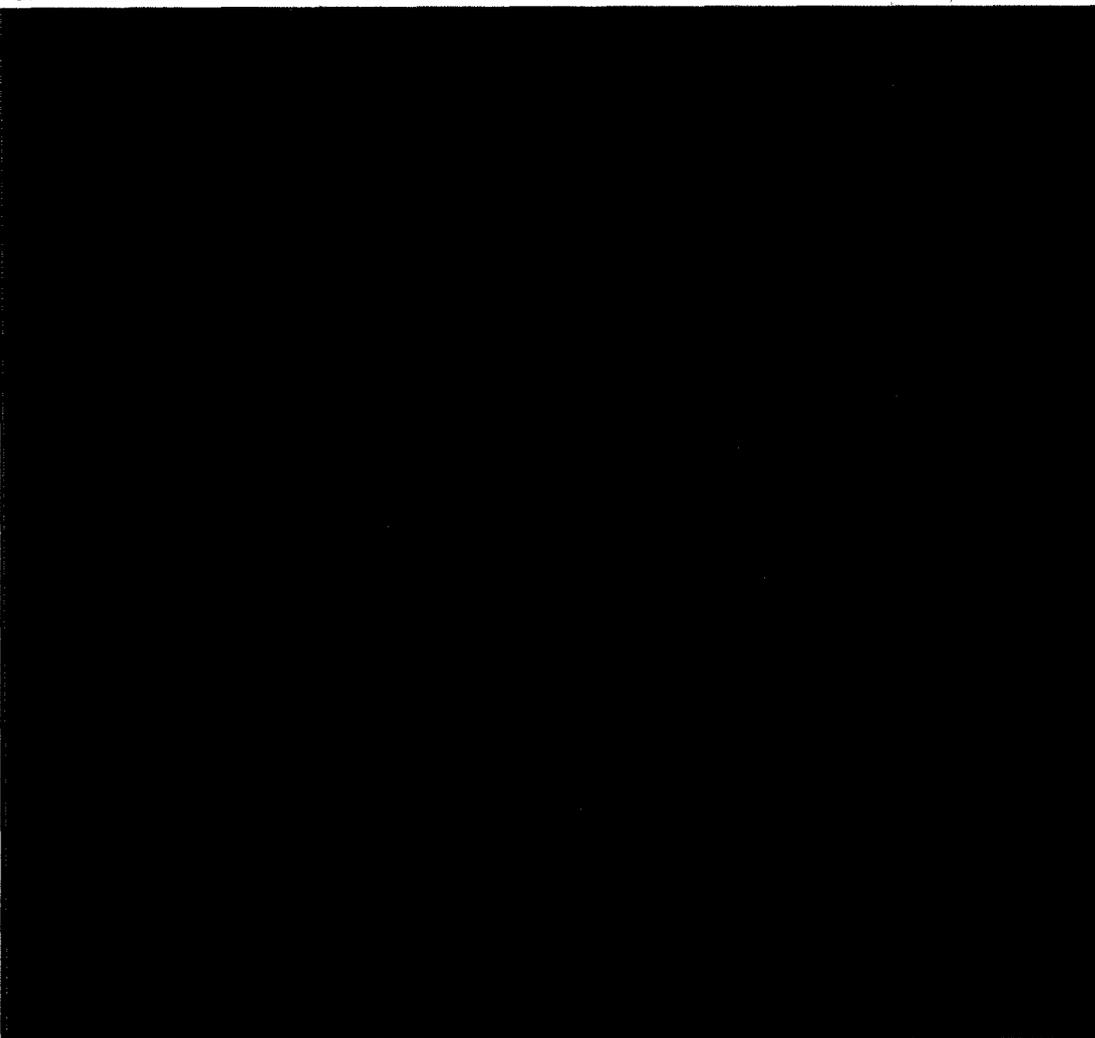
Safety evaluations indicated that Hylaform is well tolerated and has an acceptable safety profile. The majority of treatment-emergent adverse events were procedure-related. Procedure-related events were mostly mild in severity and did not require treatment. Not procedure-related events were generally unrelated to anesthetic or study device.

Hylaform®
Final Report Study Number HYLA-001-01

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Repeat Treatment Phase Evaluations of adverse events, clinical laboratory findings, and physical examinations revealed no safety issues of concern for repeat treatment with hylan B products after 4 weeks, the data cutoff date for the repeat treatment phase interim safety report.		
DATE OF REPORT: 29 July 2003		

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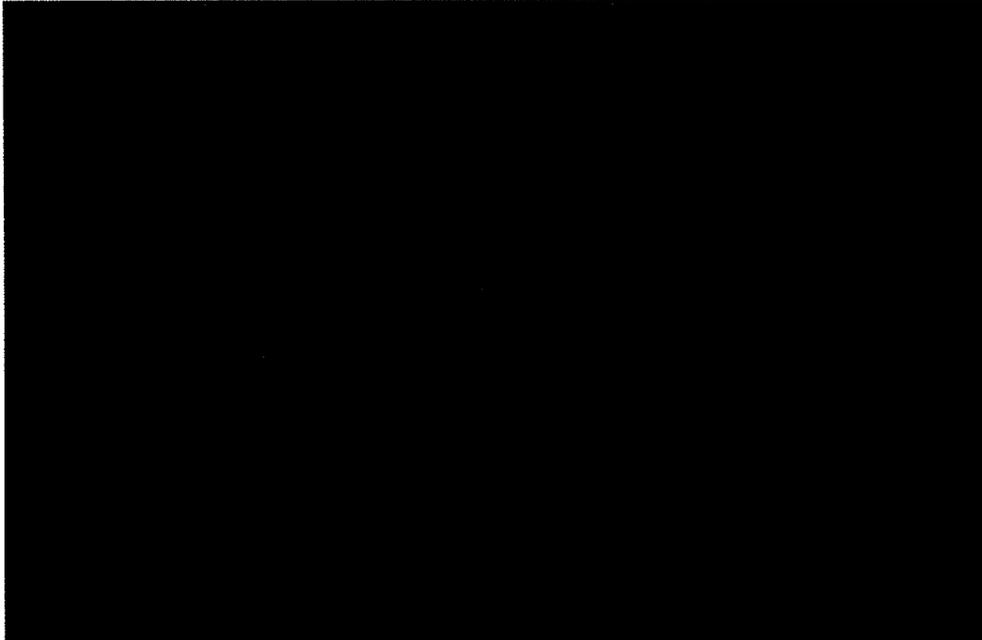


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4. ABBREVIATIONS AND TERMS

α	Alpha
ALT	Alanine aminotransferase (previously SGPT)
AST	Aspartate aminotranferase (previously SGOT)
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CRF	Case report form
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
G	Gauge
GCP	Good Clinical Practice
HA	Hyaluronan or hyaluronic acid
HIV	Human immunodeficiency virus
ICH	International Conference of Harmonisation
IgG	Immunoglobulin G
IPR	Independent Panel Review
IRB	Institutional Review Board
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
NOS	Not otherwise specified
NSAID	Nonsteroidal anti-inflammatory drug
PMA	Premarketing application
RBC	Red blood cell
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase (AST)
SGPT	Serum glutamic-pyruvic transaminase (ALT)
WBC	White blood cell
WHO	World Health Organization

5. ETHICS

5.1 Institutional Review Board (IRB)

Prior to patient enrollment, the protocol and patient informed consent form were reviewed and approved by the Institutional Review Boards (IRBs) in compliance with the requirements of 21 Code of Federal Regulations (CFR) 56 and the International Conference on Harmonisation (ICH). A list of IRBs participating in this study is provided in Appendix 16.1.3.

5.2 Ethical Conduct of the Study

This study was conducted in compliance with the principles of Good Clinical Practice (GCP) regulations as stated in the United States federal regulations and the "Guidance for Good Clinical Practice," created by ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use as well as in compliance with 21 CFR 812 under IDE # G000315.

5.3 Patient Information and Consent

In compliance with 21 CFR 50, written informed consent was required prior to patient enrollment in both the initial and repeat treatment phases of the study. Patients were free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. A sample consent form is provided in Appendix 16.1.3.

6. INVESTIGATORS AND STUDY ADMINISTRATION STRUCTURE

The study was conducted at 10 sites in the United States. The investigators and their addresses are listed in Table 6-1. Study sites and curricula vitae for investigators and Independent Panel Review (IPR) members are provided in Appendix 16.1.4.

Table 6-1 List of Investigators and Number of Randomized Patients at Each Site

Site Number	Principal Investigator	Site Location	Number of Randomized Patients	
			Initial Phase	Repeat Treatment Phase
1	[REDACTED]	Miami, FL 33125-1600	32	11
2	[REDACTED]	New York, NY 10028	31	9
3	[REDACTED]	San Francisco, CA 94117-3685	27	12
4	[REDACTED]	Beverly Hills, CA 90210-5027	26	9
5	[REDACTED]	Santa Monica, CA 90404-2115	32	14
6	[REDACTED]	San Francisco CA 94102	13	6
7	[REDACTED]	Dallas, TX 75320	23	10
8	[REDACTED]	Birmingham, AL 35205	31	10
9	[REDACTED]	Miami, FL 33156	28	11
10	[REDACTED]	New York, NY 10016	18	4
Total:			261	96

The sponsor and participants other than study site personnel are listed in Table 6-2.

Table 6-2 Sponsor and Participants Other Than Study Site Personnel

Function	Company Name and Address
Sponsor	Genzyme Corporation One Kendall Square Cambridge, MA 02139
Study management: Until 30 September 2002	Genzyme Corporation
Beginning 1 October 2002	Inamed Corporation 5540 Ekwil Street Santa Barbara, CA 93111
Packaging and labeling of clinical materials	Genzyme Clinical Pharmacy Research Services
Hylan B IgG antibody titer testing	Southern Research Institute 2000 9 th Avenue South Birmingham, AL 35205
Clinical laboratory testing	CRL-Medinet 8433 Quivara Road Lenexa, KS 66900
Photographic procedures	Canfield Scientific, Inc 253 Passaic Avenue Fairfield, NJ 07004
Independent panel reviewers (IPR)	██████████ – New York, NY ██████████ – New York, NY ██████████ Philadelphia, PA ██████████ – Cary, NC ██████████ – Wood Cliff Lake, NJ ██████████ – Philadelphia, PA
Data management, clinical monitoring, programming, biostatistics, and writing clinical study report	STATPROBE, Inc 10052 Mesa Ridge Court, Suite 200 San Diego, CA 92121

7. INTRODUCTION

Soft tissue augmentation has become a common procedure for the treatment of facial defects.¹ The ideal dermal filler would be safe, effective, reproducible in technique and result, have a high use potential and a low abuse potential, be noncarcinogenic, nonteratogenic, nonmigratory, physiologic, and permanent.² Bovine collagen has been the most successful dermal soft tissue implant material. The original collagen implant (Zyderm® 1) received Food and Drug Administration (FDA) approval in July 1981. This was followed by a more concentrated form (Zyderm® 2) in 1983, and a glutaraldehyde-crosslinked collagen (Zyplast®) in 1987. Despite its costs, limited longevity, and occasional hypersensitivity response, injectable bovine collagen is regarded as the "gold standard" against which all other soft tissue fillers are measured.³ Bovine collagen implants are not without problems. Adverse events and shorter than expected longevity of results have occurred.

Zyderm or Zyplast fills the defect with bovine collagen. A host response gradually degrades the implant and replaces it with host collagen. Zyderm 1 collagen is often no longer detectable in the human dermis within 4 months of the implant. Zyplast remains identifiable up to 6 months after implantation. Host collagen is responsible for clinical correction beyond those time intervals by first replacing the implant, then gradually remodeling itself. A sacrifice in pliability allows Zyplast to achieve greater longevity.⁴

Hylan B gel is a crosslinked hyaluronic acid (HA) that possesses many desirable implant material characteristics.⁵ Because of its insolubility, resistance to degradation and migration, and excellent biological compatibility (noninflammatory, nonimmunogenic, nontoxic), hylan B gel is appropriate for use in soft tissue augmentation. Hylaform (median particle size ~500 microns) and Hylaform Plus (median particle size ~700 microns) are composed of hylan B gel, retain the biocompatibility and biological properties of natural HA, yet have a greatly increased residence time in the dermal tissue over native HA. Hylaform is administered through a 30-gauge needle and Hylaform Plus is administered through a 27-gauge needle.

A clinical trial for the safety and efficacy of Hylaform was conducted in the United States (IDE 900060). Hylaform demonstrated an excellent profile of patient tolerance and acceptance. A second injection of Hylaform was required in approximately 53% of the patients 2 weeks after the initial implantation.⁶

Canada, Australia, New Zealand, and several European countries presently market Hylaform for the treatment and correction of soft tissue defects of the face. A low

incidence of reported adverse events (predominantly transient, localized, treatment-site reactions) has occurred. The risks to patients implanted with Hylaform or Hylaform Plus are expected to be no greater than for treatment with Zyplast. These risks include redness, local swelling, pain or tenderness, itching (pruritus), discoloration, bruising (hematoma), induration, lumpiness, and acne. These reactions are local, procedure-related and/or treatment-related responses.

8. STUDY OBJECTIVES

Initial Phase

The primary objectives of the initial phase of the study were as follows:

- Evaluate the efficacy (non-inferiority) of Hylaform viscoelastic gel for the correction of nasolabial folds as compared with Zyplast collagen implant. Assessment of wrinkle correction was performed using serial photographic documentation and blinded IPR photographic evaluation. Efficacy was based on the blinded IPR wrinkle assessment scores of the Week 12 or Week 14 photographs (12 weeks following the last device implantation).
- Evaluate the safety of Hylaform as compared with Zyplast. Safety was determined by rates of adverse events associated with the use of each product. Patients were observed for a total of 12 weeks following the last implantation of the device.

The secondary objective of the initial phase was as follows:

- Evaluate the clinical utility of Hylaform with respect to physician assessment and patient self-assessment.

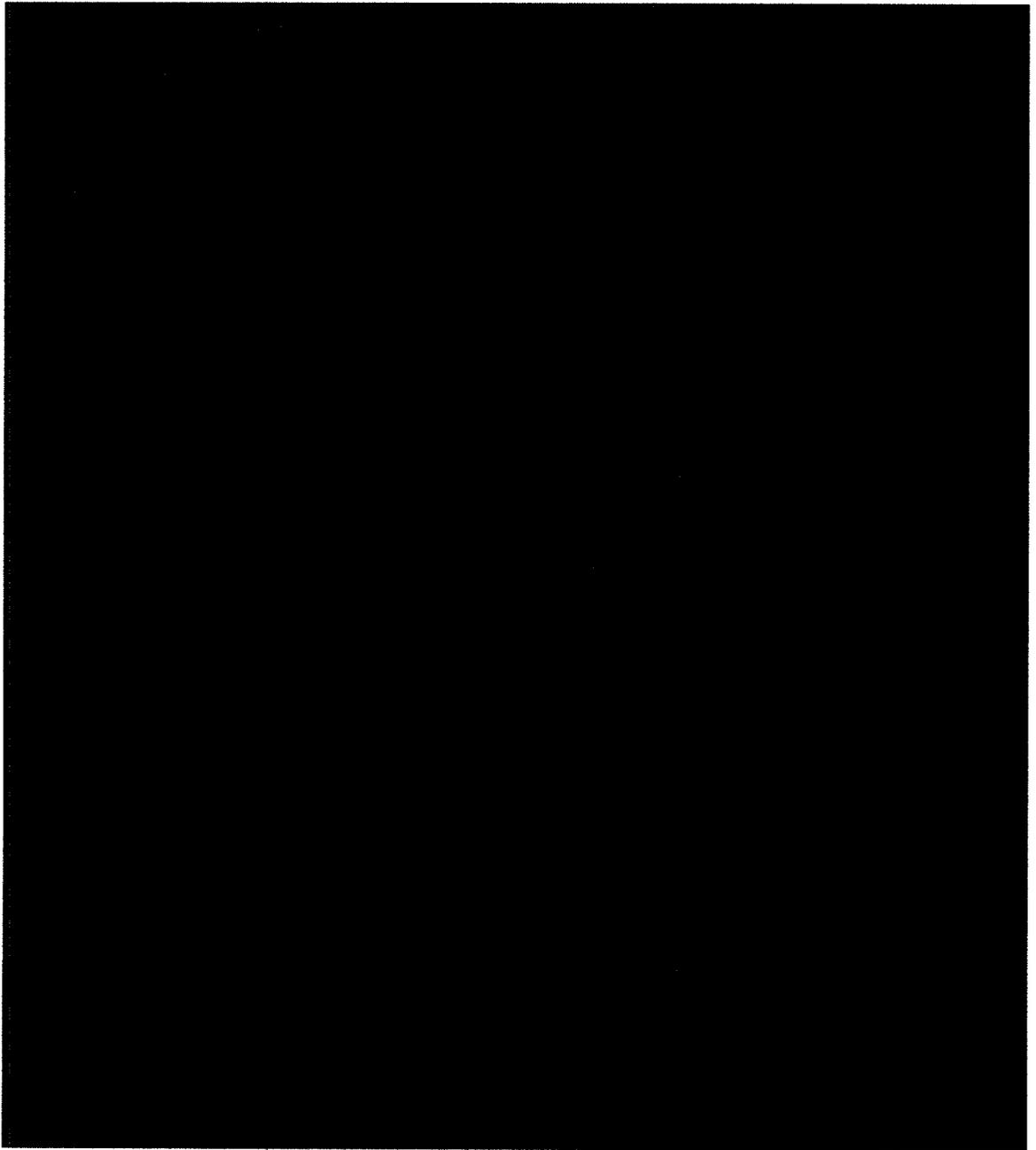
Repeat Treatment Phase

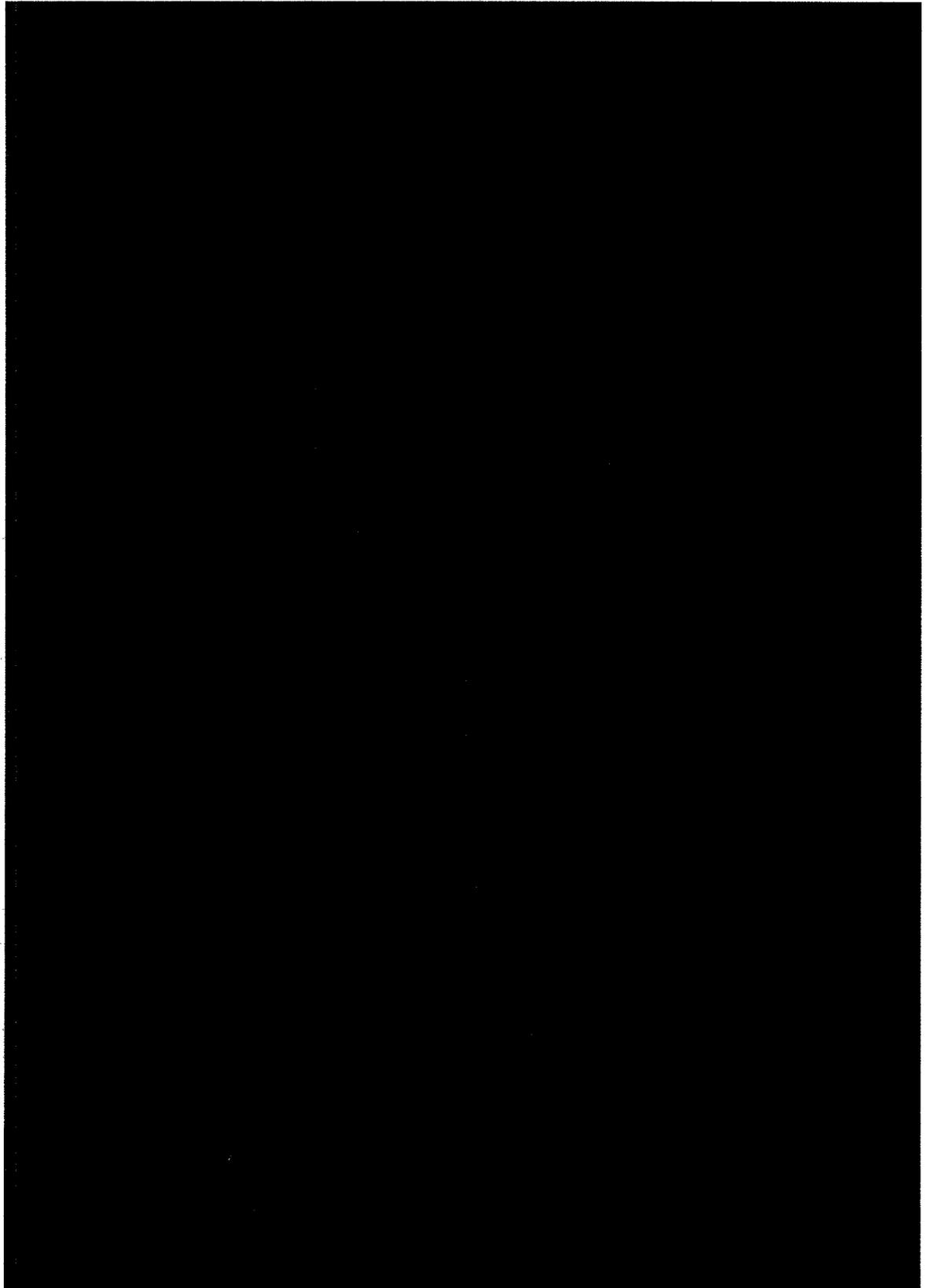
The primary objectives of the repeat treatment phase were as follows:

- Evaluate the safety of repeat treatment with hylan B viscoelastic gel products. Safety was determined through 4 weeks after treatment by rates of adverse events associated with repeat treatment with Hylaform and Hylaform Plus and by the presence or absence of a potential immune response to hylan B gel as measured by the development of hylan B (immunoglobulin G [IgG]) antibody titers after repeat device implantation.
- Evaluate the efficacy (non-inferiority) of Hylaform Plus versus Hylaform viscoelastic gel for the correction of nasolabial fold contour defects. Assessment of wrinkle correction was to be performed using serial photographic documentation and blinded IPR photographic evaluation. Efficacy was based on the blinded IPR wrinkle assessment scores of the Week 12 photographs (12 weeks following the repeat treatment). Note: The repeat treatment phase was ongoing at the time of this clinical report.

The secondary objectives of the repeat treatment phase were as follows:

- Determine safety through 12 weeks after treatment by the rates of adverse events associated with repeat treatment with Hylaform and Hylaform Plus and by the presence or absence of a potential immune response to hylan B gel as measured by the development of hylan B (IgG) antibody titers after repeat device implantation.
- Evaluate the clinical utility of Hylaform Plus and Hylaform with respect to physician assessment and patient self-assessment.







10. STUDY PATIENTS

10.1 Disposition of Patients

Of the 339 patients who consented to the initial phase of the study, 261 were randomized and treated, and 78 patients were screen failures. The most common reason for screen failure was "other" (57 patients). The "other" category consisted of patients who did not meet the nasolabial folds criteria (24 patients), had a positive skin test (11 patients), had scheduling conflicts or had moved (8 patients), did not meet the age criteria (3 patients), were ineligible (reason not specified) (3 patients), or had received prohibited dermal treatment/medication (2 patients). The following "other" reasons were given by 1 patient each: requested not to participate, blood draw was unattainable, and had a sister with history of rheumatoid arthritis, had a facial infection, was HIV-positive, or had an unhealed wound.

Of the 261 patients randomized and treated, 255 completed the 12 weeks of the initial phase (130 of the 133 patients in the Hylaform group, 125 of the 128 patients in the Zyplast group). Six patients withdrew from the study, 3 in each treatment group. In the Hylaform group, 2 patients were lost to follow-up, Patients 04-18 (Day 131) and 09-18 (Day 45); and 1 patient wished to withdraw, Patient 07-09 (Day 69). In the Zyplast group, 2 patients withdrew due to an adverse event, Patients 06-10 (Day 20) and 02-03 (Day 61), and 1 patient wished to withdraw, Patient 02-14 (Day 21). Patient disposition by treatment group is presented in Table 10-1 for the initial phase of the study.

Table 10-1 Disposition of Patients in the Initial Phase

	Number (%) of Patients		
	Hylaform N = 133	Zyplast N = 128	Total N = 339
Consented to initial phase of study	NA	NA	339 (100.0)
Screen failures	NA	NA	78 (23.0)
Reason for failure:			
Noncompliance	NA	NA	3/78 (3.8)
Wished to withdraw	NA	NA	15/78 (19.2)
Lost to follow-up	NA	NA	3/78 (3.8)
Other	NA	NA	57/78 (73.1)
Did not meet nasolabial fold criteria	NA	NA	24/57 (30.8)
Positive bovine collagen skin test	NA	NA	11/57 (14.1)
Scheduling conflict/moved	NA	NA	8/57 (10.3)
Did not meet age criteria	NA	NA	3/57 (3.8)
Ineligible, not specified	NA	NA	3/57 (3.8)
Infection/wound ^a	NA	NA	3/57 (3.8)
Prohibited dermal treatment/medication	NA	NA	2/57 (2.6)
Patient request	NA	NA	1/57 (1.3)
Unable to draw blood	NA	NA	1/57 (1.3)
Sister with history of rheumatoid arthritis	NA	NA	1/57 (1.3)
Randomized and treated (intent-to-treat population)	133 (100.0)	128 (100.0)	261 (100.0)
Completed 12 weeks	130 (97.7)	125 (97.7)	255 (97.7)
Discontinued	3 (2.3)	3 (2.3)	6 (2.3)
Primary reason for withdrawal:			
Adverse event or procedure-related event	0 (0.0)	2 (1.6)	2 (0.8)
Wished to withdraw	1 (0.8)	1 (0.8)	2 (0.8)
Lost to follow-up	2 (1.5)	0 (0.0)	2 (0.8)

Reference: Tables 14.1.1 and 14.1.2

NA = Not applicable.

^aOne patient each had a facial infection, was HIV-positive, or had an unhealed wound.

Of the 133 Hylaform patients participating in the initial phase of the study, 96 patients consented to treatment in the repeat treatment phase and 37 patients chose not to participate in the repeat treatment phase. The most common reasons for not

participating in the repeat treatment phase were scheduling conflicts (10 patients); prior restricted therapy or procedures within the required washout period (7 patients); dissatisfied, not interested, or uncomfortable (7 patients); and lost to follow-up (6 patients). Patient disposition is presented in Table 10-2 for the repeat treatment phase of the study.

Table 10-2 Disposition of Patients in the Repeat Treatment Phase

N = 133 in Initial Phase		
Not enrolled in repeat treatment phase	37	
Reasons for not participating		
Scheduling conflicts	10/133	(7.5)
Prior restricted therapy or procedure within 6 months	7/133	(5.3)
Dissatisfied, not interested, or uncomfortable	7/133	(5.3)
Lost to follow-up	6/133	(4.5)
Ineligible, did not complete initial phase of study ^a	2/133	(1.5)
Pregnant or trying to get pregnant	2/133	(1.5)
Bruising risk	1/133	(0.8)
Other planned cosmetic procedure	1/133	(0.8)
Now employee of investigator	1/133	(0.8)
Consented to repeat treatment phase	96	
Randomized and treated	96	(100.0)
Intent-to-treat population	96	(100.0)
Continuing as of 30 May 2003	96	(100.0)
Completed Day 3	96	(100.0)
Completed 2 weeks	96	(100.0)
Completed 4 weeks ^b	92	(95.8)

Reference: Table R-14.1.1 and Listing R-16.2.1.3

^aFor the initial phase, 3 patients did not complete the Week 12 visit; however, 1 patient, Patient 07-09, was allowed entry into the repeat treatment phase.

^bFour patients were continuing but had not yet reached the Week 4 visit as of the data cutoff date.

10.2 Protocol Deviations

Protocol deviations during the initial phase included off-schedule visits (83 Hylaform patients, 79 Zyplast patients), use of restricted medications/treatments (4 Hylaform patients), clinically significant laboratory results at baseline (3 Zyplast patients), baseline nasolabial fold scores other than 3 or 4 (1 Hylaform patient,

1 Zyplast patient), and randomized to one treatment but received the other treatment (2 patients randomized to receive Zyplast but received Hylaform; 1 patient randomized to receive Hylaform but received Zyplast). Additionally, photographic evaluation limitations included missing IPR scores at Week 12 or Day 0 (15 Hylaform patients, 13 Zyplast patients), incomplete IPR scores at Week 12 (3 Zyplast patients), and duplicate IPR review (1 Hylaform patient, 2 Zyplast patients). A positive skin test was not reported by 1 patient (Hylaform group) until completion of the study at Week 12. A listing of patient protocol deviations is provided in Listing 16.2.2.1.

Protocol deviations during the repeat treatment phase are not presented in this report.

11. EFFICACY EVALUATION: INITIAL PHASE

11.1 Data Sets Analyzed

The ITT population consisted of the 261 patients randomized and treated. Of the 261 ITT patients, 21 patients did not have 12-week IPR scores (10 Hylaform patients, 11 Zyplast patients), including the 6 patients who discontinued and were not included in the analysis (Listing 16.2.2.1). The per-protocol population consisted of 224 patients (115 Hylaform patients, 109 Zyplast patients). In addition to the 21 patients excluded from the ITT analysis because they did not have 12-week IPR scores, patients were excluded from the per-protocol population for the following reasons (several patients were represented by more than 1 reason):

- The 12 weeks after last treatment visit occurred 20 days or more outside the scheduled visit window (6 in the Hylaform group, 7 in the Zyplast group)
- Baseline nasolabial fold <3 or >4 (1 in the Hylaform group, 1 in the Zyplast group)
- Restricted dermal treatments or medications received prior to implantation or during study (3 in the Hylaform group)
- Randomization assignment was not followed; patient was erroneously implanted with the incorrect treatment (2 patients were randomized to receive Zyplast but received Hylaform; 1 patient was randomized to receive Hylaform but received Zyplast)

11.2 Demographic and Other Baseline Characteristics

11.2.1 Patient Demographics

A majority of the patients in each treatment group were Caucasian and female. Patient age and weight were comparable between the treatment groups. The mean age

of all patients was 46.6 years, and the mean weight was 63.6 kilograms. Table 11-1 presents patient demographics for the ITT population.

**Table 11-1 Patient Demographics
Intent-to-treat Patients**

	Hylaform N = 133		Zyplast N = 128		Total N = 261	
Age (years)						
n	133		128		261	
Mean (SD)	47.1 (5.83)		46.1 (6.37)		46.6 (6.11)	
Median	48.0		47.0		48.0	
Minimum, maximum	30.0, 56.0 ^a		30.0, 55.0		30.0, 56.0 ^a	
Sex [Number (%)]						
Male	7 (5.3)		9 (7.0)		16 (6.1)	
Female	126 (94.7)		119 (93.0)		245 (93.9)	
Ethnicity [Number (%)]						
Caucasian	107 (80.5)		101 (78.9)		208 (79.7)	
Black	3 (2.3)		2 (1.6)		5 (1.9)	
Hispanic	16 (12.0)		18 (14.1)		34 (13.0)	
Asian	5 (3.8)		4 (3.1)		9 (3.4)	
Other	2 ^b (1.5)		3 ^c (2.3)		5 (1.9)	
Weight (kg)						
n	131		128		259	
Mean (SD)	64.1 (11.61)		63.2 (11.90)		63.6 (11.74)	
Median	62.6		61.0		61.7	
Minimum, maximum	44.0, 102.1		38.6, 109.0		38.6, 109.0	
Height (cm)						
n	132		128		260	
Mean (SD)	164.0 (6.72)		163.4 (8.09)		163.7 (7.41)	
Median	162.6		162.6		162.6	
Minimum, maximum	149.9, 190.5		134.6, 185.4		134.6, 190.5	

Reference: Table 14.1.3

SD = Standard deviation.

^aPatient 07-10 entered the study at 55 years of age, but had a birthday before receiving the initial device implantation.

^bOther was either African American/Native American or Lebanese.

^cOther was Latina, Western European, or Bangladeshi South Asian.

11.2.2 Smoking and Sun Exposure History

Over 50% of patients in each treatment group never smoked. The number of current and former smokers was comparable for the treatment groups; however, current smokers smoked more cigarettes per day in the Zyplast group (12/day) than in the Hylaform group (7/day). The number of hours per day of sun exposure was also

similar between the treatment groups. Table 11-2 presents the smoking and sun exposure history for the ITT population.

**Table 11-2 Smoking and Sun Exposure History
 Intent-to-treat Patients**

	Hylaform N = 133	Zyplast N = 128	Total N = 261
Smoking history [Number (%)]			
Current smoker	23 (17.3)	22 (17.2)	45 (17.2)
Former smoker	35 (26.3)	35 (27.3)	70 (26.8)
Never smoked	75 (56.4)	71 (55.5)	146 (55.9)
Current smoker (cigarettes/day)			
n	23	22	45
Mean (SD)	6.5 (6.30)	11.5 (9.82)	8.9 (8.51)
Median	4.0	8.5	5.0
Minimum, maximum	1.0, 20.0	1.0, 30.0	1.0, 30.0
Former smoker (years since quitting)			
n	32	33	65
Mean (SD)	16.4 (12.25)	16.4 (10.33)	16.4 (11.23)
Median	15.0	17.0	15.0
Minimum, maximum	0.3, 39.0	0.3, 38.0	0.3, 39.0
Sun exposure (hours/day)^a			
n	133	128	261
Mean (SD)	1.6 (1.14)	1.5 (1.06)	1.5 (1.10)
Median	1.0	1.0	1.0
Minimum, maximum	0.0, 8.0	0.0, 5.0	0.0, 8.0

Reference: Table 14.1.4

SD = Standard deviation.

^aExposure times reported as a range were converted to midpoints (eg, the range of 4 to 6 hours was converted to 5 hours) for summarization purposes.

11.2.3 Prior Dermal Treatments and Medications

Dermal treatment (face lift, dermabrasion, tissue augmentation with bulking agents) within 6 months prior to study entry and throughout study duration was prohibited. Previous tissue augmentation with permanent implants was prohibited prior to and throughout the study. Patients were restricted from using over-the-counter wrinkle products and prescription treatments (topical alpha hydroxy agents, Renova, Retin-A, and other prescription treatments; microdermabrasion; and chemical peels) on the nasolabial fold area within 4 weeks prior to study start and throughout study duration. Aspirin and NSAIDs within 1 week (7 days) prior to device implantation were

prohibited, but these medications could be used after study treatment and throughout the study duration as required. Concomitant anticoagulant or antiplatelet therapies were restricted during the study duration. More Zyplast patients had undergone tissue augmentation (bulking agents) than Hylaform patients. Other dermal medication and treatments were comparable between the treatment groups. Prior dermal treatments and medications for the ITT population are summarized in Table 11-3 and listed in Listing 16.2.4.4.

**Table 11-3 Prior Dermal Treatments and Medications
Intent-to-treat Patients**

	Number (%) of Patients		
	Hylaform N = 133	Zyplast N = 128	Total N = 261
Dermal treatments			
Tissue augmentation (bulking agents)	22 (16.5)	30 (23.4)	52 (19.9)
Microdermabrasion	8 (6.0)	12 (9.4)	20 (7.7)
Chemical peels	8 (6.0)	7 (5.5)	15 (5.7)
Face lift	7 (5.3)	2 (1.6)	9 (3.4)
Dermabrasion	4 (3.0)	4 (3.1)	8 (3.1)
Dermal medications			
Renova, Retin-A, and other prescription treatments	15 (11.3)	15 (11.7)	30 (11.5)
Alpha hydroxy agents (topical)	10 (7.5)	13 (10.2)	23 (8.8)
Other restricted medications			
NSAIDs	14 (10.5)	16 (12.5)	30 (11.5)
Aspirin	10 (7.5)	14 (10.9)	24 (9.2)
Anticoagulation therapy	1 (0.8)	0 (0.0)	1 (0.4)

Reference: Table 14.1.5

The dermal medication and treatment washout period was not met by 4 patients. In the Hylaform group, Patient 02-20 took aspirin on Day 0, Patient 8-10 used alpha hydroxy agents through Day -27, Patient 8-14 used alpha hydroxy agents, Renova, Retin-A, and other treatments through Day -27, and Patient 8-26 had chemical peels on Day 18.

11.2.4 Baseline Medical History and Physical Examination

The medical history and physical examinations were unremarkable. Changes in physical findings from baseline were to be reported as adverse events at subsequent

examinations. Medical history and physical examination findings are listed by patient in Listings 16.2.4.5 and 16.2.4.6, respectively.

11.2.5 Concomitant Medications

Concomitant medications were taken by 121 (91.0%) Hylaform patients and 115 (89.8%) Zyplast patients. Ibuprofen was the most frequently used medication in each treatment group (19.5% in each group). Table 11-4 summarizes concomitant medications used by $\geq 5\%$ of patients in either treatment group. Concomitant medications are summarized by medication class and drug name in Table 14.1.6. Prior and concomitant medications are listed by patients in Listing 16.2.4.7.

Table 11-4 Concomitant Medications Taken by $\geq 5\%$ of Patients Within a Treatment Group Intent-to-treat Patients

Medication Class/ Drug Name	Number (%) of Patients	
	Hylaform N = 133	Zyplast N = 128
Any concomitant medication	121 (91.0)	115 (89.8)
Propionic acid derivatives		
Ibuprofen	26 (19.5)	25 (19.5)
Multivitamins, plain		
Multivitamins, plain	23 (17.3)	23 (18.0)
Calcium		
Calcium	21 (15.8)	18 (14.1)
Other plain vitamins preparations		
Tocopherol	17 (12.8)	13 (10.2)
Ascorbic acid (vit C), plain		
Ascorbic acid	14 (10.5)	11 (8.6)
Anilides		
Paracetamol	12 (9.0)	13 (10.2)
Natural and semisynthetic estrogens, plain		
Estrogens conjugated	11 (8.3)	8 (6.3)
Salicylic acid and derivatives		
Acetylsalicylic acid	11 (8.3)	14 (10.9)
Thyroid hormones		
Levothyroxine sodium	11 (8.3)	4 (3.1)
Other antihistamines for systemic use		
Fexofenadine hydrochloride	7 (5.3)	2 (1.6)
Other muscle relaxants, peripherally acting		
Botulinum toxin type A	7 (5.3)	8 (6.3)
Aminoalkyl ethers		
Diphenhydramine hydrochloride	3 (2.3)	7 (5.5)

Reference: Table 14.1.6

11.2.6 Collagen Skin Test

Screen failures due to positive collagen skin tests were reported for 11 patients (Table 10-1). In addition, Patient 02-07 in the Hylaform group completed the study, but had a positive collagen skin test reported as an off-study adverse event after completion of the study. Collagen skin test assessments are provided in Listing 16.2.4.8.

11.2.7 Pregnancy Test

Patient 05-09 in the Hylaform group had a positive pregnancy test at Week -6; however, her pregnancy test was negative at Day 0, and she received treatment. Pregnancy test results are provided in Listing 16.2.4.9.

11.3 Measurements of Treatment Compliance

Study treatment and anesthetic administrations are listed by patient in Listings 16.2.5.1 and 16.2.5.2, respectively. The investigator administered the treatment; therefore, treatment compliance was not an issue.

11.4 Efficacy Results and Tabulations of Individual Patient Data

The number of nasolabial folds and the number of patients reported vary across visits because data were analyzed as observed with no data imputation applied.

11.4.1 Analysis of Efficacy

11.4.1.1 Primary Efficacy Endpoint: IPR Scores at 12 Weeks After Last Treatment

The mean IPR median score for Hylaform patients (2.3) was similar to Zyplast patients (2.2). The criterion for demonstrating the non-inferiority of Hylaform was met since the lower bound of the 1-sided 97.5% confidence interval for the difference in mean IPR median scores (-0.38) was larger than the prespecified maximum tolerable difference of -0.5 points. Therefore, it was demonstrated that Hylaform was not inferior to Zyplast in the correction of nasolabial folds as assessed by the 6-point grading scale 12 weeks after last treatment. Although non-inferiority was demonstrated, superiority of Hylaform was not; the lower bound of the 1-sided 97.5% confidence interval for the difference in mean IPR median scores was not above 0. Results of the IPR nasolabial fold assessment are presented in Table 11-5. Results are listed by patient in Listing 16.2.6.2 and summarized in Table 14.2.1.1 for the ITT population. Ten patients in the Hylaform group and 11 patients in the Zyplast group had missing IPR median scores at 12 weeks after last treatment and were excluded from these analyses. Descriptive summaries were based on the number of nasolabial folds, while the inferential summaries were based on the number of patients (using the repeated measures analysis of covariance model).

Table 11-5 IPR Nasolabial Fold Assessment at 12 Weeks After Last Treatment Intent-to-treat Patients

	Hylaform N = 133	Zyplast N = 128
Independent Panel Review (IPR) Median Score ^a		
n (number of nasolabial folds)	246 ^b	234 ^c
Mean (SD)	2.3 (1.11)	2.2 (1.12)
Median	2.0	2.0
Minimum, maximum	0.0, 5.0	0.0, 5.0
97.5% confidence interval lower-bound (Zyplast – Hylaform) ^d		-0.38
Patients with ≥1-point improvement from baseline, n (%) ^e	5 (4.1)	11 (9.5)
Difference in proportions (Hylaform – Zyplast) 95% confidence interval		-5.4 -11.8, 1.1

Reference: Table 14.2.1.1

Note: Baseline score was defined as the closest assessment on or before Day 0.

SD = Standard deviation.

- ^a Median of the 3 IPR member scores for each nasolabial fold: 0 = no wrinkles; 1 = just perceptible wrinkle; 2 = shallow wrinkle; 3 = moderately deep wrinkle; 4 = deep wrinkle, well-defined edges; and 5 = very deep wrinkle, redundant fold.
- ^b Ten patients in the Hylaform group had missing IPR median scores for the 12 weeks after last treatment assessment.
- ^c Eleven patients in the Zyplast group had missing IPR median scores for the 12 weeks after last treatment assessment.
- ^d Confidence interval constructed from a repeated measures analysis of covariance model with factors for treatment group, site, patient, nasolabial fold, and baseline score.
- ^e Patients showed an improvement of at least 1 point in both right and left nasolabial folds.

The proportion of patients with at least a 1-point improvement in both nasolabial folds at 12 weeks after last treatment was slightly higher for Zyplast patients (9.5%) than Hylaform patients (4.1%). However, this difference was not determined to be statistically significant at the $\alpha = 0.05$ level based on the 95% confidence interval for the difference in proportions (-11.8%, 1.1%).

The treatment effect appears consistent across study centers (similar differences in mean IPR median scores between treatment groups). Results of the IPR nasolabial fold assessment 12 weeks after last treatment are summarized by center in Table 14.2.2.

Exploratory analysis

An exploratory analysis not documented in the protocol was performed on patients who showed improvement in both nasolabial folds of at least 0.5 points on the 6-point

grading scale as assessed by the IPR median score at 12 weeks. The proportion of patients with at least a 0.5-point improvement in both nasolabial folds at 12 weeks after last treatment was higher for Zyplast patients (25.0%) than Hylaform patients (16.5%) (Table 14.2.1.1). However, this difference was not determined to be statistically significant at the $\alpha = 0.05$ level based on the 95% confidence interval for the difference in proportions (-18.8%, 1.8%).

11.4.1.2 IPR Scores at 12 Weeks After Last Treatment for the Per-protocol Population

Although 18 patients in the Hylaform group and 19 patients in the Zyplast group were excluded from the per-protocol analysis due to major protocol deviations, the results of the IPR median scores at 12 weeks after last treatment for the per-protocol population were similar to the results found for the ITT population. The mean IPR median score for Hylaform patients (2.3) was similar to Zyplast patients (2.2). The criterion for demonstrating the non-inferiority of Hylaform was met for the per-protocol population; the lower bound of the 1-sided 97.5% confidence interval for the difference in mean IPR median scores (-0.36) was larger than the prespecified maximum tolerable difference of -0.5 points. Results of the IPR nasolabial fold assessment for the per-protocol population are summarized in Table 14.2.1.2.

11.4.1.3 IPR Median Scores at 12 Weeks After Last Treatment by Subgroups

The Hylaform and Zyplast IPR median scores were comparable within patient subgroups defined by touch-up status, smoking history, and sun exposure. Touch-up patients typically had higher IPR median scores than patients without touch-up treatment (Tables 14.2.4.1 and 14.2.4.2). The difference in median IPR scores between treatment groups at 12 weeks after touch-up treatment were similar in magnitude and direction to that observed in the primary analysis. No significant differences in median IPR scores between treatment groups were noted based on smoking history or sun exposure. Results of the IPR nasolabial fold assessment 12 weeks after last treatment by patient subgroups are summarized in Table 14.2.3.

11.4.1.4 IPR scores by Visit

Patients in both treatment groups showed similar improvement at Day 3 after the initial treatment. Similar trends for the improvement to slightly lessen over time were also observed, and by 12 weeks after last treatment, the mean IPR median scores returned to near baseline values in both groups. Results of the IPR scores by visit are

presented in Table 11-6. Change from baseline results in IPR scores are summarized for ITT patients in Table 14.2.5.

**Table 11-6 IPR Assessment of Nasolabial Folds by Visit
Intent-to-treat Patients**

	IPR Median Score ^a	
	Hylaform N = 133	Zyplast N = 128
Baseline (Day 0)		
N (number of nasolabial folds)	256 ^b	252 ^c
Mean (SD)	2.2 (1.02)	2.3 (1.04)
Median	2.0	2.5
Minimum, maximum	0, 5	0, 5
Day 3 after initial treatment		
N (number of nasolabial folds)	257	256
Mean (SD)	1.6 (0.81)	1.5 (0.88)
Median	1.5	1.5
Minimum, maximum	0, 4	0, 4
2 weeks after last treatment		
N (number of nasolabial folds)	252	249
Mean (SD)	1.7 (1.00)	1.5 (0.87)
Median	1.5	1.5
Minimum, maximum	0, 5	0, 4
4 weeks after last treatment		
N (number of nasolabial folds)	249	242
Mean (SD)	2.0 (0.97)	1.6 (0.90)
Median	2.0	1.5
Minimum, maximum	0, 5	0, 4
8 weeks after last treatment		
N (number of nasolabial folds)	257	242
Mean (SD)	2.2 (1.02)	1.9 (1.04)
Median	2.0	2.0
Minimum, maximum	0, 5	0, 5
12 weeks after last treatment		
N (number of nasolabial folds)	246	234
Mean (SD)	2.3 (1.11)	2.2 (1.12)
Median	2.0	2.0
Minimum, maximum	0, 5	0, 5

Reference: Table 14.2.4

SD = Standard deviation.

^a Median of the 3 IPR member scores for each nasolabial fold: 0 = no wrinkles; 1 = just perceptible wrinkles; 2 = shallow wrinkles; 3 = moderately deep wrinkle; 4 = deep wrinkle, well-defined edges; 5 = very deep wrinkle, redundant fold.

^b Five patients in the Hylaform group did not have baseline (Day 0) assessments.

^c Two patients in the Zyplast group did not have baseline (Day 0) assessments.

11.4.1.5 Investigator's Wrinkle (Live) Assessment

Live assessments made by the investigator showed similar patterns of improvement when compared with the blinded IPR assessments; a substantial improvement in mean scores immediately after treatment (Day 3 mean of 1.4 for Hylaform group and 1.3 for Zyplast group) followed by a weak trend for the improvement to lessen over time for both treatment groups (12 weeks after last treatment mean of 2.4 for Hylaform group and 2.3 for Zyplast group). The results support the general findings from the primary analysis. The investigator's live wrinkle assessment scores by visit and change from baseline are summarized in Tables 14.2.6 and 14.2.7, respectively.

11.4.1.6 IPR and Investigator Wrinkle (Live) Assessment

The live assessments tended to result in higher scores at baseline (mean of 3.5 for Hylaform patients and 3.6 for Zyplast patients) than the blinded IPR assessments at baseline (mean of 2.2 for Hylaform patients and 2.3 for Zyplast patients). The initial improvements (change from baseline scores at Day 3) were larger when assessed by the investigators (mean change of -2.1 for Hylaform patients and -2.3 for Zyplast patients) than when assessed from photographs by the blinded IPR (mean change of -0.5 for Hylaform patients and -0.8 for Zyplast patients). Improvements at 12 weeks after last treatment (change from baseline scores at 12 weeks after last treatment) were also larger when assessed by the investigators. However, in both cases (improvements at Day 3 and Week 12), the differences between treatment groups were almost identical whether assessed by investigator live assessment or IPR. Results of the combined IPR and investigator's wrinkle assessments are summarized in Tables 14.2.8 (actual values) and 14.2.9 (change from baseline).

11.4.1.7 Investigator and Patient's Global Assessment of Overall Treatment Response

Overall, patients and investigators tended to assign similar assessment scores. The mean patient global assessments were similar between treatment groups at each visit; results were also similar for the investigator assessments. Results of the overall treatment response are presented in Table 11-7. Global assessment scores are listed in Listing 16.2.6.3.

**Table 11-7 Investigator and Patient's Global Assessment
of Overall Treatment Response
Intent-to-treat Patients**

	Investigator		Patient	
	Hylaform (N = 133)	Zyplast (N = 128)	Hylaform (N = 133)	Zyplast (N = 128)
2 weeks after last treatment				
N	131	125	131	124
Mean (SD)	1.7 (0.45)	1.8 (0.39)	1.4 (0.70)	1.5 (0.59)
Median	2.0	2.0	1.0	2.0
Minimum, maximum	1, 2	1, 2	-2, 2	0, 2
4 weeks after last treatment				
N	128	123	128	123
Mean (SD)	1.5 (0.52)	1.7 (0.44)	1.2 (0.72)	1.4 (0.69)
Median	2.0	2.0	1.0	1.0
Minimum, maximum	0, 2	1, 2	-1, 2	-1, 2
8 weeks after last treatment				
N	130	123	129	122
Mean (SD)	1.2 (0.49)	1.4 (0.55)	1.0 (0.71)	1.1 (0.73)
Median	1.0	1.0	1.0	1.0
Minimum, maximum	0, 2	0, 2	-1, 2	-2, 2
12 weeks after last treatment				
N	130	123	130	124
Mean (SD)	0.9 (0.51)	1.0 (0.53)	0.8 (0.69)	0.9 (0.79)
Median	1.0	1.0	1.0	1.0
Minimum, maximum	0, 2	0, 2	0, 2	-2, 2

Reference: Table 14.2.10

SD = Standard deviation.

Note: Overall response to treatment: -2 = much worse, -1 = worse, 0 = no change, 1 = better, and 2 = much better.

11.4.1.8 Duration of Effect for Hylaform-treated Group

Duration of effect was measured as the proportion of Hylaform-treated nasolabial folds which returned to their baseline scores at 12 weeks after last treatment, as assessed by the blinded IPR median score. Therefore, for this definition of duration of effect, a higher value (larger proportion of nasolabial folds that returned to baseline) indicates a less favorable duration of effect. Nasolabial folds were cross-classified based on the IPR median score assessed at baseline and at 2, 4, 8, and

12 weeks after last treatment (Table 14.2.11). At each timepoint, the number and percentage of nasolabial folds that returned to baseline are presented for each baseline score category and overall (total nasolabial folds). For this table, IPR median scores were rounded to whole numbers (eg, scores from 1.5 to <2.5 would be categorized as "2"), and presented in categories represented by the points (0 to 5) of the 6-point grading scale. The proportions of nasolabial folds that returned to their baseline values are presented for 2, 4, 8, and 12 weeks after last treatment.

Of the 243 total Hylaform-treated nasolabial folds with IPR median scores available at both baseline and 12 weeks after last treatment, 178 (73.3%) had 12-week scores that returned to their baseline values. At 2 weeks, the proportion was only 38.2%, and then the proportion consistently increased at each subsequent timepoint; 56.1%, 68.9%, and 73.3% of nasolabial folds returned to their baseline values by 4, 8, and 12 weeks after implantation. In general, the more severe nasolabial folds were at baseline, the more likely they were to maintain the treatment effect at 12 weeks. This trend was observed at each timepoint.

11.4.2 Statistical/Analytical Issues

11.4.2.1 Adjustments for Covariates

Evaluation of the primary efficacy endpoint was performed adjusting for study site and baseline IPR median score.

11.4.2.2 Handling of Dropouts or Missing Data

If patient photographs were not available from the Day 0 visit, test photographs taken at Visit 1 or Visit 2 were used as baseline for the IPR blinded evaluations. Baseline laboratory values were taken as the closest assessment prior to Day 0. All other data were analyzed as observed with no data imputation. Missing data were not estimated in summaries or statistical analyses.

11.4.2.3 Interim Analyses and Data Monitoring

An interim safety report through 4 weeks after repeat treatment with hylan B gel products in the repeat treatment phase of this study is submitted in this report. Ninety-six patients were randomized to treatment, 92 patients had data available through Week 4. Interim analyses of efficacy were not done for this study.

11.4.2.4 Multicenter Studies

Study site was included as a fixed effect in the repeated measures analysis of the primary efficacy endpoint. No formal evaluation of a possible treatment group by site interaction was performed, but outcomes are reported separately by site for comparison. Data from all study sites were pooled for other analyses.

11.4.2.5 Multiple Comparison/Multiplicity

Not applicable to this study.

11.4.2.6 Use of an “Efficacy Subset” of Patients

The primary efficacy analysis was performed on the ITT population. This analysis was repeated using the per-protocol population, in which patients with major protocol violations were excluded.

11.4.2.7 Active-Control Studies Intended to Show Non-inferiority

The non-inferiority of Hylaform treatment was demonstrated at the $\alpha \leq 0.025$ level if the lower bound of the 97.5% 1-sided confidence interval calculated on the difference between the 2 means (Zyplast group mean score minus Hylaform group mean score) was greater than the maximum tolerable difference for non-inferiority that was prespecified at -0.5, based on the mean IPR median score 12 weeks after final treatment.

11.4.2.8 Examination of Subgroups

The primary efficacy analysis was repeated separately for ITT patients who received and who did not receive a touch-up procedure. Treatment response, measured by the IPR median scores at 12 weeks after last study treatment, was summarized by treatment group for subgroups of the population based on smoking habit and sunlight exposure (Table 14.2.3).

11.4.3 Tabulation of Individual Response Data

Patient data listings are provided in Appendices 16.2.6.1 through 16.2.6.3.

11.4.4 Drug Dose, Drug Concentration, and Relationships to Response

Dose was not applicable to this study but the volume injected is discussed in Section 12.1.1.

11.4.5 Drug-Drug and Drug-Disease Interactions

Not applicable to this study.

11.4.6 By-Patient Displays

Not applicable to this study.

11.4.7 Efficacy Conclusions

Hylaform was demonstrated to be non-inferior to Zyplast in the correction of nasolabial folds as assessed using the blinded IPR evaluation of photographs by the 6-point grading scale 12 weeks after last treatment. The mean IPR median score 12 weeks after last treatment for nasolabial folds treated with Hylaform was similar to that for Zyplast-treated nasolabial folds (2.3 and 2.2 points, respectively; a smaller score indicates less severe wrinkle). The lower bound of a 1-sided 97.5% confidence interval calculated on the difference in group means (Zyplast minus Hylaform) was -0.38, greater than the non-inferiority threshold value of -0.5, thereby demonstrating the non-inferiority of Hylaform to Zyplast for correction of nasolabial folds. Since the lower bound was not >0 (1-sided 97.5% confidence interval = 2-sided 95% confidence interval), superiority could not be claimed.

Secondary evaluations were supportive of the non-inferiority conclusion made for the primary efficacy variable. When evaluated based on investigator live assessments, the mean score 12 weeks after last treatment was again almost the same for Hylaform-treated patients (2.4 points) as for Zyplast-treated patients (2.3 points). The mean score for the patient's global assessment of overall response 12 weeks after last treatment was similar for Zyplast-treated and Hylaform-treated patients (0.9 and 0.8 points, respectively; a larger score indicates more improvement), with similar results for the mean score of the investigator's global assessment of overall response 12 weeks after last treatment (1.0 points for Zyplast and 0.9 points for Hylaform). A larger proportion of Zyplast patients achieved at least a 1-point improvement in both nasolabial folds at 12 weeks than Hylaform patients (9.5% vs. 4.1%); however, this difference was not statistically significant at $\alpha = 0.05$ level based on the associated 2-sided 95% confidence interval. In general, the more severe the nasolabial folds were at baseline, the more likely they were to maintain the treatment effect at 12 weeks. This trend was observed at each timepoint.

12. SAFETY EVALUATION**12.1 Safety Evaluation: Initial Phase****12.1.1 Extent of Exposure: Initial Phase**

Time on study during the initial phase of the study was similar between the two treatment groups. The mean time on study was 89.1 days (range: 46 to 140 days) for Hylaform patients and 87.2 days (range: 21 to 149 days) for Zyplast patients (Table 14.1.1). All touch-up patients (22 Hylaform patients and 9 Zyplast patients) completed the study (Listing 16.2.1.1). Six patients (3 Hylaform patients, 3 Zyplast patients) discontinued after initial treatment but before completion of the 12-week visit.

During the initial phase of the study, the mean total volume injected in both nasolabial folds for patients receiving initial treatment was larger in the Zyplast group (1.6 mL for Hylaform patients, 2.2 mL for Zyplast patients). The mean volume injected was the same for each nasolabial fold (right and left) within a treatment group (0.8 mL for Hylaform patients; 1.1 mL for Zyplast patients) (Table 12-1). The syringe-fill size was approximately 1.0 mL for Zyplast and approximately 0.75 mL for Hylaform indicating, on average, that 1 full syringe of study device was used in the correction of a nasolabial fold. The mean duration of treatment (stop time minus start time) was slightly longer for Hylaform patients (14.2 minutes for Hylaform patients; 12.6 minutes for Zyplast patients) (Table 14.1.8).

Twenty-two (16.5%) of 133 Hylaform patients and 9 (7.1%) of the 128 Zyplast patients required a touch-up treatment (the difference in proportions [Zyplast minus Hylaform] was -9.5%). The 95% confidence interval for the difference in proportions was -17.2% to -1.7%, indicating the difference in proportions is significantly different from 0 at $\alpha = 0.05$. As with the initial treatment, the total volume injected for touch-up of both nasolabial folds was greater for the Zyplast patients (1.3 mL for Zyplast patients; 0.7 mL for Hylaform patients). Exposure to study treatment is summarized in Table 14.1.8.

**Table 12-1 Exposure to Study Treatment
Intent-to-treat Patients**

	Hylaform N = 133	Zyplast N = 128
Initial treatment - Baseline (Day 0)		
Volume injected (mL) - right nasolabial fold		
n	133	128
Mean (SD)	0.8 (0.38)	1.1 (0.44)
Median	0.8	1.0
Minimum, maximum	0.2, 2.4	0.3, 2.6
Volume injected (mL) - left nasolabial fold		
n	133	128
Mean (SD)	0.8 (0.39)	1.1 (0.44)
Median	0.8	1.0
Minimum, maximum	0.2, 2.4	0.2, 2.6
Volume injected (mL) - both nasolabial folds		
n	133	128
Mean (SD)	1.6 (0.76)	2.2 (0.84)
Median	1.5	2.0
Minimum, maximum	0.5, 4.8	0.5, 4.0
Patients requiring touch-up, n (%)	22 (16.5)	9 (7.1)
Difference in proportions of touch-up patients (Zyplast – Hylaform)		-9.5%
95% confidence interval		-17.2, -1.7
Touch-up treatment (Week 2)		
Volume injected (mL) - right nasolabial fold		
n	21	9
Mean (SD)	0.3 (0.21)	0.5 (0.36)
Median	0.3	0.5
Minimum, maximum	0.0, 0.7	0.0, 1.0
Volume injected (mL) - left nasolabial fold		
n	22	9
Mean (SD)	0.4 (0.32)	0.7 (0.44)
Median	0.4	0.5
Minimum, maximum	0.0, 1.5	0.3, 1.7
Volume injected (mL) – both nasolabial folds		
n	22	9
Mean (SD)	0.7 (0.40)	1.3 (0.63)
Median	0.6	1.0
Minimum, maximum	0.3, 1.9	0.5, 2.3

Reference: Table 14.1.8
SD = Standard deviation.

Patients were asked to assess which treatment they believed they received (Table 14.1.9). Over 50% of the patients in each treatment group did not know what treatment they received. In the Hylaform group, 36 (27.1%) believed that they

received Hylaform; 18 (13.5%) believed that they received Zyplast, and 76 (57.1%) did not know. In the Zyplast group, 31 (24.2%) believed that they received Zyplast, 25 (19.5%) believed that they received Hylaform, and 69 (53.9%) did not know.

12.1.2 Adverse Events: Initial Phase

12.1.2.1 Brief Summary of Adverse Events

Adverse events were classified as follows:

- **Baseline:** adverse events with onset time after signing of informed consent but prior to first implantation of study device. Disease signs, symptoms, and/or laboratory abnormalities existing prior to device implantation were not to be considered adverse events if present after treatment unless they recurred after the patient recovered from a preexisting condition, or represented a clinically significant exacerbation in intensity or frequency, in the opinion of the investigator.
- **Treatment-emergent:** adverse events with onset time on or after the first implantation of study device, or baseline findings or adverse events that worsened in severity or frequency before the patient's last initial phase study visit.
- **Off-study:** adverse events that occurred after patient's last initial phase visit and prior to enrollment (signing the informed consent) in the repeat treatment phase of the study, if applicable.

Treatment-emergent adverse events were further classified as follows:

- **Procedure-related events:** adverse events occurring from the day of study device injection (Day 0) to Day 3 that were reported by the investigator as procedure-related. Procedure-related adverse events that had a duration greater than 2 weeks or changed in severity, frequency, or causality were reevaluated (see discussion in Section 9.7.1.2.2).
- **Not procedure-related:** all other adverse events reported by the investigator; ie, anesthetic-related; device-related; or unrelated to anesthetic, device, or procedure.

In the Hylaform group, 117 (88%) of 133 patients reported 342 treatment-emergent events. Of these 342 events, 281 were procedure-related events, and 61 were not procedure-related events. Of these 61 events, 3 were considered device-related. No deaths or discontinuations due to adverse events were reported; 1 serious unrelated treatment-emergent adverse event was reported (hemorrhoids). Three (2%) patients experienced 3 severe adverse events.

In the Zyplast group, 112 (88%) of 128 patients reported 322 treatment-emergent events. Of these 322 events, 259 were procedure-related events, and 63 were not

procedure-related events. Of these 63 events, 14 were considered device-related. No deaths or serious treatment-emergent adverse events were reported.

Two (2%) patients reported unrelated baseline serious adverse events. Two patients (2%) discontinued the study due to an adverse event (migraines and mobilization decreased). Seven (6%) patients experienced 7 severe adverse events. An overview of adverse events reported during the initial phase of the study is provided in Table 12-2.

Table 12-2 Initial Phase: Overview of Treatment-emergent Adverse Events Intent-to-treat Patients [Number (%) of Patients and Number of Events]

Adverse Event	Hylaform N = 133			Zyplast N = 128		
	n	(%)	Events	n	(%)	Events
At least 1 adverse event	117	(88)	342	112	(88)	322
Procedure-related	111	(84)	281	109	(85)	259
Not procedure-related	39	(29)	61	43	(34)	63 ^a
Anesthetic-related	0	(0)	0	1	(1)	1
Device-related	2	(2)	3	9	(7)	14
Unrelated ^b	38	(29)	58	34	(27)	49
Deaths	0	(0)	0	0	(0)	0
Discontinuations due to adverse event	0	(0)	0	2	(2)	2
Serious adverse event	1	(1)	1	0	(0)	0
Severe adverse events	3	(2)	3	7	(6)	7

References: Tables 14.3.1.2 through 14.3.1.8, and 14.3.2.1 through 14.3.2.3 and Listing 16.2.7.7

^aOne patient (Patient 02-25) had an adverse event that was considered both anesthetic-related and device-related.

^bUnrelated to either procedure, anesthetic, or device.

12.1.2.2 Display of Adverse Events: Initial Phase

12.1.2.2.1 Baseline Adverse Events: Initial Phase

Adverse events with an onset time at the signing of the consent form, but prior to first implantation of the study device were reported as baseline adverse events. Skin test evaluations during the screening period were considered inclusion/exclusion criteria and were not reported as baseline adverse events.

Baseline adverse events were reported in 16 (12%) of the 133 Hylaform patients (26 events), 19 (15%) of the 128 Zyplast patients (29 events), and 2 (3%) of the 78 screen failures (4 events). Baseline adverse events reported by more than 1 patient in a treatment group were: headache (6 events for 6 Hylaform patients; 3 events for 3 Zyplast patients), injection (skin test) site bruising (2 events for 2 Hylaform patients; 2 events for 2 Zyplast patients), and sinusitis (2 events for 2 Hylaform patients).

Two patients in the Zyplast group reported serious baseline adverse events (foot fracture and nephrolithiasis). Baseline adverse events are listed by patient in Listing 16.2.7.1 and summarized in Table 14.3.1.1.

12.1.2.2.2 Treatment-emergent Adverse Events: Initial Phase

Treatment-emergent adverse events for the initial phase of the study include procedure-related and not procedure-related adverse events reported from the time of initial study device implantation to the completion of the initial phase or discontinuation from initial phase participation.

Treatment-emergent adverse events occurring in $\geq 2\%$ of patients in either treatment group are presented in Table 12-3. Treatment-emergent adverse events were reported for 117 (88%) of Hylaform patients (342 events) and 112 (88%) of Zyplast patients (322 events). The adverse event of rash was experienced by 4 Hylaform patients; all were reported as unrelated to treatment. The 95% confidence intervals for the incidence rate of treatment-emergent adverse events were similar for Hylaform patients (81.2% to 93.0%) and Zyplast patients (80.5% to 92.7%). There was no evidence of a statistical difference in incidence rates between treatment groups; the difference in proportions (Zyplast minus Hylaform) was -0.5% (95% confidence interval: -8.4% to 7.5%).

One patient in the Zyplast group (Patient 02-03) experienced a treatment-emergent adverse event of mobilization decreased after undergoing partial knee replacement surgery for localized osteoarthritis. As a result of this decreased mobilization, the patient discontinued from the study. Prior to database lock, the investigator reported that the patient experienced localized osteoarthritis unrelated to treatment, which is noted in the adverse event listings; however, upon further clarification post-database lock, the investigator reported that the localized osteoarthritis was not an adverse event because the osteoarthritis was present at baseline, did not worsen during study participation, and that the partial knee replacement surgery was preplanned. This

post-data lock information is reflected in this report but is not indicated in the data listings. This clarification from the investigator does not effect the categorization or analysis of adverse events given that both medical entities were treatment-emergent and unrelated to treatment.

**Table 12-3 Treatment-emergent Adverse Events
Occurring in $\geq 2\%$ of Patients
[Number (%) of Patients and Number of Events]**

Primary System Organ Class/ Preferred Term	Hylaform N = 133			Zyplast N = 128		
	n	(%)	Events	n	(%)	Events
At least 1 adverse event	117	(88)	342	112	(88)	322
General disorders and administration site conditions	113	(85)	281	109	(85)	275
Injection site erythema	84	(63)	93	86	(67)	100
Injection site bruising	54	(41)	59	39	(31)	41
Injection site swelling	47	(35)	50	53	(41)	54
Injection site pain	42	(32)	44	29	(23)	33
Injection site pruritus	11	(8)	13	12	(9)	12
Injection site desquamation	3	(2)	3	7	(6)	7
Injection site induration	3	(2)	3	1	(1)	1
Injection site paraesthesia	3	(2)	4	2	(2)	2
Application site dryness	2	(2)	2	3	(2)	3
Application site scabbing	1	(1)	1	3	(2)	3
Injection site nodule	0	(0)	0	4	(3)	7
Application site papules	0	(0)	0	3	(2)	3
Infections and infestations	20	(15)	22	9	(7)	9
Nasopharyngitis	7	(5)	7	3	(2)	3
Influenza	5	(4)	5	2	(2)	2
Nervous system disorders	9	(7)	10	5	(4)	5
Headache	6	(5)	6	3	(2)	3
Skin and subcutaneous tissue disorders	7	(5)	8	8	(6)	8
Rash NOS	4	(3)	5	0	(0)	0

Reference: Table 14.3.1.2
NOS = Not otherwise specified.

12.1.2.2.3 Treatment-emergent Adverse Events by Relatedness

Procedure-related Adverse Events

A total of 111 (84%) of 133 patients in the Hylaform group (281 events) and 109 (85%) of 128 patients in the Zyplast group (259 events) experienced procedure-related adverse events. The 95% confidence interval for the incidence rate of procedure-related adverse events was 76.0% to 89.3% for Hylaform patients and

77.8% to 90.8% for Zyplast patients. There was no evidence of a statistical difference in incidence rates between treatment groups; the difference in proportions (Zyplast minus Hylaform) was 1.70% (95% confidence interval: -7.1% to 10.5%).

Procedure-related adverse events occurring in greater than 5% of patients in the Hylaform group were injection site erythema, 84 (63%) patients; injection site bruising, 54 (41%) patients; injection site swelling, 47 (35%) patients; injection site pain, 42 (32%) patients; and injection site pruritus, 10 (8%) patients.

Procedure-related adverse events occurring in greater than 5% of patients in the Zyplast group were injection site erythema, 86 (67%) patients; injection site bruising 39 (31%) patients; injection site swelling, 53 (41%) patients; injection site pain, 29 (23%) patients; injection site pruritus, 11 (9%) patients; and injection site desquamation, 7 (6%) patients. A complete summary of procedure-related adverse events is presented in Table 14.3.1.3; procedure-related adverse events occurring in $\geq 2\%$ of patients in either treatment group are displayed in Table 12-4.

**Table 12-4 Procedure-related Adverse Events
Occurring in $\geq 2\%$ of Patients
[Number (%) of Patients and Number of Events]**

Primary System Organ Class/ Preferred Term	Hylaform N = 133			Zyplast N = 128		
	n	(%)	Events	n	(%)	Events
At least 1 adverse event	111	(84)	281	109	(85)	259
General disorders and administration site conditions	111	(84)	274	109	(85)	258
Injection site erythema	84	(63)	92	86	(67)	94
Injection site bruising	54	(41)	59	39	(31)	39
Injection site swelling	47	(35)	50	53	(41)	54
Injection site pain	42	(32)	44	29	(23)	32
Injection site pruritus	10	(8)	12	11	(9)	11
Injection site paraesthesia	3	(2)	4	2	(2)	2
Injection site desquamation	3	(2)	3	7	(6)	7
Application site dryness	1	(1)	1	3	(2)	3
Application site scabbing	1	(1)	1	3	(2)	3
Injection site nodule	0	(0)	0	3	(2)	3
Application site papules	0	(0)	0	3	(2)	3

Reference: Table 14.3.1.3

Not Procedure-related Adverse Events

Adverse events not related to the procedure were reported for 39 (29%) of 133 patients (61 events) in the Hylaform group and 43 (34%) of 128 patients (63 events) in the Zyplast group. Not procedure-related adverse events are summarized in Table 14.3.1.4.

Subcategories of not procedure-related adverse events (anesthetic-related adverse events, device-related adverse events, and unrelated adverse events) are discussed in the following paragraphs.

Anesthetic-related Adverse Events

Anesthetic-related adverse events were not experienced by patients in the Hylaform group. One (1%) of the 128 patients in the Zyplast group had 1 anesthetic-related adverse event (injection site erythema), which did not require treatment. Anesthetic-related adverse events are summarized in Table 14.3.1.5.

Device-related Adverse Events

Two (2%) of 133 patients had 3 device-related adverse events in the Hylaform group and 9 (7%) of 128 patients had 14 device-related adverse events in the Zyplast group (Table 12-5). Device-related adverse events experienced by Hylaform patients were injection site erythema, injection site induration, and injection site pruritus (1 event each). The most common device-related adverse events experienced by patients in the Zyplast group were injection site erythema (5 patients) and injection site nodule (2 patients). The 95% confidence interval for the difference in proportions was 0.6% to 10.4%, indicating the difference in proportions is significantly different from 0 at $\alpha = 0.05$.

Table 12-5 Treatment-emergent, Device-related Adverse Events
[Number (%) of Patients and Number of Events]

Primary System Organ Class/ Preferred Term	Hylaform N = 133			Zyplast N = 128		
	n	(%)	Events	n	(%)	Events
At least 1 adverse event	2	(2)	3	9	(7)	14
Gastrointestinal disorders	0	(0)	0	1	(1)	1
Stomatitis	0	(0)	0	1	(1)	1
General disorders and administration site conditions	2	(2)	3	8	(6)	13
Injection site bruising	0	(0)	0	1	(1)	2
Injection site erythema	1	(1)	1	5	(4)	5
Injection site induration	1	(1)	1	0	(0)	0
Injection site necrosis	0	(0)	0	1	(1)	1
Injection site nodule	0	(0)	0	2	(2)	4
Injection site pain	0	(0)	0	1	(1)	1
Injection site pruritus	1	(1)	1	0	(0)	0

Reference: Table 14.3.1.6

Unrelated Adverse Events

A total of 38 (29%) of 133 patients in the Hylaform group (58 events) and 34 (27%) of 128 patients in the Zyplast group (49 events) experienced adverse events that were unrelated to either procedure, anesthetic, or device (Table 14.3.1.7). Nasopharyngitis (7 patients), headache (6 patients), influenza (5 patients), rash (4 patients), conjunctivitis (2 patients), and sinusitis (2 patients) occurred for more than 1 patient in the Hylaform group. In the Zyplast group, nasopharyngitis and headache (3 patients each), and viral gastroenteritis, influenza, and acne (2 patients each) occurred for more than 1 patient.

12.1.2.2.4 Treatment-emergent Adverse Events by Severity

Maximum severity was determined from the maximum intensity occurring for each patient for a particular adverse event. The majority of adverse events reported were mild or moderate in severity (Table 12-6). Three (2%) of the 133 Hylaform patients and 7 (6%) of 128 patients in the Zyplast group experienced severe adverse events; none of these events was device-related.

**Table 12-6 Overview of Treatment-emergent Adverse Events
by Maximum Severity
[Number (%) of Patients]**

Adverse Event	Hylaform N = 133						Zyplast N = 128					
	Mild		Mod		Severe		Mild		Mod		Severe	
At least 1 adverse event	99	(74)	15	(11)	3	(2)	96	(75)	9	(7)	7	(6)
Procedure-related	105 ^a	(79)	6	(5)	0	(0)	105 ^a	(82)	2	(2)	2	(2)
Not procedure-related	26	(20)	10	(8)	3	(2)	28	(22)	10	(8)	5	(4)
Anesthetic-related	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)	0	(0)
Device-related	2	(2)	0	(0)	0	(0)	7	(6)	2	(2)	0	(0)
Unrelated ^b	25	(19)	10	(8)	3	(2)	21	(16)	8	(6)	5	(4)

Reference: Tables 14.3.1.8, 14.3.1.9, 14.3.1.10, 14.3.1.11, 14.3.1.12, and 14.3.1.13

Mod = Moderate.

^aThe total number of patients in each row equals the total number of patients reporting 1 or more events within that category. In each of the table rows, a patient is counted once by severity only if the patient experienced an event in that specific event category. For example, a patient with a maximum severity of mild for procedure-related events and a maximum severity of severe for a not-procedure-related adverse event would be counted as 'severe' in the 'At least 1 adverse event' and 'Not-procedure-related' rows, but as 'mild' in the procedure-related row.

^bUnrelated to either procedure, anesthetic, or device.

Procedure-related Adverse Events by Severity

In the Hylaform group, the maximum severity of procedure-related adverse events was mild for 105 (79%) patients and moderate for 6 (5%) patients. No severe procedure-related adverse events occurred in the Hylaform group. Injection site erythema, injection site bruising, injection site swelling, and injection site pain were the most commonly reported procedure-related events for this treatment group. (Table 12-7).

In the Zyplast group, the maximum severity of procedure-related adverse events was mild for 105 (82%) patients, moderate for 2 (2%) patients, and severe for 2 (2%) patients (injection site pain). Injection site erythema, injection site swelling, injection site bruising, and injection site pain were the most commonly reported procedure-related events for this treatment group (Table 12-7).

**Table 12-7 Procedure-related Adverse Events by Maximum Severity Occurring in ≥2% of Patients
[Number (%) of Patients]**

Primary System Organ Class/Preferred Term ^a	Hylaform N = 133						Zyplast N = 128					
	Mild		Mod		Severe		Mild		Mod		Severe	
At least 1 adverse event	105	(79)	6	(5)	0	(0)	105	(82)	2	(2)	2	(2)
General disorders and administration site conditions	105	(79)	6	(5)	0	(0)	105	(82)	2	(2)	2	(2)
Injection site erythema	83	(63)	1	(1)	0	(0)	85	(66)	1	(1)	0	(0)
Injection site bruising	52	(39)	2	(2)	0	(0)	37	(29)	2	(2)	0	(0)
Injection site swelling	45	(34)	2	(2)	0	(0)	52	(41)	1	(1)	0	(0)
Injection site pain	40	(30)	2	(2)	0	(0)	26	(20)	1	(1)	2	(2)
Injection site pruritus	10	(8)	0	(0)	0	(0)	11	(9)	0	(0)	0	(0)
Injection site desquamation	3	(2)	0	(0)	0	(0)	7	(6)	0	(0)	0	(0)
Injection site paraesthesia	3	(2)	0	(0)	0	(0)	2	(2)	0	(0)	0	(0)
Application site dryness	1	(1)	0	(0)	0	(0)	3	(2)	0	(0)	0	(0)
Application site scabbing	1	(1)	0	(0)	0	(0)	3	(2)	0	(0)	0	(0)
Injection site nodule	0	(0)	0	(0)	0	(0)	3	(2)	0	(0)	0	(0)
Application site papules	0	(0)	0	(0)	0	(0)	3	(2)	0	(0)	0	(0)

Reference: Table 14.3.1.9

Mod = Moderate.

^aPatients are represented by the event with the highest severity for each Preferred Term.

Not Procedure-related Adverse Events by Severity

In the Hylaform group, the maximum severity of not procedure-related adverse events was mild for 26 (20%) patients, moderate for 10 (8%) patients, and severe for 3 (2%) patients (conjunctivitis, headache).

In the Zyplast group, the maximum severity of not procedure-related adverse events was mild for 28 (22%) patients, moderate for 10 (8%) patients, and severe for 5 (4%) patients (road traffic accident, localized osteoarthritis, headache, migraine NOS, endometriosis). Not procedure-related adverse events are summarized by maximum intensity in Table 14.3.1.10.

Anesthetic-related Adverse Events by Severity

No anesthetic-related adverse events occurred for Hylaform patients. One anesthetic-related adverse event occurred in the Zyplast group (mild injection site erythema) (Table 14.3.1.11).

Device-related Adverse Events by Severity

Two patients in the Hylaform group had device-related adverse events of mild severity; no moderate or severe device-related adverse events occurred in the Hylaform group. In the Zyplast group, 7 patients had mild events, 2 patients had moderate events, and no patient had a severe device-related adverse event. The only device-related adverse event experienced by more than 1 patient in a treatment group was mild injection site erythema, reported for 5 patients in the Zyplast group. Device-related adverse events are presented by maximum severity in Table 12-8.

Unrelated Adverse Events by Severity

Twenty-five (19%) patients in the Hylaform group had unrelated adverse events of mild severity; 10 (8%) patients had events of moderate severity, and 3 (2%) patients had events of severe intensity (headache, conjunctivitis, headache). In the Zyplast group, 21 (16%) patients had mild events, 8 (6%) patients had moderate events, and 5 (4%) patients had severe events (road traffic accident, mobilization decreased, headache, migraine NOS, endometriosis) (Table 14.3.1.13). Refer to Section 12.4.2 regarding mobilization decreased.

**Table 12-8 Device-related Adverse Events by Maximum Severity
[Number (%) of Patients]**

Primary System Organ Class/Preferred Term ^a	Hylaform N = 133						Zyplast N = 128					
	Mild		Mod		Severe		Mild		Mod		Severe	
At least 1 adverse event	2	(2)	0	(0)	0	(0)	7	(6)	2	(2)	0	(0)
Gastrointestinal disorders	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)	0	(0)
Stomatitis	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)	0	(0)
General disorders and administration site conditions	2	(2)	0	(0)	0	(0)	6	(5)	2	(2)	0	(0)
Injection site erythema	1	(1)	0	(0)	0	(0)	5	(4)	0	(0)	0	(0)
Injection site induration	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Injection site pruritus	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Injection site bruising	0	(0)	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)
Injection site necrosis	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)	0	(0)
Injection site nodule	0	(0)	0	(0)	0	(0)	1	(1)	1	(1)	0	(0)
Injection site pain	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)	0	(0)

Reference: Table 14.3.1.12

Mod = Moderate; NOS = Not otherwise specified.

^aPatients are represented by the event with the highest severity for each Preferred Term.

12.1.2.2.5 Treatment-emergent Adverse Events in Hylaform-treated Patients and Hylan B IgG Antibody Titers

Only one of 133 patients in the Hylaform group had a greater than fourfold increase (compared to baseline) in hylan B IgG antibody titer after initial treatment (Listing 16.2.8.1). However, the only adverse events for this patient (Patient 01-09) were injection site bruising and headache, which are not consistent with an allergic response. Evaluation of adverse events and hylan B IgG antibody titers was not required for the remaining 132 patients, due to the absence of a greater than fourfold increase in hylan B IgG antibody titers. See Section 12.1.6 for further discussion regarding hylan B IgG antibody titers.

12.1.2.2.6 Off-study Adverse Events

Off-study adverse events were reported, per the discretion of the investigators, for those patients who experienced adverse events after discontinuation from the study prior to Week 12 of the initial phase, and for those patients who experienced adverse events after completion of the initial phase of the study but before signing the consent form if they enrolled in the repeat treatment phase of the study. Since off-study adverse events occurred in an uncontrolled setting and were reported at the discretion of the investigators, off-study adverse events were not summarized or analyzed with treatment-emergent adverse events. Off-study adverse events are included in this clinical study report for completeness. Two off-study adverse events were reported. Patient 02-07 (Hylaform group) reported a mild reaction to the collagen skin test 127 days after treatment in the initial phase. This patient entered the repeat phase of the study and the adverse event was ongoing at Week 4. The investigator considered this event to be related to skin test device. Patient 04-15 (Hylaform group) reported a mild headache 100 days after treatment. This patient did not enter the repeat phase of the study; the investigator did not consider this event to be related to study device (Listing 16.2.7.8).

12.1.2.3 Analysis of Adverse Events: Initial Phase

Adverse events occurred with similar incidence and were of similar types for both treatment groups. The majority of treatment-emergent adverse events were procedure-related. Procedure-related events were mostly mild and did not require treatment. Not-procedure-related events were generally unrelated to anesthetic or study device.

Treatment-emergent adverse events were reported for 117 (88%) of the 133 Hylaform patients (342 events) and 112 (88%) of 128 Zyplast patients (322 events). Three (2%) of the Hylaform patients and 7 (6%) of the Zyplast patients reported severe adverse events; none was device-related. The most common treatment-emergent adverse event in both treatment groups was local injection site reaction.

Anesthetic-related adverse events were reported by 1 patient in the Zyplast group (1 event). Device-related adverse events were reported by 2 patients (3 events) in the Hylaform group and 9 patients (14 events) in the Zyplast group.

Adverse events unrelated to procedure, anesthetic, or device were reported by 38 (29%) Hylaform patients and 34 (27%) Zyplast patients. Nasopharyngitis, headache, and influenza were reported by more than 1 patient in each treatment group. In addition, rash, conjunctivitis, and sinusitis were reported by more than 1 Hylaform patient; and viral gastroenteritis and acne were reported by more than 1 Zyplast patient.

12.1.2.4 Listing of Adverse Events by Patient: Initial Phase

Baseline; procedure-related; not procedure-related; anesthetic-related; device-related; treatment-emergent adverse events unrelated to procedure, anesthetic, or device; all treatment-emergent adverse events; and off-study adverse events are provided in Listings 16.2.7.1 through 16.2.7.8, respectively.

12.1.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events: Initial Phase

12.1.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.1.3.1.1 Deaths

No deaths were reported during the initial phase of the study.

12.1.3.1.2 Other Serious Adverse Events

Two unrelated baseline serious adverse events were experienced by 2 patients in the Zyplast group. One unrelated treatment-emergent serious adverse event was experienced by a patient in the Hylaform group (Table 12-9).

Table 12-9 Serious Adverse Events by Treatment Group

Patient ID	Treatment Duration at Onset (Days)	MedDRA Preferred Term	Severity	Relatedness	Outcome
Treatment group: Hylaform					
07-05	52	Hemorrhoids	Mild	Not related	Recovered
Treatment group: Zyplast					
01-01	-38 ^a	Foot fracture	Moderate	Not related	Recovered
04-10	-48 ^a	Nephrolithiasis	Moderate	Not related	Recovered

Reference: Table 14.3.2.2 and Listing 16.2.7.1.

^aBaseline adverse event**12.1.3.1.3 Other Significant Adverse Events**

Two patients, both in the Zyplast treatment group, discontinued the initial phase due to adverse events. Patient 02-03 (Zyplast group) underwent a preplanned, partial knee replacement surgery for baseline localized osteoarthritis. Refer to Section 12.1.2.2.2 regarding this patient's discontinuation from the study. Patient 06-10 (Zyplast group) discontinued the study due to worsening of pretreatment migraines. Both events were not related to the study device.

Two patients, both in the Zyplast treatment group, experienced injection site necrosis (Patient 02-03 and Patient 04-04). Details of these events are provided in Section 12.1.3.2.

12.1.3.2 Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Narratives for serious adverse events, discontinuations due to adverse events, and significant adverse events are provided in this section.

Baseline serious adverse events**Patient 01-01 (Zyplast group): Foot fracture**

A 47-year-old female patient broke her right second toe on 23 July 2002. The patient had consented to the study, but had not yet received any study treatment. The patient underwent outpatient surgery on 24 July 2002. The patient was treated from 1 to 7 August 2002 with cephalexin, 500 mg, by mouth, every 6 hours, as prophylaxis for the postoperative, open surgical wound, and from 1 to 5 August 2002 with hydrocodone, 5 mg, by mouth, whenever necessary, for postoperative pain. The patient recovered from the serious adverse event on 7 August 2002. Although the patient had consented to the study, she had not yet received study device at the time

the serious event occurred; therefore, no relationship existed between the serious adverse event and the study device.

Patient 04-10 (Zyplast group): Nephrolithiasis

A 49-year-old female patient was hospitalized with kidney stones on 2 September 2002. The patient consented to the study 1 week before the hospitalization and was due to receive the second collagen test implant on 9 September 2002. The patient had not been randomized, and no study treatment had been administered at the time of this event. The patient had no past history of kidney stones. The patient was treated with pyridium (phenazopyridine hydrochloride), 200 mg, by mouth, 4 times a day from 12 to 22 September 2002 and darvocet (acetaminophen/propoxyphene napsylate), 1 tablet, by mouth, twice a day from 12 to 14 September 2002. At the time of hospital discharge, the patient had been ambulatory, voiding, tolerating diet well, afebrile, and had pain tolerably managed by oral medications. The patient recovered without sequelae.

Treatment-emergent serious adverse events

Patient 07-05 (Hylaform group): Hemorrhoids

A 38-year-old male patient was diagnosed with internal and external hemorrhoids and underwent a subsequent hemorrhoidectomy. The patient's medical history was significant for occasional headaches, a tonsillectomy (date unspecified), and seasonal allergies. No concomitant medications were reported. The patient received 3.0 mL of Hylaform for the correction of the nasolabial folds by route of intradermal injection; approximately 1.5 mL was injected on 6 September 2002 at initial treatment and approximately 1.5 mL was injected on 4 October 2002 at touch-up treatment. The patient was diagnosed with a case of mild, internal and external hemorrhoids on 28 October 2002 and underwent a surgical hemorrhoidectomy via out-patient day surgery on 29 October 2002. The patient was treated for postoperative pain with oxycodone HCl (1 tablet, by mouth, every 6 to 8 hours, whenever necessary) from 29 to 31 October 2002, oxycodone/acetaminophen (1 tablet, by mouth, every 6 to 8 hours, whenever necessary) on 1 November 2002, and with propoxyphene napsylate/acetaminophen (1 tablet, by mouth, every 4 to 6 hours, whenever necessary) from 2 to 4 November 2002. In the opinion of the investigator, the event was not related to either the study device or the anesthetic. The patient recovered from the adverse events on 29 October 2002 without sequelae.

Discontinuations due to adverse events**Patient 02-03 (Zyplast group): Mobilization decreased**

A 54-year-old female patient was hospitalized for knee replacement due to osteoarthritis on 27 October 2002 (Day 61). The patient had prestudy knee osteoarthritis of severe intensity, for which she underwent a preplanned, elective surgical intervention in the form of a partial knee replacement to alleviate the pain associated with the osteoarthritis. The patient recovered from the localized osteoarthritis without sequelae. In the opinion of the investigator, the localized osteoarthritis (knee) was unrelated to the study treatment, anesthetic, or procedure. The patient received a total of 2.65 mL of Zyplast on 27 August 2002. Due to her immobility during the surgical recovery, the patient chose to discontinue from the study. The patient discontinued the study due to this adverse event on Day 61.

Patient 06-10 (Zyplast group): Migraines

A 38-year-old female patient experienced a migraine on 21 October 2002 (Day 20), which was reported as a nonserious adverse event. The patient had a history of occasional migraines and vertigo. The patient received a total of 1.0 mL of Zyplast on 1 October 2002. The patient was treated with sumatriptan succinate on 21 October 2002 for the worsening migraines. In the opinion of the investigator, the adverse event of worsening migraines was unrelated to the study treatment, anesthetic, or procedure. The event was ongoing at the time of study discontinuation.

Significant adverse events**Patient 02-03 (Zyplast group): Injection site necrosis**

A 54-year-old female patient experienced a procedure-related event of injection site necrosis on 28 August 2002 (Day 1). The event was mild in severity. The patient was treated with bacitracin ointment. The patient recovered on 3 September 2002 (Day 7).

Patient 04-04 (Zyplast group): Injection site necrosis

A 46-year-old female patient experienced a procedure-related event of injection site necrosis on 21 September 2002 (Day 3). The event was moderate in severity. The patient was treated with ultravate ointment (topical), twice a day, from 21 to 22 September 2002, and ibuprofen, as necessary, from 23 September 2002. On 14 November 2002 (Day 57), the investigator reassessed the severity as mild, and

changed the causality of the adverse event of injection site necrosis from procedure-related to study device-related. The event was ongoing at the time of study completion.

12.1.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths were reported during the initial phase of the study. Two baseline serious adverse events and 1 treatment-emergent serious adverse event were reported; none of these events were related to study device. Two patients withdrew from the study due to unrelated adverse events (worsening migraines, localized osteoarthritis). Both patients had histories of their findings prior to study entry. Two significant adverse events were procedure-related events (injection site necrosis) reported for Zyplast patients. One event of injection site necrosis resolved by Day 7; however, the other event of injection site necrosis was ongoing at study completion, and the investigator changed the causality of the event on Day 57 from procedure-related to study device-related.

12.1.4 Clinical Laboratory Evaluation: Initial Phase

12.1.4.1 Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value

Hematology and chemistry data are provided in Listings 16.2.8.2.1 through 16.2.8.3.3.

12.1.4.2 Evaluation of Each Laboratory Parameter

12.1.4.2.1 Laboratory Values Over Time

No apparent clinical trends were noted in laboratory parameters over the course of the initial phase of the study. Actual and change from baseline laboratory values are summarized in Table 14.3.4.2 for hematology and Table 14.3.4.3 for chemistry.

12.1.4.2.2 Individual Patient Changes

Changes in laboratory values resulted in reports of treatment-emergent adverse events for 5 patients (3 Hylaform patients, 2 Zyplast patients). These changes were determined to be clinically significant by the investigator and are discussed in Section 12.1.4.2.3.

12.1.4.2.3 Individual Clinically Significant Abnormalities

Four Hylaform patients and 2 Zyplast patients had clinically significant laboratory results after device implantation (Table 14.3.4.4).

Patient 02-29 (Hylaform group) had a platelet value of 448 k/mm³ at Week 12, which was considered a clinically significant elevation at this visit; however, it had not worsened since baseline or Week 4, which were not reported as clinically significant elevations. The investigator referred the patient to her internist for further evaluation.

Patient 03-08 (Hylaform group) had an LDH value of 349 U/L, AST (SGOT) of 265 U/L, and ALT (SGPT) of 197 U/L at Week 4. The baseline laboratory values for AST (SGOT) and ALT (SGPT) were also elevated at 52 U/L and 96 U/L, respectively, while LDH was within normal limits at 180 U/L. Elevated liver enzymes with a severity of moderate were reported as an adverse event on Day 30. The patient recovered on Day 56. The values for LDH (180 U/L) and AST (SGOT) (37 U/L) returned to normal by Week 12. Although the value for ALT (SGPT) (58 U/L) was still elevated at Week 12, the investigator did not consider it to be clinically significant. The investigator considered the event of elevated liver enzymes unrelated to study device.

Patient 04-16 (Hylaform group) had elevated eosinophil values of 23% at Day 28 and 11% at Day 40. Baseline value was normal (0.3%). Increased eosinophil count was reported as an adverse event on Day 28. The patient recovered on Day 91. Eosinophils returned to within normal range at Week 12 (5.7%). The investigator considered this event unrelated to study device.

Patient 06-02 (Hylaform group) had elevated AST (SGOT) (123 U/L) and ALT (SGPT) (57 U/L) values and a low lymphocyte (11%) value at the Week 12 visit. Baseline values were 17 U/L for AST (SGOT), 18 U/L for ALT (SGPT), and 20.2% for lymphocytes. On Day 81, adverse events of AST (SGOT) increased, low lymphocytes, and ALT (SGPT) increased, all mild in severity, were reported. The investigator considered these events unrelated to study device. These adverse events are ongoing.

Patient 06-16 (Zyplast group) had a low glucose value (45 mg/dL) at Week 4 after touch-up. Baseline blood glucose was 77 mg/dL. Decrease in blood glucose was reported as a mild adverse event on Day 47. The event resolved on Day 63 when an

unscheduled laboratory test was performed (glucose value of 78 mg/dL). At Week 12, blood glucose level was noted to be 104 mg/dL. The investigator considered this event unrelated to study device.

Patient 09-29 (Zyplast group) had increased white blood cell count (from $7.02 \times 10^3/\text{mm}^3$ at baseline to $12.96 \times 10^3/\text{mm}^3$), mild in severity, reported on Day 86 (Week 12). The investigator considered this event unrelated to study device. The outcome of this event is unknown at this time.

In addition, clinically significant laboratory results were reported for 3 patients prior to device implantation (Week -4). Patient 01-17 (Zyplast group) had significant low values for hematocrit (32.4%), hemoglobin (9.7 g/mL), and RBC ($3.7 \times 10^6/\text{mm}^3$); this patient has had anemia since 1995. Values for these parameters were within normal ranges at all other initial treatment phase observations after device implantation. Patient 01-38 (Zyplast group) had an LDH value of 566 U/L; while this value was clinically significant, the investigator did not consider it significant for this study, and the patient was to see the primary physician. Patient 03-02 (Zyplast group) had clinically significant values for lymphocytes (57.8%), monocytes (14%), and neutrophils (23.8%). This patient had resolving mild upper respiratory symptoms compatible with these clinical laboratory findings, and a baseline adverse event for influenza-like illness was reported. The patient recovered in 6 days.

12.1.5 Vital Signs, Physical Findings, and Other Observations Related to Safety: Initial Phase

No apparent clinical trends were noted in vital sign parameters. However, an adverse event was reported for Patient 04-14 (Zyplast group) whose blood pressure at Week -6 was 138/82 mmHg and at Week 12 was 142/94 mm/Hg. This event of increase in blood pressure started in 2002 (month and day unknown) and is ongoing. Vital signs are provided in Listing 16.2.8.4.

Physical examination findings were unremarkable between the screening physical examination and the final visit examination except for the following changes that were noted in the facial area and were reported as adverse events: left cheek with slight scaly plaque (Patient 09-27, Hylaform group); slight redness at lower right nasolabial fold and palpable lumps at nasolabial lines (Patient 02-35, Zyplast group); swollen left and right lymph nodes in neck, in a patient who had a cold (Patient 04-01, Zyplast group); necrosis on face by nose (Patient 04-04, Zyplast group); localized

acne on right cheek (Patient 05-32; Zyplast group); and scar on left nose and scar on right cheek (Patient 09-15, Zyplast group). Physical examination findings are provided in Listing 16.2.4.6. Baseline conditions that did not worsen during the study and that were treated with preplanned elective surgeries were not reported as adverse events. Four patients had documented preexisting conditions treated with elective surgery while enrolled in this clinical study: Patient 02-12 had bilateral cataracts since 1996 and underwent cataract surgery; Patient 02-14 had breast reduction surgery; Patient 06-09 had eyelid surgery; and Patient 02-03 underwent partial knee replacement for localized osteoarthritis. While these events were not considered adverse events, Patient 02-03 experienced immobility after surgery and was therefore discontinued due to an adverse event. These elective surgeries are only mentioned for completeness in reporting.

12.1.6 Serum Hylan B IgG Antibody Titer Testing: Initial Phase

Hylan B IgG antibody titers ≥ 50 were identified in normal serum antibody titers from a validated study (Appendix 16.1.13). The large number of patients with baseline titer values ≥ 50 suggests that these patients had prior avian protein-based exposure. Therefore, it was determined that a fourfold increase from baseline would be considered an increase in hylan B IgG antibody titers in response to treatment.

One patient in the Hylaform group (Patient 01-09) had a greater than fourfold increase in hylan B IgG antibody titers compared to baseline: 100 at Visit 3 (Day 0), and 1600 at Visit 7 (Week 4) and Visit 11 (Week 12). This patient did not experience any signs or symptoms consistent with an allergic response. The patient experienced 2 adverse events during the study, injection site bruising of moderate intensity that lasted 11 days before complete resolution, and headache of severe intensity that lasted 2 days before complete resolution. The patient did not enter the repeat treatment phase in order not to risk additional bruising.

There were 2 patients in each treatment group who did not have Week 4 hylan B IgG antibody titers available (Hylaform Patients 04-18 and 09-18/Zyplast Patients 02-14 and 06-10), and therefore, changes in titer could not be assessed for response to treatment. Serum samples for Patients 05-13, 07-16, and 09-32 in the Hylaform group were retested due to variability in their initial titer values. For Visits 3, 7, and 11, the titer values were 100, 50, and 200 for Patient 05-13; 400, 400, and 200 for Patient 07-16; and 800, 200, and 800 for Patient 09-32, respectively. The repeat assay confirmed that the titer values were positive but did not increase significantly after treatment.

Serum hylan B IgG antibody titers are provided in Listing 16.2.8.1 and summarized by visit in Table 14.3.4.1.

12.1.7 Safety Conclusions: Initial Phase

Adverse events occurred with similar incidence and were of similar types for both treatment groups. The majority of treatment-emergent adverse events were procedure-related. Procedure-related events were mostly mild and did not require treatment. Not-procedure-related events were generally unrelated to anesthetic and device.

The serious adverse events (2 baseline events for Zyplast patients and 1 treatment-emergent event for a Hylaform patient) and the 2 discontinuations due to an adverse event (Zyplast patients) were unrelated to study device. Two significant adverse events were noted for Zyplast patients (injection site necrosis). Adverse trends were not identified from laboratory values, physical findings, or vital signs over the course of the study.

One patient in the Hylaform group had a greater than fourfold increase in hylan B IgG antibody titer compared to baseline. However, the only adverse events for this patient were injection site bruising and headache, which were not consistent with an allergic response.

12.2 Safety Evaluation: Repeat Treatment Phase

Of the 133 patients treated with Hylaform in the initial phase of the study, 96 patients participated in the repeat treatment phase, which involved randomized treatment with Hylaform in one nasolabial fold and Hylaform Plus in the opposite fold. Patient diaries were created to allow patients to record specific signs and symptoms experienced during the first 7 days after repeat treatment (Appendix 16.1.2). Diary entries were captured as adverse events on the appropriate CRF pages. Safety data through Week 4 are presented in this report. A separate report will provide efficacy and safety data through Week 12.

12.2.1 Extent of Exposure: Repeat Treatment Phase

For the repeat treatment, the mean total volume injected was 1.1 mL each for Hylaform nasolabial fold and Hylaform Plus nasolabial fold (Table 12-10). The mean duration of treatment (stop time minus start time) was similar for the two treatments (8.1 minutes for Hylaform; 8.2 minutes for Hylaform Plus). The mean time on study was 28.0 days (range: 15 to 48 days) (Listing R-16.2.1.1).

At the cutoff date for this report (30 May 2003), all 96 patients were continuing in the study. Safety data presented for this repeat treatment phase includes Week 2 data for 96 patients and Week 4 data for 92 patients. The 4 patients who had not yet completed Week 4 were Patients 05-11, 05-37, 07-23, and 09-31.

**Table 12-10 Exposure to Study Treatment in the Repeat Treatment Phase
Intent-to-treat Patients**

	Hylaform NLFs N = 96	Hylaform Plus NLFs N = 96	Both NLFs N = 96
Repeat treatment - Baseline (Day 0)			
Volume injected (mL)			
n	96	96	96
Mean (SD)	1.1 (0.53)	1.1 (0.55)	2.2 (1.05)
Median	0.9	0.8	1.8
Minimum, maximum	0.3, 2.6	0.2, 2.8	0.5, 5.0
Duration of treatment (minutes) ^a			
n	96	96	96
Mean (SD)	8.1 (7.10)	8.2 (8.24)	17.2 (14.84)
Median	5.0	5.0	11.5
Minimum, maximum	2, 30	1, 35	3, 60

Reference: Table R-14.1.7

SD = Standard deviation; NLFs = Nasolabial folds.

^aDuration of treatment = Stop time minus start time.

12.2.2 Adverse Events: Repeat Treatment Phase

12.2.2.1 Brief Summary of Adverse Events

Adverse events in the repeat treatment phase were classified as one of the following:

- Off-study (baseline): adverse events reported by subjects who enrolled in the repeat treatment that occurred between the final visit of the initial phase (12 weeks after last treatment during the initial phase), but before enrollment (signing of informed consent) in the repeat treatment phase of the study
- Treatment-emergent: adverse events with onset time on or after the repeat treatment (implantation of study device), or off-study adverse events that worsened in severity or frequency

Treatment-emergent adverse events were further classified as follows:

- Procedure-related events: adverse events occurring from the day of injection (Day 0) to Day 3 that were reported by the investigator as related to procedure

- Not procedure-related: all other treatment-emergent adverse events; ie, anesthetic-related, device-related, or unrelated to anesthetic, device, or procedure adverse events

Treatment-emergent adverse events CRFs (procedure-related events and not procedure-related adverse events) were collected after repeat treatment at 4 weeks for 92 patients and at 2 weeks for 4 patients who had not yet completed their 4-week visits by 30 May 2003, the visit cut-off date for this report. Events that were ongoing at CRF collection were reentered on new CRFs for reassessment and follow-up through the remainder of the 12-week follow-up period (see Section 9.7.1.2.2).

Overall, 92 (96%) patients experienced 589 events; 87 (91%) patients reported 269 events for the Hylaform side; 92 (96%) patients experienced 286 events for the Hylaform Plus side, and 21 (22%) patients experienced 34 events that developed at sites other than the nasolabial fold. Of these 589 events, 550 were procedure-related and 39 were not procedure-related. No deaths or discontinuations due to adverse events were reported. Two serious adverse events were experienced by 1 patient. Three patients experienced 6 severe adverse events. An overview of adverse events reported during the repeat treatment phase of the study is provided in Table 12-11.

**Table 12-11 Overview of Treatment-emergent Adverse Events in the Repeat Treatment Phase
Intent-to-treat Patients
[Number (%) of Patients]**

Adverse Event	Hylaform Side N = 96 ^a			Hylaform Plus Side N = 96 ^a			Non -NLF N = 96 ^a			Overall N = 96 ^{b, c}		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
At least 1 adverse event	87	(91)	269	92	(96)	286	21	(22)	34	92	(96)	589
Deaths	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Discontinuations due to adverse event	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Procedure-related	87	(91)	267	92	(96)	283	NA	NA	NA	92	(96)	550
Not procedure-related	2	(2)	2	3	(3)	3	21	(22)	34	23	(24)	39
Anesthetic-related	0	(0)	0	1	(1)	1	1	(1)	1	2	(2)	2
Device-related	1	(1)	1	2	(2)	2	1	(1)	1	3	(3)	4
Unrelated to either procedure, anesthetic, or device	1	(1)	1	1	(1)	1	20	(21)	33	21	(22)	35
Serious adverse event	1	(1)	1	1	(1)	1	0	(0)	0	1	(1)	2
Severe adverse event	0	(0)	0	1	(1)	2	2	(2)	4	3	(3)	6

References: Tables R-14.3.1.1 through R-14.3.1.8, R-14.3.2.1 through R-14.3.2.3, Listings R-16.2.7.2 and R-16.2.7.3

E = Events; NLF = Nasolabial fold; NA = Not applicable.

^a96 patients had completed Week 2 follow-up visits and 92 patients had completed Week 4 follow-up visits.

^bOverall counts each patient only once and includes any event reported by Preferred Term – Hylaform side or Hylaform Plus side for events occurring at the treatment site or non-NLF for events not occurring at the treatment site.

^cThe number of patients who experienced a given adverse event in both NLFs was calculated as the difference between the overall count and the sum of the counts for the Hylaform and Hylaform Plus sides.

12.2.2.2 Display of Adverse Events: Repeat Treatment Phase**12.2.2.2.1 Off-study (Baseline) Adverse Events: Repeat Treatment Phase**

Off-study (baseline) adverse events were reported for 7 (7%) of the 96 Hylaform patients (11 events) who participated in the repeat treatment phase. Ten of the 11 off-study adverse events were mild in severity, and 1 event was moderate (tooth injury). None were related to study device. Off-study adverse events are listed in Listing R-16.2.7.1.

12.2.2.2.2 Treatment-emergent Adverse Events: Repeat Treatment Phase

Treatment-emergent adverse events in the repeat treatment phase included procedure-related and not-procedure-related adverse events reported from the day of injection through the cutoff date for this report (30 May 2003). Treatment-emergent adverse events that occurred in $\geq 2\%$ of patients in either treatment group are summarized in Table 12-12. Treatment-emergent adverse events were reported for 87 (91%) patients (269 events) on the Hylaform side; 92 (96%) patients (286 events) on the Hylaform Plus side, and 21 (22%) patients (34 events) at sites other than a nasolabial fold. The 95% confidence intervals for the incidence rate of treatment-emergent adverse events were similar for Hylaform side (83.0% to 95.6%) and Hylaform Plus side (89.7% to 98.9%). There was evidence of a statistical difference in incidence rates between the two sides; the difference in proportions (Hylaform side minus Hylaform Plus side) was -5.2% (95% confidence interval: -9.7% to -0.8%) (Table R-14.3.1.1).

The vast majority of treatment-emergent adverse events were procedure-related. The Hylaform Plus side had more incidences of injection site bruising, injection site pain, and injection site nodule than did the Hylaform side: 34 patients with 34 events for the Hylaform side, 41 patients with 41 events on the Hylaform Plus side for injection site bruising; 49 patients with 49 events on the Hylaform side, 54 patients with 55 events on the Hylaform Plus side for injection site pain; and 22 patients with 22 events on the Hylaform side, 25 patients with 25 events on the Hylaform Plus side for injection site nodule. The difference between the 2 sides in these procedure-related events might be related to the needle size used for device implantation (27-gauge for Hylaform Plus versus 30-gauge for Hylaform).

**Table 12-12 Treatment-emergent Adverse Events Occurring in ≥2% of Patients in the Repeat Treatment Phase
Intent-to-treat Patients
[Number (%) of Patients]**

Primary System Organ Class/ Preferred Term	Hylaform Side			Hylaform Plus			Non-NLF			Overall ^{a, b}		
	N = 96			N = 96			N = 96			N = 96		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
At least 1 adverse event	87	(91)	269	92	(96)	286	21	(22)	34	92	(96)	589
General disorders and administration site conditions	87	(91)	265	92	(96)	282	1	(1)	1	92	(96)	548
Injection site erythema	72	(75)	73	70	(73)	72	0	(0)	0	73	(76)	145
Injection site swelling	50	(52)	50	50	(52)	50	0	(0)	0	57	(59)	100
Injection site pain	49	(51)	49	54	(56)	55	0	(0)	0	59	(62)	104
Injection site bruising	34	(35)	34	41	(43)	41	0	(0)	0	48	(50)	75
Injection site nodule	22	(23)	22	25	(26)	25	0	(0)	0	32	(33)	47
Injection site pruritus	11	(12)	11	10	(10)	11	0	(0)	0	13	(14)	22
Injection site tenderness	10	(10)	10	9	(9)	9	0	(0)	0	10	(10)	19
Injection site discoloration	7	(7)	7	7	(7)	7	0	(0)	0	9	(9)	14
Application site papules	2	(2)	2	2	(2)	2	0	(0)	0	3	(3)	4
Injection site desquamation	2	(2)	2	2	(2)	2	0	(0)	0	2	(2)	4
Injection site pigmentation changes	1	(1)	1	1	(1)	1	0	(0)	0	2	(2)	2
Injection site hemorrhage	0	(0)	0	2	(2)	2	0	(0)	0	2	(2)	2
Infections and infestations	1	(1)	1	1	(1)	1	5	(5)	6	5	(5)	8
Herpes simplex	0	(0)	0	0	(0)	0	2	(2)	2	2	(2)	2
Skin and subcutaneous tissue disorders	2	(2)	2	1	(1)	1	3	(3)	9	5	(5)	12
Contusion	0	(0)	0	0	(0)	0	2	(2)	8	2	(2)	8
Gastrointestinal disorders	0	(0)	0	0	(0)	0	6	(6)	7	6	(6)	7
Lip blister	0	(0)	0	0	(0)	0	2	(2)	2	2	(2)	2

Reference: Table R-14.3.1.1

E = Events.

^aOverall counts each patient only once and includes any event reported by Preferred Term - Hylaform side or Hylaform Plus side for events occurring at the treatment site or non-nasolabial fold (NLF) events not occurring at the treatment site.

^bThe number of patients who experienced a given adverse event in both NLFs was calculated as the difference between the overall count and the sum of the counts for the Hylaform and Hylaform Plus sides.

12.2.2.2.3 Treatment-emergent Adverse Events by Relatedness: Repeat Treatment Phase**Procedure-related Adverse Events**

Ninety-two (96%) of the 96 patients reported 550 procedure-related events (267 events on the Hylaform side and 283 on the Hylaform Plus side). The 95% confidence interval for the incidence rate of procedure-related adverse events was 83.0% to 95.6% for the Hylaform side and 89.7% to 98.9% for the Hylaform Plus side. There was evidence of a statistical difference in incidence rates between the treatment sides; the difference in proportions was -5.2% (95% confidence interval: -9.7% to -0.8%). As previously stated, the increase in adverse events on the Hylaform Plus side may be related to a larger needle size used for treatment administration. Procedure-related events were not reported for the non-nasolabial fold areas.

Procedure-related adverse events occurring in greater than 5% of patients overall (either nasolabial fold side) were injection site erythema, 73 (76%) patients; injection site swelling, 57 (59%) patients; injection site pain, 59 (62%) patients; injection site bruising 48 (50%) patients; injection site nodule, 32 (33%) patients; injection site pruritus, 13 (14%) patients; injection site tenderness, 10 (10%) patients; and injection site discoloration, 9 (9%) patients. A complete summary of procedure-related adverse events is summarized in Table R-14.3.1.2; procedure-related adverse events occurring in $\geq 2\%$ of patients in a treatment group are displayed in Table 12-13.

A comparison between initial phase and repeat treatment phase procedure-related events of injection site nodule, injection pain, injection site swelling, injection site tenderness, and injection site discoloration was undertaken for total volume injected, days between last initial phase treatment and repeat treatment phase, duration of event, and severity of events. Patients reporting these procedure-related events had a slightly higher mean total volume of Hylaform injected during the initial phase of the study than the repeat treatment phase. Severity of events was similar between the 2 phases, and duration of events was shorter for certain events (injection site pain) in the initial phase but longer for other events (injection site swelling, injection site tenderness) compared to the repeat treatment phase. Most of the injection site nodules noted during the repeat treatment phase were reported by patients via their diary cards. This helps to explain the finding of an increased incidence of injection site nodules during the repeat treatment phase compared to the initial phase of the study. Other adverse events for which incidence rates were increased during repeat treatment, although to a lesser degree, compared to initial treatment and which can be

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explained by the use of patient diary cards include: injection site swelling, injection site pain, injection site tenderness, and injection site discoloration.

Table 12-13 Procedure-related Adverse Events Occurring in ≥2% of Patients in Either Treatment Group in the Repeat Treatment Phase Intent-to-treat Patients [Number (%) of Patients]

Primary System Organ Class/ Preferred Term	Hylaform Side N = 96			Hylaform Plus Side N = 96			Both Sides N = 96			Overall ^a N = 96		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
At least 1 adverse event	87	(91)	267	92	(96)	283	87	(91)	228	92	(96)	550
General disorders and administration site conditions	87	(91)	265	92	(96)	282	87	(91)	227	92	(96)	547
Injection site erythema	72	(75)	73	70	(73)	72	69	(72)	70	73	(76)	145
Injection site swelling	50	(52)	50	50	(52)	50	43	(45)	43	57	(59)	100
Injection site pain	49	(51)	49	54	(56)	55	44	(46)	44	59	(62)	104
Injection site bruising	34	(35)	34	41	(43)	41	27	(28)	27	48	(50)	75
Injection site nodule	22	(23)	22	25	(26)	25	15	(16)	15	32	(33)	47
Injection site pruritus	11	(12)	11	10	(10)	11	8	(8)	8	13	(14)	22
Injection site tenderness	10	(10)	10	9	(9)	9	9	(9)	9	10	(10)	19
Injection site discoloration	7	(7)	7	7	(7)	7	5	(5)	5	9	(9)	14
Injection site desquamation	2	(2)	2	2	(2)	2	2	(2)	2	2	(2)	4
Application site papules	2	(2)	2	2	(2)	2	1	(1)	1	3	(3)	4
Injection site hemorrhage	0	(0)	0	2	(2)	2	0	(0)	0	2	(2)	2

Reference: Table R-14.3.1.2

E = Events.

^aOverall counts each patient only once and includes any events reported by Preferred Term - Hylaform side or Hylaform Plus side are for events occurring at the treatment site.

Not-procedure-related Adverse Events

Adverse events not related to the procedure were reported for 23 (24%) patients (39 events) overall; 2 (2%) patients (2 events) on the Hylaform side; 3 (3%) patients (3 events) on the Hylaform Plus side; and 21 (22%) patients (34 events) at sites other than the nasolabial fold (Table R-14.3.1.3). Subcategories of not procedure-related adverse events (anesthetic-related adverse events, device-related adverse events, and unrelated adverse events) are discussed in the following paragraphs.

Anesthetic-related Adverse Events

Two (2%) patients had 2 anesthetic-related adverse events overall; no events were reported for the Hylaform side, 1 event was reported for the Hylaform Plus side, and 1 event was reported for the non-nasolabial fold areas. One patient (Patient 01-10) experienced involuntary muscle contractions described as eye fasciculations (Hylaform Plus side) and 1 patient (Patient 01-34) experienced dizziness (non-nasolabial fold area). Both of these patients received a topical anesthetic. Anesthetic-related adverse events are summarized in Table R-14.3.1.4.

Device-related Adverse Events

Three (3%) patients had 4 device-related adverse events overall. Injection site abscess (Patient 02-08) was reported for both nasolabial folds (both events were reported as serious adverse events and are further described in Section 12.2.3.2); involuntary muscle contractions (Patient 01-10) were reported for the Hylaform Plus side only, and dizziness (Patient 01-34) was reported for the non-nasolabial fold areas. Device-related adverse events are summarized in Table R-14.3.1.5.

Unrelated Adverse Events

Twenty-one (22%) patients had 35 unrelated adverse events overall; 1 (1%) patient had 1 event associated with both the Hylaform side and the Hylaform Plus side, and 20 (21%) patients had 33 events associated with the non-nasolabial fold areas. The events of lip blister, herpes simplex, and contusion were each reported by 2 patients. All other events were reported by 1 patient each. Treatment-emergent adverse events unrelated to either procedure, anesthetic, or device are presented in Table R-14.3.1.6.

12.2.2.2.4 Treatment-emergent Adverse Events by Severity: Repeat Treatment Phase

As in the initial treatment phase, maximum intensity of adverse events for the repeat treatment phase was calculated by taking the maximum intensity occurring for each patient for a particular adverse event. The majority of adverse events reported for either nasolabial fold side were mild, 83 (87%) patients for the Hylaform side and 88 (92%) patients for the Hylaform Plus side. Moderate adverse events were reported for 4 (4%) patients (Hylaform side) and 3 (3%) patients (Hylaform Plus side) (Table 12-14). Two severe adverse events (injection site bruising and application site scabbing) were reported for 1 (1%) patient (Patient 01-26, Hylaform Plus side) (Table R-14.3.1.7).

Adverse events reported for non-nasolabial fold areas were mild for 13 (14%) patients, moderate for 6 (6%) patients, and severe for 2 (2%) patients. Lip blister and herpes simplex (both mild events) were each reported by 2 patients for non-nasolabial fold areas (Table 14.3.1.8). Treatment-emergent adverse events by maximum severity are summarized in Tables R-14.3.1.7 and R-14.3.1.8.

**Table 12-14 Overview of Treatment-emergent Adverse Events by Severity in the Repeat Treatment Phase
Intent-to-treat Patients
[Number (%) of Patients]**

Adverse Event	Hylaform Side N = 96 ^a			Hylaform Plus Side N = 96 ^a			Non-NLF N = 96 ^a			Overall N = 96 ^b		
	M	Mod	Sev	M	Mod	Sev	M	Mod	Sev	M	Mod	Sev
At least 1 adverse event	83 (87)	4 (4)	0 (0)	88 (92)	3 (3)	1 (1)	13 (14)	6 (6)	2 (2)	79 (82)	10 (10)	3 (3)
Procedure-related	83 (87)	4 (4)	0 (0)	88 (92)	3 (3)	1 (1)	NA NA	NA NA	NA NA	87 (91)	4 (4)	1 (1)
Not procedure-related	2 (2)	0 (0)	0 (0)	3 (3)	0 (0)	0 (0)	13 (14)	6 (6)	2 (2)	15 (16)	6 (6)	2 (2)
Anesthetic-related	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
Device-related	1 (1)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	3 (3)	0 (0)	0 (0)
Unrelated ^c	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	12 (13)	6 (6)	2 (2)	13 (14)	6 (6)	2 (2)

Reference: Tables R-14.3.1.7 through R-14.3.1.18.

NA = Not applicable; NLF = Nasolabial fold; M = Mild; Mod = Moderate; Sev = Severe.

Note: The total number of patients in each row equals the total number of patients reporting 1 or more events within that category. In each of the rows of the table, a patient is counted once by severity only if the patient experienced an event in that specific event category. For example, a patient with a maximum severity of mild for procedure-related events and a maximum severity of severe for a not-procedure-related adverse event would be counted as 'severe' in the 'At least 1 adverse event' and 'Not-procedure-related' rows, but as 'mild' in the procedure-related row.

^aA total of 96 patients had completed Week 2 follow-up visits and 92 patients had completed Week 4 follow-up visits.

^bOverall counts each patient only once and includes any event reported by Preferred Term – Hylaform side or Hylaform Plus side for events occurring at the treatment site or non-NLF for events not occurring at the treatment site.

^cUnrelated to either procedure, anesthetic, or device.

Procedure-related adverse events

The majority of procedure-related adverse events reported for either nasolabial fold side were mild, 83 (87%) patients for the Hylaform side and 88 (92%) patients for the Hylaform Plus side. Moderate adverse events were reported for 4 (4%) patients (Hylaform side) and 3 (3%) patients (Hylaform Plus side). Two severe procedure-related adverse events, injection site bruising and application site scabbing, were reported for 1 (1%) patient (Patient 01-26, Hylaform Plus side).

A complete summary of procedure-related adverse events is provided in Tables R-14.3.1.9 and R-14.3.1.10. Procedure-related adverse events occurring in $\geq 2\%$ of patients in either treatment group are displayed in Table 12-15.

Table 12-15 Procedure-related Adverse Events by Severity Occurring in ≥2% of Patients in Either Treatment Group in the Repeat Treatment Phase Intent-to-treat Patients [Number (%) of Patients]

Primary System Organ Class/Preferred Term ^a	Hylaform Side N = 96			Hylaform Plus Side N = 96			Both Sides N = 96			Overall ^b N = 96		
	M	Mod	Sev	M	Mod	Sev	M	Mod	Sev	M	Mod	Sev
At least 1 adverse event	83 (87)	4 (4)	0 (0)	88 (92)	3 (3)	1 (1)	85 (89)	2 (2)	0 (0)	87 (91)	4 (4)	1 (1)
General disorders and administration site conditions	83 (87)	4 (4)	0 (0)	88 (92)	3 (3)	1 (1)	85 (89)	2 (2)	0 (0)	87 (91)	4 (4)	1 (1)
Injection site erythema	71 (74)	1 (1)	0 (0)	69 (72)	1 (1)	0 (0)	68 (71)	1 (1)	0 (0)	72 (75)	1 (1)	0 (0)
Injection site swelling	50 (52)	0 (0)	0 (0)	50 (52)	0 (0)	0 (0)	43 (45)	0 (0)	0 (0)	57 (59)	0 (0)	0 (0)
Injection site pain	47 (49)	2 (2)	0 (0)	53 (55)	1 (1)	0 (0)	43 (45)	1 (1)	0 (0)	57 (59)	2 (2)	0 (0)
Injection site bruising	34 (35)	0 (0)	0 (0)	40 (42)	0 (0)	1 (1)	27 (28)	0 (0)	0 (0)	47 (49)	0 (0)	1 (1)
Injection site nodule	21 (22)	1 (1)	0 (0)	25 (26)	0 (0)	0 (0)	15 (16)	0 (0)	0 (0)	31 (32)	1 (1)	0 (0)
Injection site pruritus	11 (12)	0 (0)	0 (0)	9 (9)	1 (1)	0 (0)	8 (8)	0 (0)	0 (0)	12 (13)	1 (1)	0 (0)
Injection site discoloration	7 (7)	0 (0)	0 (0)	7 (7)	0 (0)	0 (0)	5 (5)	0 (0)	0 (0)	9 (9)	0 (0)	0 (0)
Injection site tenderness	9 (9)	1 (1)	0 (0)	8 (8)	1 (1)	0 (0)	8 (8)	0 (0)	0 (0)	9 (9)	1 (1)	0 (0)
Application site papules	2 (2)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	3 (3)	0 (0)	0 (0)
Injection site desquamation	2 (2)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)
Injection site hemorrhage	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)

Reference: Tables R-14.3.1.9 and R-14.3.1.10.

M= Mild; Mod = Moderate; Sev = Severe.

Note: The total number of patients in each row equals the total number of patients reporting 1 or more events within that category. In each of the rows above, a patient is counted once by severity only if the patient experienced an event in that specific event category. For example, a patient with a maximum severity of mild for procedure-related events and a maximum severity of severe for a not-procedure-related adverse event would be counted as 'severe' in the 'At least 1 adverse event' and 'Not-procedure-related' row, but as 'mild' in the procedure-related row.

^aFor each preferred term, patients are represented by the event with highest severity.

^bOverall counts each patient only once and includes any event reported by Preferred Term.

Not-procedure related adverse events

The maximum severity of not-procedure-related adverse events reported overall was mild for 15 (16%) patients, moderate for 6 (6%) patients, and severe for 2 (2%) patients. Only mild events were reported for the Hylaform side (2 patients) and Hylaform Plus side (3 patients). The maximum severity reported for non-nasolabial fold areas was mild for 13 (14%) patients, moderate for 6 (6%) patients, and severe for 2 (2%) patients. Not-procedure-related adverse events by maximum severity are summarized in Tables R-14.3.1.11 and R-14.3.1.12.

Anesthetic-related adverse events

The maximum severity of anesthetic-related adverse events reported was mild for 2 (2%) patients. One patient reported involuntary muscle contractions, described as eye fasciculations on the Hylaform Plus side, and 1 patient experienced dizziness (non-nasolabial fold areas). Anesthetic-related adverse events are summarized in Tables R-14.3.1.13 and R-14.3.1.14.

Device-related adverse events

The maximum severity of device-related adverse events reported was mild for 3 (3%) patients. One patient reported injection site abscesses (Hylaform side and Hylaform Plus side); these events were of mild severity and reported as serious adverse events. Another patient reported involuntary muscle contractions (Hylaform Plus side) and 1 patient experienced dizziness (non-nasolabial fold areas). Device-related adverse events are summarized in Tables R-14.3.1.15 and R-14.3.1.16.

Unrelated adverse events

The maximum severity of unrelated adverse events (ie, not anesthetic-related, device-related, or procedure-related) was mild for 13 patients, moderate for 6 patients, and severe for 2 patient (abdominal pain NOS, multiple severe bruises) (Table R-14.3.1.18).

12.2.2.2.5 Treatment-emergent Adverse Events in Patients and Hylan B IgG Antibody Titers: Repeat Treatment Phase

As of 30 May 2003, there were 92 patients with Day 0 and Week 4 hylan B IgG antibody titers. No patient had a greater than fourfold increase in hylan B IgG antibody titers from Day 0 to Week 4 in the repeat treatment phase (Listing R-16.2.8.1). The 4 patients missing Week 4 hylan B IgG antibody titer

values had not yet reached Week 4 at the cutoff date. Because none of the patients had a greater than fourfold increase in hylan B IgG antibody titers, an evaluation of a possible association between titer and adverse events was not required.

12.2.2.3 Analysis of Adverse Events: Repeat Treatment Phase

The majority of treatment-emergent adverse events were procedure-related. Procedure-related events were mostly mild in severity and did not require treatment. Not-procedure-related events were generally unrelated to anesthetic or study device.

Overall, 92 (96%) of the 96 patients reported 589 treatment-emergent adverse events. Of these, 269 events were reported for the Hylaform side (87 patients), 286 events were reported for the Hylaform Plus side (92 patients), and 34 events were reported for non-nasolabial fold areas (21 patients). One patient reported 2 serious adverse events (one for each nasolabial fold side). Two severe adverse events were reported for the Hylaform Plus side in 1 patient. Two patients reported 4 events of severe adverse events for non-nasolabial fold areas; these were unrelated to study device.

Ninety-two (96%) of the 96 patients reported 550 procedure-related events (267 events on the Hylaform side and 283 on the Hylaform Plus side). Procedure-related adverse events occurring in greater than 5% of patients overall (either nasolabial fold side) were injection site erythema, 73 (76%) patients; injection site pain, 59 (62%) patients; injection site swelling, 57 (59%) patients; injection site bruising, 48 (50%) patients; injection site nodule, 32 (33%) patients; injection site pruritus, 13 (14%) patients; injection site tenderness, 10 (10%) patients; and injection site discoloration, 9 (9%) patients.

Anesthetic-related adverse events were reported by 2 patients; none for the Hylaform side, 1 patient for the Hylaform Plus side (involuntary muscle contractions), and 1 patient for the non-nasolabial fold areas (dizziness). These events were mild in severity. Device-related adverse events were reported by 3 patients overall; 1 patient for both the Hylaform and Hylaform Plus sides (injection site abscesses), 1 patient for the Hylaform Plus side (involuntary muscle contractions), and 1 patient for the non-nasolabial fold areas (dizziness).

Adverse events unrelated to either procedure, anesthetic, or device were reported by 21 (22%) patients overall (35 events); 1 patient had 1 event associated with both the Hylaform side and the Hylaform Plus side, and 20 patients for non-nasolabial fold areas.

12.2.2.4 Listing of Adverse Events by Patient

Off-study (baseline); procedure-related; not procedure-related; anesthetic-related; device-related, and treatment-emergent adverse events unrelated to either procedure, anesthetic, or device are provided in Listings R-16.2.7.1 through R-16.2.7.6.

12.2.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events: Repeat Treatment Phase

12.2.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.2.3.1.1 Deaths

No deaths were reported as of the 30 May 2003 data cutoff date for this 4-week interim safety report of the repeat treatment phase.

12.2.3.1.2 Other Serious Adverse Events

Two serious treatment-emergent adverse events (sterile abscess at each nasolabial fold) were reported by 1 patient (Patient 02-08) as of the 30 May 2003 data cutoff date (See Section 12.2.3.2). Hylan b IgG antibody titers in this patient were 200 at baseline and remained at this level through the initial treatment phase and Week 4 of the repeat treatment phase.

12.2.3.1.3 Other Significant Adverse Events

No patients discontinued due to an adverse event as of the 30 May 2003 data cutoff date for this interim repeat treatment safety report.

12.2.3.2 Narratives for Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Treatment-emergent serious adverse events for the repeat treatment phase

Patient 02-08: Sterile abscesses at injection site

A 51-year-old female patient experienced sterile abscesses to bilateral nasal labial folds after receiving injections of Hylaform to one nasolabial fold and Hylaform Plus to the other nasolabial fold. The patient's past medical history is significant for hypercholesterolemia, allergies, edema, and osteoporosis. The patient had no prior facial augmentation treatments. On 14 April 2003, the patient received injections of 0.95 mL Hylaform and 0.75 mL Hylaform Plus into right- and left-sided nasolabial lines, respectively. A 27-gauge needle and a 30-gauge needle was used on the right and left nasolabial folds, respectively, using a mid-dermis, serial puncture technique.

On 05 May 2003 (Visit R4), the patient was seen by the investigator, and a "pimple cyst" was noticed to have developed lateral to the patient's left nasolabial fold where the study product had been injected. Upon examination, the "pimple cyst" was found to be tender and somewhat fluctuant. The area was drained by the investigator and, at that time, was considered to be an infected cyst. The patient was instructed to use warm compresses.

The patient was seen again by the investigator on 07 May 2003 complaining that a similar problem had developed on the right side of her face, lateral to the nasolabial fold where the study device had been injected. The patient reported that the event on the right side of her face looked and felt like the one on the left side of her face. Physical examination revealed oval shaped, somewhat fluctuant nodules, approximately 5 mm in diameter, located along the nasolabial fold lines, close to the ala nasi. The surrounding tissue was described as tender, with little to no redness present. The investigator incised and drained small amounts of both serous and yellow, purulent fluid containing some oily substance from the right-sided nodule, and bacterial cultures were performed, results of which were negative.

On 12 May 2003, the bilateral nodules were incised, and small amounts of serous and yellow fluid had been drained. Intralesional Kenalog was subsequently injected. In the opinion of the investigator, the nodules were described as "sterile abscesses" of moderate intensity and related to both the procedure and study treatments. On 13 May 2003, the patient was reportedly improving but had not yet recovered from the adverse events. The patient was last seen by the investigator on 15 May 2003, at which time she had developed a "mild" case of impetigo inside the right nostril. The investigator considered the impetigo to be not serious and treated it with Bactroban cream. The investigator reported that the impetigo was not related to the study device or to the sterile abscesses.

12.2.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths or discontinuations due to adverse events were reported by the data cutoff date of this repeat treatment phase interim safety report. Two serious adverse events were reported by 1 patient; both events were considered related to study device and were not associated with increased hylan B IgG antibody titers.

12.2.4 Clinical Laboratory Evaluation: Repeat Treatment Phase

12.2.4.1 Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value

Hematology and chemistry data are provided in Listings R-16.2.8.2.1 through R-16.2.8.3.3.

12.2.4.2 Evaluation of Each Laboratory Parameter

12.2.4.2.1 Laboratory Values Over Time

No apparent clinical trends were noted in laboratory parameters over the 4 weeks reported for the repeat treatment phase. Actual and change from baseline laboratory values are summarized in Table R-14.3.4.2 for hematology and Table R-14.3.4.3 for chemistry.

12.2.4.2.2 Individual Patient Changes

No changes in laboratory values that resulted in treatment-emergent adverse events were reported over the time period of this 4-week safety report. However, 4 patients entered the repeat treatment phase with clinically significant laboratory values. Patients 01-06 and 01-26 had elevated AST and ALT levels at the time of enrollment into the repeat treatment phase (Day 0), and the levels remained high at the data cutoff for this report. Patient 06-02 had decreased lymphocyte count and increased AST and ALT, which were reported during the initial phase of the study; these events resolved on Day 2 in the repeat treatment phase. Patient 06-12 had elevated eosinophils at the time of enrollment into the repeat treatment phase (Day 0) that resolved on Day 14. These events were all mild in severity and had no relationship to study device. None of these abnormal findings were reported as adverse events in the repeat treatment phase.

12.2.4.2.3 Individually Clinically Significant Abnormalities

No clinically significant laboratory values were reported by the data cutoff date of this repeat treatment phase interim safety report.

12.2.5 Vital Signs, Physical Findings, and Other Observations Related to Safety: Repeat Treatment Phase

No apparent clinical trends were noted in vital sign parameters. Vital signs are provided in Listing R-16.2.8.4.

Physical examination findings were unremarkable between the screening physical examination and the 4-week examination except for these few notations related to the facial area at Week 4 which were associated with a reported adverse event (large, cystic pimple on the left cheek, Patient 02-08; right eye injected negative discharge, Patient 02-10). Physical examination findings are listed in Listing R-16.2.4.6.

12.2.6 Serum Hylan B IgG Antibody Titer Testing: Repeat Treatment Phase

As of 30 May 2003, there were 92 patients with Day 0 and Week 4 hylan B IgG antibody titers. No patient had a greater than fourfold increase in antibody titers from Day 0 to Week 4 in the repeat treatment phase. Serum hylan B IgG antibody titers by visit are summarized in Table R-14.3.4.1 and listed in Listing R-16.2.8.1.

12.2.7 Safety Conclusions: Repeat Treatment Phase

The majority of treatment-emergent adverse events were procedure-related. Procedure-related events were mostly mild in severity and did not require treatment. Not procedure-related events were generally unrelated to anesthetic or study device.

The serious adverse events of sterile abscesses (on left cheek above nasolabial fold and on right nasolabial fold) were possibly related to the study device. Three patients entered the repeat treatment phase with laboratory values which were reported as adverse events in the initial phase; these were all mild in severity and had no relationship to study device. Adverse trends were not identified from laboratory values, physical examination findings, or vital signs by the data cutoff date of this repeat treatment phase interim safety report. Hylan B IgG antibody titers were not observed to have significantly increased after repeat treatment with hylan B products, and therefore, an evaluation of the relationship between patient adverse event profiles and IgG titers was not required.

13. DISCUSSION AND OVERALL CONCLUSIONS

This double-blind, randomized, multicenter study was designed to assess the efficacy (non-inferiority) and safety of Hylaform viscoelastic gel compared with Zyplast collagen implant for the correction of nasolabial folds during the initial phase of the study. The primary efficacy variable, mean IPR median score 12 weeks after last treatment, was not statistically different between the Hylaform group and the Zyplast group, demonstrating the non-inferiority of Hylaform to Zyplast for corrections of

nasolabial folds. Evaluations of secondary efficacy variables (investigator live assessments and patient's global assessment) supported the non-inferiority conclusion of the primary efficacy variable.

Evaluations of adverse events, hematology, chemistry, vital signs, and physical examinations during the initial phase of the study indicated that Hylaform is well tolerated and has an acceptable safety profile.

The interim safety data from the repeat treatment phase of the study also evaluated adverse events, hematology, chemistry, vital signs, and physical examinations and, to date, supports the safety findings demonstrated during the initial phase of the study.

14. TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data

Initial Phase

- 14.1.1 Summary of Patient Disposition, All Patients
- 14.1.2 Summary of Screen Failures, All Patients
- 14.1.3 Summary of Demographic Information and Baseline Characteristics, Intent-to-Treat Patients
- 14.1.4 Summary of Smoking and Sun Exposure History, Intent-to-Treat Patients
- 14.1.5 Summary of Prior Dermal Treatments and Medications, Intent-to-Treat Patients
- 14.1.6 Summary of Concomitant Medications, Intent-to-Treat Patients
- 14.1.7 Summary of Visits Occurring Off-Schedule by Visit, Intent-to-Treat Patients
- 14.1.8 Summary of Exposure to Study Treatment, Intent-to-Treat Patients
- 14.1.9 Summary of Patient's Assessment of Treatment Group Assignment, Intent-to-Treat Patients

Repeat Treatment Phase

- R-14.1.1 Summary of Patient Disposition, All Patients
- R-14.1.2 Summary of Demographic Information and Baseline Characteristics, Intent-to-Treat Patients
- R-14.1.3 Summary of Smoking and Sun Exposure History, Intent-to-Treat Patients
- R-14.1.4 Summary of Prior Dermal Treatments and Medications, Intent-to-Treat Patients
- R-14.1.5 Summary of Concomitant Medications, Intent-to-Treat Patients
- R-14.1.6 Summary of Visits Occurring Off-Schedule by Visit, Intent-to-Treat Patients
- R-14.1.7 Summary of Exposure to Study Treatment, Intent-to-Treat Patients

14.2 Efficacy Data

- 14.2.1.1 Independent Panel Review Nasolabial Fold Assessment, 12 Weeks After Last Treatment, Intent-to-Treat Patients
- 14.2.1.2 Independent Panel Review Nasolabial Fold Assessment, 12 Weeks After Last Treatment, Per-Protocol Patients
- 14.2.2 Independent Panel Review Nasolabial Fold Assessment, 12 Weeks After Last Treatment by Site, Intent-to-Treat Patients
- 14.2.3 Independent Panel Review Nasolabial Fold Assessment, 12 Weeks After Last Treatment by Patient Subgroups, Intent-to-Treat Patients
- 14.2.4 Independent Panel Review Assessment of Nasolabial Folds by Visit, Intent-to-Treat Patients
 - 14.2.4.1 Independent Panel Review Assessment of Nasolabial Folds by Visit, Patients Requiring Touch-Up, Intent-to-Treat Patients
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- 14.2.5 Independent Panel Review Assessment of Nasolabial Folds, Change From Baseline by Visit, Intent-to-Treat Patients
- 14.2.6 Investigator's Live Assessment of Nasolabial Folds by Visit, Intent-to-Treat Patients
- 14.2.7 Investigator's Live Assessment of Nasolabial Folds, Change From Baseline by Visit, Intent-to-Treat Patients
- 14.2.8 Independent Panel Review and Investigator's Live Assessment of Nasolabial Folds by Visit, Intent-to-Treat Patients
- 14.2.9 Independent Panel Review and Investigator's Live Assessment of Nasolabial Folds, Change From Baseline by Visit, Intent-to-Treat Patients
- 14.2.10 Investigator and Patient's Global Assessment of Overall Treatment Response by Visit, Intent-to-Treat Patients
- 14.2.11 Duration of Effect Using Independent Panel Review Median Score, Intent-to-Treat Hylaform Patients

14.3 Safety Data

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Initial Phase

- 14.3.1.1 Incidence of Baseline Adverse Events, All Patients
- 14.3.1.2 Incidence of Treatment-Emergent Adverse Events, Intent-to-Treat Patients
- 14.3.1.3 Incidence of Procedure-Related Adverse Events, Intent-to-Treat Patients
- 14.3.1.4 Incidence of Not Procedure-Related Adverse Events, Intent-to-Treat Patients
- 14.3.1.5 Incidence of Anesthetic-Related Adverse Events, Intent-to-Treat Patients
- 14.3.1.6 Incidence of Device-Related Adverse Events, Intent-to-Treat Patients
- 14.3.1.7 Incidence of Treatment-Emergent Adverse Events Unrelated to Either Procedure, Anesthetic, or Device, Intent-to-Treat Patients
- 14.3.1.8 Incidence of Treatment-Emergent Adverse Events by Maximum Severity, Intent-to-Treat Patients
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- R-14.3.1.4 Incidence of Anesthetic-Related Adverse Events, Intent-to-Treat Patients
- R-14.3.1.5 Incidence of Device-Related Adverse Events, Intent-to-Treat Patients
- R-14.3.1.6 Incidence of Treatment-Emergent Adverse Events Unrelated to Either Procedure, Anesthetic, or Device, Intent-to-Treat Patients
- R-14.3.1.7 Incidence of Treatment-Emergent Adverse Events by Maximum Severity, Part 1 of 2, Intent-to-Treat Patients, Repeat Treatment Phase
- R-14.3.1.8 Incidence of Treatment-Emergent Adverse Events by Maximum Severity, Part 2 of 2, Intent-to-Treat Patients, Repeat Treatment Phase
- R-14.3.1.9 Incidence of Procedure-Related Adverse Events by Maximum Severity, Part 1 of 2, Intent-to-Treat Patients, Repeat Treatment Phase
- R-14.3.1.10 Incidence of Procedure-Related Adverse Events by Maximum Severity, Part 2 of 2, Intent-to-Treat Patients, Repeat Treatment Phase
- R-14.3.1.11 Incidence of Not Procedure-Related Adverse Events by Maximum Severity, Part 1 of 2, Intent-to-Treat Patients, Repeat Treatment Phase
- R-14.3.1.12 Incidence of Not Procedure-Related Adverse Events by Maximum Severity, Part 2 of 2, Intent-to-Treat Patients, Repeat Treatment Phase
- R-14.3.1.13 Incidence of Anesthetic-Related Adverse Events by Maximum Severity, Part 1 of 2, Intent-to-Treat Patients, Repeat Treatment Phase
- R-14.3.1.14 Incidence of Anesthetic-Related Adverse Events by Maximum Severity, Part 2 of 2, Intent-to-Treat Patients, Repeat Treatment Phase
- R-14.3.1.15 Incidence of Device-Related Adverse Events by Maximum Severity, Part 1 of 2, Intent-to-Treat Patients, Repeat Treatment Phase
- R-14.3.1.16 Incidence of Device-Related Adverse Events by Maximum Severity, Part 2 of 2, Intent-to-Treat Patients, Repeat Treatment Phase

R-14.3.1.17 Incidence of Treatment-Emergent Adverse Events Unrelated to Either Procedure, Anesthetic, or Device by Maximum Severity, Part 1 of 2, Intent-to-Treat, Repeat Treatment Phase

R-14.3.1.18 Incidence of Treatment-Emergent Adverse Events Unrelated to Either Procedure, Anesthetic, or Device by Maximum Severity, Part 2 of 2, Intent-to-Treat, Repeat Treatment Phase

14.3.2 Listings of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Initial Phase

14.3.2.1 Patient Deaths During the Study, Intent-to-Treat Patients

14.3.2.2 Serious Treatment-Emergent Adverse Events, Intent-to-Treat Patients

14.3.2.3 Discontinuation Due to Adverse Events, Intent-to-Treat Patients

Repeat Treatment Phase

R-14.3.2.1 Patient Deaths During the Study, Intent-to-Treat Patients

R-14.3.2.2 Serious Treatment-Emergent Adverse Events, Intent-to-Treat Patients

R-14.3.2.3 Discontinuation Due to Adverse Events, Intent-to-Treat Patients

14.3.3 Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

14.3.4 Abnormal Laboratory Value Listing

Initial Phase

14.3.4.1 Summary of Serum IgG Antibody Titers by Visit, Intent-to-Treat Patients

14.3.4.2 Summary of Laboratory Values: Hematology, Actual and Change From Baseline by Visit, Intent-to-Treat Patients

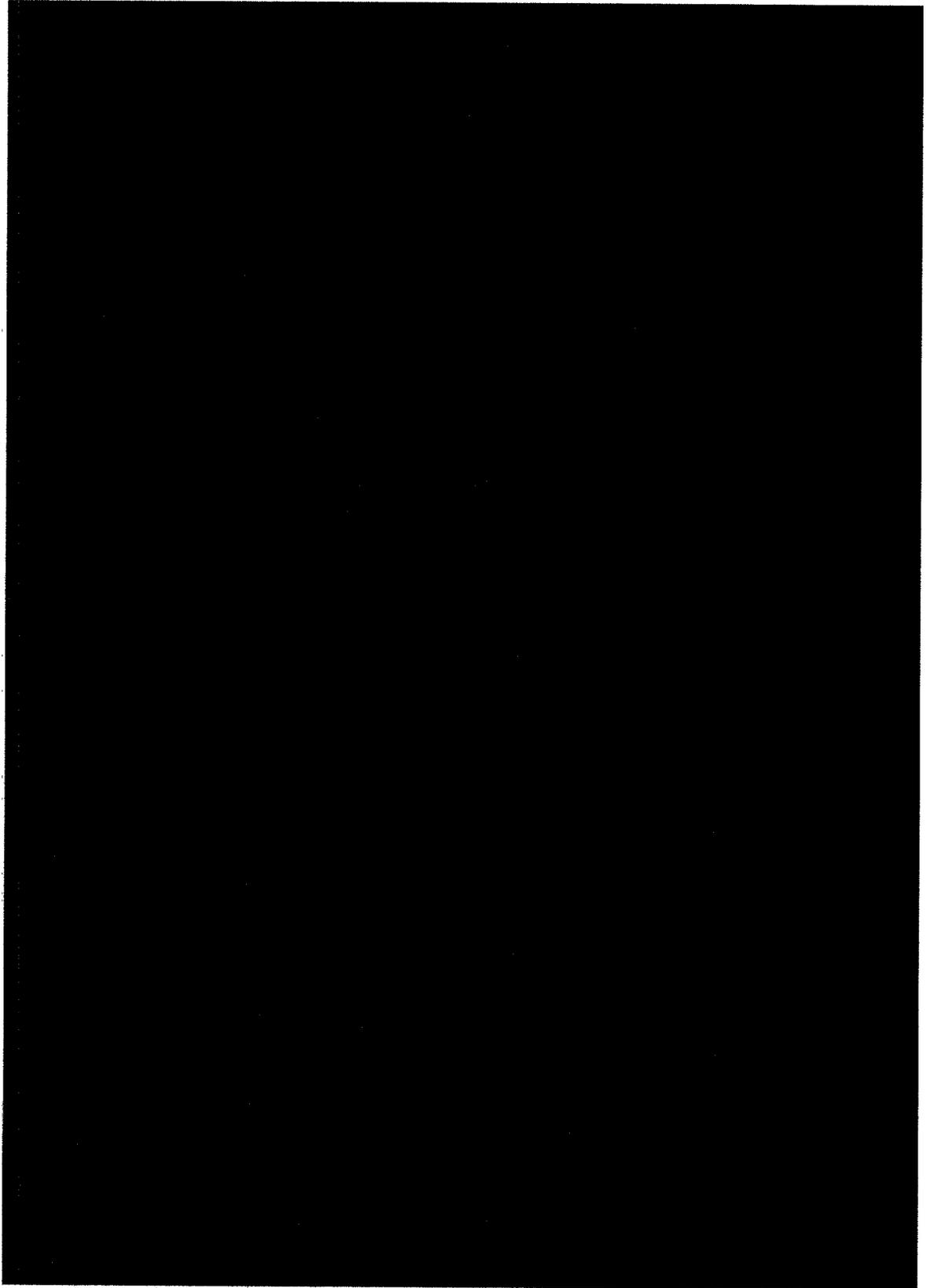
14.3.4.3 Summary of Laboratory Values: Chemistry, Actual and Change From Baseline by Visit, Intent-to-Treat Patients

14.3.4.4 Clinically Significant Laboratory Results, Intent-to-Treat Patients

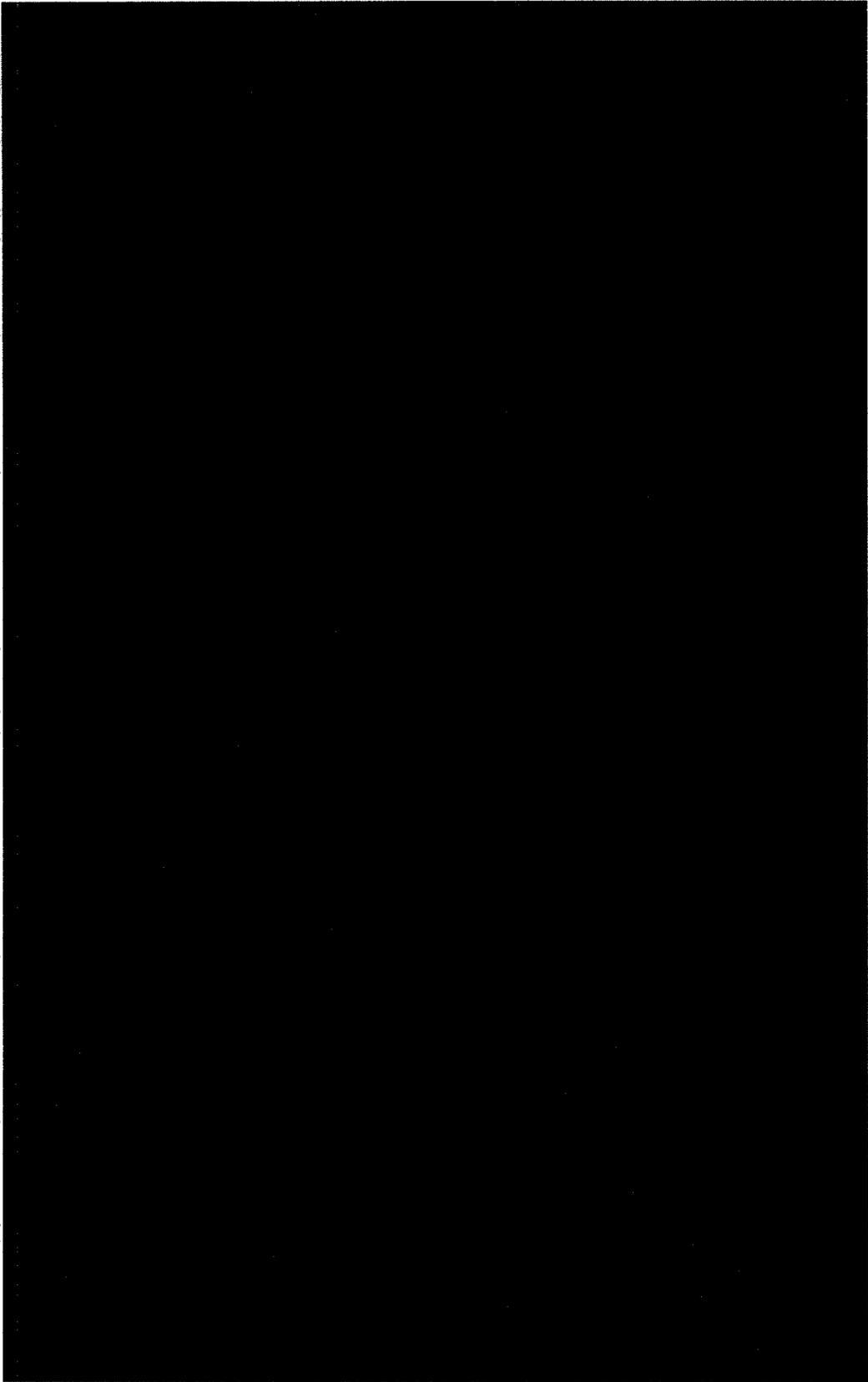
Repeat Treatment Phase

R-14.3.4.1 Summary of Serum IgG Antibody Titers by Visit, Intent-to-Treat Patients, Repeat Treatment Phase

- R-14.3.4.2 Summary of Laboratory Values: Hematology, Actual and Change From Baseline by Visit, Intent-to-Treat Patients, Repeat Treatment Phase
- R-14.3.4.3 Summary of Laboratory Values: Chemistry, Actual and Change From Baseline by Visit, Intent-to-Treat Patients, Repeat Treatment Phase
- R-14.3.4.4 Clinically Significant Laboratory Results, Intent-to-Treat Patients, Repeat Treatment Phase



Genzyme Corporation
Protocol HYL-001-01, Amendment 3



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16.2.4.2 Demographic Information and Baseline Characteristics

16.2.4.3 Smoking and Sun Exposure History

16.2.4.4 Prior Dermal Treatments and Medications (Medication Washout and Restricted Medications)

16.2.4.5 Medical History

16.2.4.6 Physical Examination Findings

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16.2.4.10 Visits Occurring Off-Schedule

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R-16.2.4.1.1 Inclusion/Exclusion Criteria, Reference Page

R-16.2.4.1.2 Inclusion/Exclusion Criteria

R-16.2.4.2 Demographic Information and Baseline Characteristics

R-16.2.4.3 Smoking and Sun Exposure History

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R-16.2.5.1 Study Treatment Administration

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16.2.7.7 Treatment-Emergent Adverse Events

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- R-16.2.7.6 Treatment-Emergent Adverse Events Unrelated to Either Procedure, Anesthetic, or Device

16.2.8 Listing of Individual Laboratory Measurements by Patient

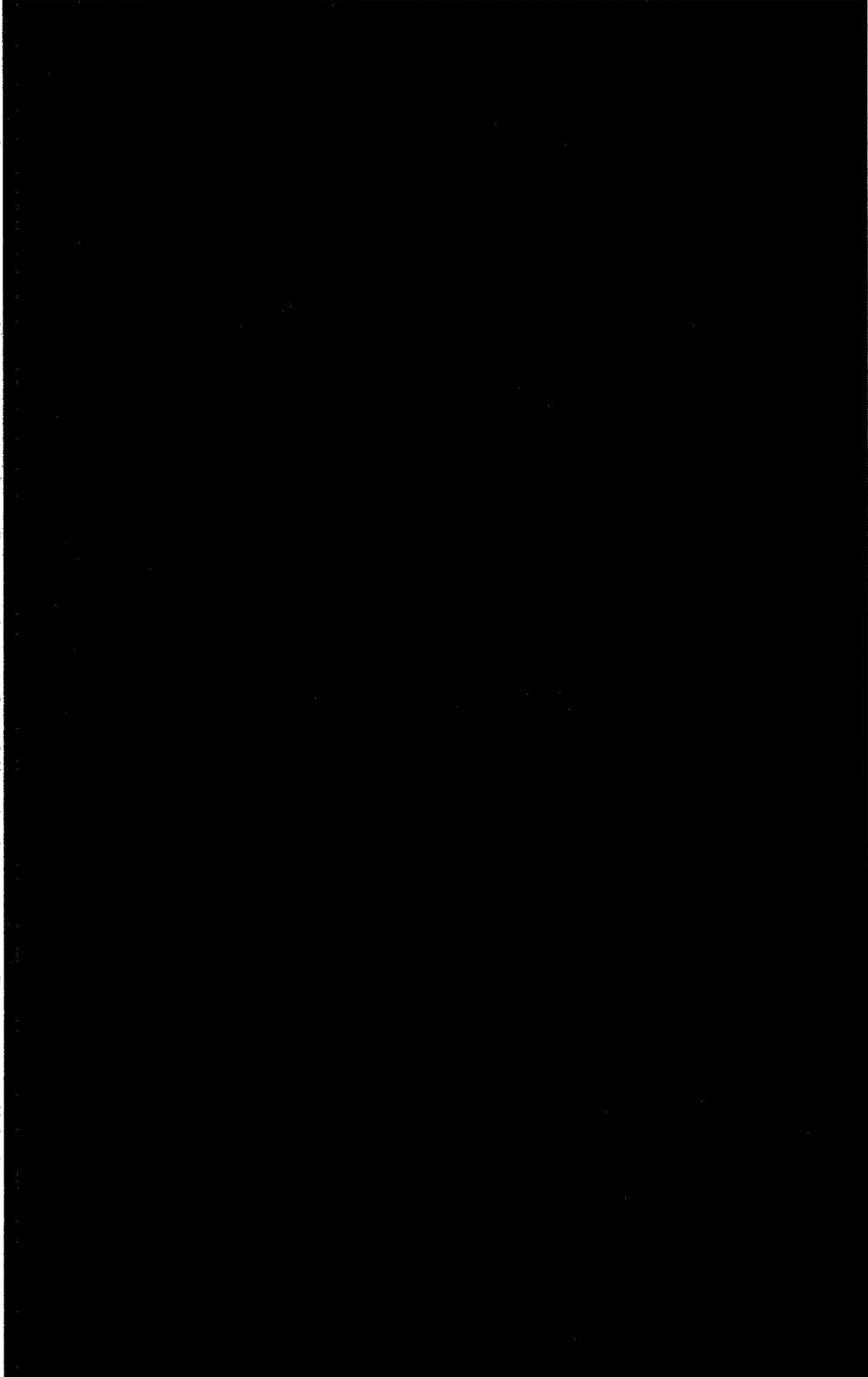
Initial Phase

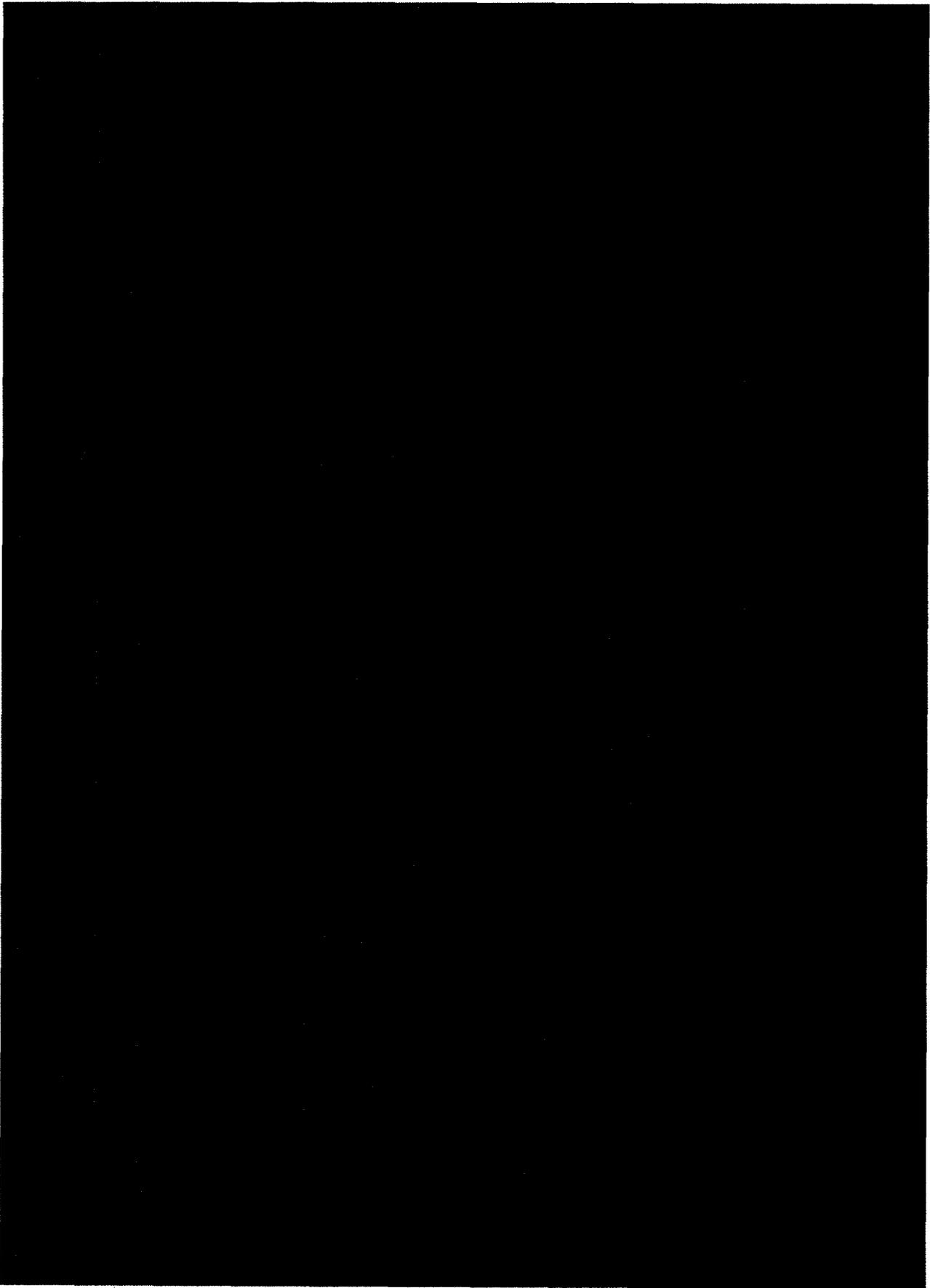
- 16.2.8.1 Serum IgG Antibody Titers
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- R-16.2.8.1 Serum IgG Antibody Titers
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- 16.3 Case Report Forms**
- 16.3.1 CRFs for Deaths, Other Serious Adverse Events, and Withdrawals Due to Adverse Events**
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- 16.4 Individual Patient Data Listings**





ZYPLAST® COLLAGEN IMPLANT PHYSICIAN PACKAGE INSERT

DESCRIPTION

Zyplast® collagen implant is a sterile device composed of highly purified bovine dermal collagen that is lightly crosslinked with glutaraldehyde and dispersed in a phosphate-buffered physiological saline containing 0.3% lidocaine.

MODE OF ACTION

ZYPLAST collagen implant is introduced into mid to deep dermal tissues for correction of contour deficiencies. After injection, the suspended collagen forms a soft cohesive network of fibers, which is responsible for restoring contour. Over a period of months the implant is colonized by host connective tissue cells; once established, the implant takes on the texture and appearance of normal host tissue and is subject to the same stresses and aging processes.

INDICATIONS AND USAGE

ZYPLAST collagen implant is indicated for the correction of contour deficiencies of soft tissue. The etiology and distensibility of the defect, tissue stress at the implant site, and plane of placement of the implant will affect the degree and duration of contour restoration. Results of *in vitro* and *in vivo* studies suggest that ZYPLAST collagen implant, because it is crosslinked, may persist in tissue to a greater extent than non-crosslinked Zyderm® collagen implant; therefore, it is recommended that during treatment, correction should be limited to no more than 100% of the defect. Two or more implant sessions at intervals of at least two weeks may be required to achieve the desired effect.

Collagen implants have been employed successfully in many areas of the body to correct distensible acne scars, atrophy from disease or trauma, glabellar frown lines, nasolabial folds, or defects secondary to rhinoplasty, skin graft or other surgery, and other soft tissue defects. Severely indurated, sharply marginated and very superficial lesions (e.g., ice-pick acne scars, viral pockmarks, and superficial rhytides such as some perioral lines) have proved difficult to distend and, therefore, are difficult to correct. If a defect cannot be distended because of extensive scarring or nonelastic tissue, the course of correction will be prolonged, if correction is achievable.

Touch-up implantations at 6-18 month intervals will be required to maintain maximum correction. The interval at which touch-up implantations are needed depends on the nature of the lesion, the amount of implant introduced, the plane of placement and the stresses that may exist at corrected sites. For example, ongoing mechanical stresses eventually cause these defects to recur. Correction tends to persist longer in areas in which disease processes have become quiescent. Nevertheless, if a stable level of correction is desired, all patients should be counselled to anticipate supplemental implantations.

CONTRAINDICATIONS

ZYPLAST collagen implant therapy must not be initiated if the patient has a positive response to the required Collagen Test Implant. Refer to Collagen Test Implant Physician Package Insert for complete instructions for administration and evaluation of the test implant.

ZYPLAST collagen implant must not be used in patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.

ZYPLAST collagen implant contains lidocaine and must not be used in patients with known lidocaine hypersensitivity.

ZYPLAST collagen implant must not be used in patients with a history of allergies to any bovine collagen products, including but not limited to collagen injectables, collagen sponges, hemostatic sponges and collagen-based sutures, because these patients are likely to have hypersensitivity to ZYPLAST collagen implant.

ZYPLAST collagen implant must not be used in patients undergoing or planning to undergo desensitization injections to meat products, as these injections can contain bovine collagen.

ZYPLAST collagen implant is contraindicated for use in breast augmentation, and for implantation into bone, tendon, ligament, or muscle.

WARNINGS

A Collagen Test Implant must be administered and evaluated prior to soft tissue deficiency correction using ZYPLAST collagen implant. (Refer to Collagen Test Implant Physician Package Insert.) **Note: The Collagen Test Implant is non-crosslinked collagen, while ZYPLAST collagen implant is crosslinked collagen.** If the Collagen Test Implant response is equivocal, it is recommended that a second test implantation be administered in the opposite arm and evaluated prior to the initiation of treatment.

Some physicians have reported the occurrence of connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis (PM), and dermatomyositis (DM) subsequent to collagen injections in patients with no previous history of these disorders. Conflicting studies have been published (27,28) in peer reviewed journals regarding the association between PM/DM and injectable collagen. A causal relationship between collagen injections and the onset of PM/DM, or the other connective tissue diseases listed, has not been established.

Also, an increased incidence of cell-mediated and humoral immunity to various collagens have been found in systemic connective tissue diseases such as rheumatoid arthritis, juvenile rheumatoid arthritis, and progressive systemic sclerosis (scleroderma). 19-24 Patients with these diseases may thus have an increased susceptibility to hypersensitivity responses and/or accelerated clearance of their implants when injected with bovine dermal collagen preparations. Therefore, caution should be used when treating these patients including consideration for multiple skin testing (see Skin Test Package Insert).

Local necrosis is a rare event which has been observed following collagen implantation. Most necroses reported through post-marketing surveillance have occurred in the glabella. It is thought to result from the injury, obstruction, or compromise of blood vessels. ZYPLAST collagen implant is more often injected deeper into the dermis closer to the local vascular supply than is ZYDERM collagen implant. Additionally, ZYPLAST collagen implant does not undergo syneresis after injection. Therefore, interruption of the local blood supply may more likely occur with ZYPLAST collagen implant. It is recommended that corrections in the glabellar region be performed using ZYDERM collagen implant rather than ZYPLAST collagen implant.

Patients with a history of dietary beef allergy should be carefully evaluated before injectable bovine collagen therapy, since it is possible that the collagen component of the beef may be causing the allergy. More than one skin test is highly recommended prior to treating these patients.

ZYPLAST collagen implant must not be implanted into blood vessels. Collagen can initiate platelet aggregation, and implantation of ZYPLAST collagen implant into dermal vessels may cause vascular occlusion, infarction, or embolic phenomena.

PRECAUTIONS

Use of ZYDERM 1 collagen implant in an individual patient should be limited to 30 cc over a one-year period. Use of ZYDERM 2 collagen implant in an individual patient should be limited to 15 cc over a one-year period. The combination of these products or of ZYDERM in conjunction with ZYPLAST in an individual patient should be limited to 30 cc over a one-year period. The safety of injecting greater amounts on an annual basis has not been established.

ZYPLAST collagen implant should be used with caution in patients with histories of allergic reactions to other substances, as injectable collagen use has been associated with allergic hypersensitivity responses, especially in patients with such histories.

The injection of ZYPLAST collagen implant carries an inherent, yet minimal, risk of infection, as does any transcutaneous procedure.

Use of ZYPLAST collagen implant at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present should be deferred until the underlying process has been controlled.

The safety of ZYPLAST collagen implant for use during pregnancy or in infants has not been established.

ZYPLAST collagen implant should be used with caution in patients on immunosuppressive therapy.

Patients who are using substances which reduce coagulation, such as aspirin and non-steroidal anti-inflammatory drugs may, as with any injection, experience increased

bruising or bleeding at injection sites.

ZYPLAST collagen implant is not recommended for use in the periorbital area. Over-correction of the vermilion border of the lip has been slow to resolve due to minimal tissue stresses at this site. Therefore, caution is advised for ZYPLAST collagen implant use in this area.

Clinical experience with injectable collagen implants was not available prior to 1976; the safety of this product for a longer duration is not known.

Since it has been reported that host collagen may be deposited at the site of collagen implantation, the patient should be informed that part or all of the correction may last for 2 years or more.

TREATMENT RESPONSES

Transient or minimal swelling, mild redness, and discomfort will probably occur at the implant site immediately following implantation. Increasing discomfort or swelling, or spreading redness should be brought immediately to the physician's attention.

Transient pain and tenderness at injection sites has been associated with the injection of the collagen implants.

On occasion, transient painless bruising or discoloration has been noted to develop at one or more of the implantation sites. Resolution has always been spontaneous.

Fewer than 1% of patients receiving ZYDERM collagen implant have at some time reported an intermittent swelling response, involving moderate induration at the implant site and edema within the surrounding tissues. In some cases, these responses have been found to be associated with antibodies to bovine collagen. At times this has been accompanied by mild pruritus or minimal erythema which may persist for a period up to several months. These reactions may last only a few hours and are usually associated with causes of peripheral vasodilatation, such as consumption of alcohol, prolonged exposure to sun and/or heat, exercise, and flare-ups of hay fever and other causes of nasal and sinus congestion. To date, these reactions have been self-limiting and have not been shown to affect adversely the long-term success of collagen implant correction, although they may persist throughout the life of the implant.

Infections at collagen implant sites have occurred in fewer than one per thousand treated patients, and reactivation of a pre-existing herpes simplex infection at implantation sites has been reported in fewer than one per ten thousand patients. These responses resolved quickly and without sequelae.

As with any injection into the head or neck, the injected material may be inadvertently implanted into a blood vessel. Forceful injection into dermal arterial branches of the face and scalp could cause retrograde movement of the implant material into retinal arteries, resulting in vascular occlusion. Such a complication, although unlikely, has been reported with the use of ZYDERM collagen implant in one patient, and resulted in the sudden and permanent loss of vision in one eye. Similar complications have been associated with other injectable preparations, including corticosteroids, local anesthetics, and angiographic agents. These findings emphasize the importance of avoiding implantation into blood vessels.

ADVERSE REACTIONS

Patients treated intradermally with ZYPLAST collagen implant have reported temporary palpable lumpiness or visible material (milia-like yellow or white papules) at injection sites. Both of these types of treatment responses resolved spontaneously without sequelae, and are believed to reflect reduced shrinkage of crosslinked implants due to water resorption, compared with non-crosslinked collagen implants.

Sensitization reactions to injectable collagen implants have occurred in 1-2% of treated patients. Most reactions have been of a hypersensitivity nature and have consisted of erythema, swelling, induration and/or urticaria at implantation sites. Often these reactions have occurred following an unrecognized or unreported positive collagen skin test.

Typically, allergic reactions persist between one and nine months, with an average duration of four months. These reactions may be intermittent or continuous in nature. In rare instances, reactions have resolved in one or two weeks, or have persisted for more than one year. Although several forms of therapy (antihistamines, NSAIDs, oral, topical and intralesional steroids) have been tried, usually they

resulted in only temporary improvement. In most cases, time has proved to be the determining factor in the resolution of these reactions. In rare instances, patients have been left with residual firmness at the site of a resolved adverse reaction.

On rare occasions, abscess formation has occurred at implantation sites. In some cases this reaction has been associated with elevated titers of anti-bovine collagen antibodies, and can be multiple or recurrent. These reactions develop weeks to months following injections and may result in induration and/or scar formation. Most of the remaining responses occurred in patients who became sensitized to collagen implants at some point during their course of treatment.

The antigenic specificity of ZYPLAST collagen implant has been determined to be identical to that of ZYDERM collagen implant. During clinical trials and post-marketing surveillance, the incidence of hypersensitivity responses to ZYPLAST collagen implant has been significantly lower than to ZYDERM collagen implant; however, because of the potential for prolonged local availability of antigen, it is possible that the long-term rate of response to ZYPLAST collagen implant may exceed the low rate experienced to date.

Systemic complaints have been reported by fewer than 0.5% of collagen implant patients. During clinical testing and subsequent monitoring of patient complaints following exposure to ZYPLAST collagen implant, a variety of systemic complaints have been reported. These reports have included flu-like symptoms (fever, headache, myalgia, neuralgia, nausea, malaise, or dizziness); pruritus; rash, transient visual disturbances including blurred vision; tingling and numbness; transient polyarthralgia; and various systemic diseases including immune-mediated diseases. Rare anaphylactoid responses have been reported, including acute episodes of hypotension, difficulty in breathing, tightness in chest, and/or shortness of breath.

Localized necrosis and/or sloughing, resulting in a scab and/or a scar, has occurred following interruption of blood flow such as through blood vessel laceration or occlusion. The extent of necrosis has varied and is in the pattern of the tissue served by the vessel involved. This phenomenon has been reported more frequently in the glabellar region of the face than in other areas; nevertheless, the incidence of this scab or scar formation is less than 1%, and may occur in conjunction with either infection and/or hypersensitivity response. In these patients, implantation can be followed by prolonged blanching or development of ecchymosis at the treatment site. It is possible that overdilatation of tissue in areas of compromised vascularity may lead to similar complications, caused by interruption of blood supply to an injection site.

To report an adverse reaction, phone the Medical Monitoring Department, INAMED Corporation, toll-free: 800.624.4261.

DIRECTIONS FOR USE

NOTE: ZYPLAST collagen implant should be stored at standard refrigerator temperatures. **DO NOT FREEZE.**

1. Prior to a Collagen Test Implant, the patient should be provided with a copy of the Patient Brochure.
2. Prior to treatment with ZYPLAST collagen implant, the results of the test implantation must be carefully evaluated; the patient must not have a response to the required Collagen Test Implant. For a complete discussion of the Collagen Test Implant, refer to the Collagen Test Implant Physician Package Insert supplied with test syringes.
3. Prior to treatment with ZYPLAST collagen implant, the patient should be fully apprised of the indications, contraindications, warnings, precautions, treatment responses, adverse reactions, and method of administration. Patients also should be advised that supplemental touch-up implantations will be required to maintain maximum correction.
4. A complete medical history should be obtained to determine whether the patient is an appropriate candidate for treatment with ZYPLAST collagen implant.
5. The patient's soft tissue deficiencies should be characterized with regard to etiology, distensibility, stress at the site, and depth of lesion. Pretreatment photographs are recommended.
6. After ensuring that the patient has thoroughly washed the treatment area with soap and water, the area should be swabbed with alcohol or other antiseptic.

7. ZYPLAST collagen implant is implanted through a fine-gauge needle. The needle should be placed into the plane(s) of apparent deformity and the defect should not be overcorrected. Best results with ZYPLAST collagen implant are achieved in defects requiring mid to deep dermal implant placement. The rate and degree of subsidence of correction in the implanted area varies with patient, treatment site, and plane of implant placement. Correction should be conservative during initial treatment. Clinical experience has shown that overcorrection has been slow to resolve in the periorbital area and in treatment sites around the vermilion border of the lip. Therefore, caution is advised for ZYPLAST collagen implant use in these areas. Severely indurated defects such as scars, which initially resist distention, may require several treatment sessions before desired correction is obtained.

Needles may become occluded or dull during a treatment session, and replacement may be necessary.

8. Vigorous massage of the treated areas is recommended following implantation.
9. Successive implantations at intervals of two or more weeks may be necessary to achieve the desired level of correction.
10. The physician should instruct the patient to report to her/him any evidence of adverse texture change in the surrounding implantation site. Other problems possibly associated with the use of ZYPLAST collagen implant should be promptly brought to the attention of the physician.
11. The syringe and any unused material should be discarded after a single treatment visit.

HOW SUPPLIED

ZYPLAST collagen implant is sterile and supplied in individual treatment syringes packaged with sterile needles, ready for use.

To place an order, phone toll-free:

In USA: 800.624.4261

In Canada: 800.336.3793

STORAGE DIRECTIONS

ZYPLAST collagen implant should be stored at standard refrigerator temperatures. **DO NOT FREEZE.**

ZYPLAST collagen implant has an off-white opaque appearance. In the event that a syringe contains material that is clear (like water), do not use the syringe and notify INAMED Corporation immediately at 800.624.4261. In Canada, notify INAMED Canada Inc. immediately at 800.336.3793.

CAUTION: US FEDERAL LAW RESTRICTS THIS DEVICE TO SALE, DISTRIBUTION, OR USE BY OR ON THE ORDER OF A LICENSED PHYSICIAN OR AN ORAL AND MAXILLOFACIAL SURGEON.

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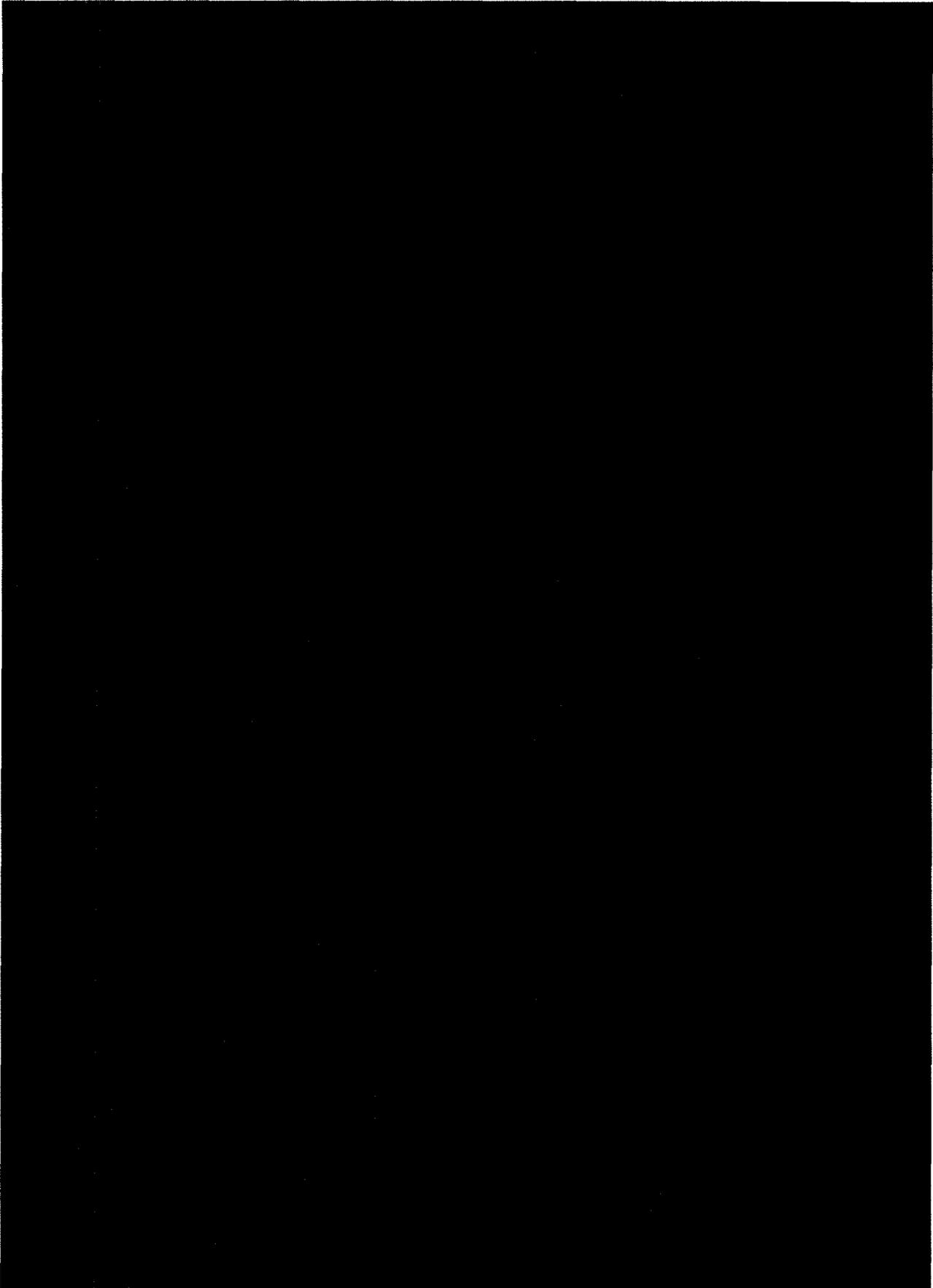
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A complete bibliography on Injectable Collagen Implant may be requested from INAMED Corporation.

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COLLAGEN TEST IMPLANT PHYSICIAN PACKAGE INSERT

DESCRIPTION

The Collagen Test Implant is a sterile device composed of highly purified bovine dermal collagen that is dispersed in phosphate-buffered physiological saline containing 0.3% lidocaine

MODE OF ACTION

The Collagen Test Implant is administered intradermally into the volar forearm to screen out individuals who might develop hypersensitivity to injectable bovine dermal collagen devices.

CONTRAINDICATIONS

Collagen Test Implant must not be used in patients with a history of allergies to any bovine collagen products, including but not limited to collagen injectables (except to verify questionable allergy), collagen implants, hemostatic sponges, and collagen-based sutures, because these patients are likely to have hypersensitivity to the Collagen Test Implant.

Collagen Test Implant must not be used in patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies

Collagen Test Implant contains lidocaine, and must not be used in patients with known hypersensitivity to lidocaine

Collagen Test Implant must not be used in patients undergoing or planning to undergo desensitization injections to meat products, as these injections can contain bovine collagen

Collagen Implants are contraindicated for use in breast augmentation, and for implantation into bone, tendon, ligament, or muscle

WARNINGS

If the test implantation response is positive, the patient must not be treated with Collagen Implant devices. If the test implantation response is equivocal, it is recommended that a second test implantation be administered in the opposite arm and evaluated prior to the initiation of treatment

Some physicians have reported the occurrence of connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis (PM), and dermatomyositis (DM) subsequent to collagen injections in patients with no previous history of these disorders. Conflicting studies have been published (10,11) in peer reviewed journals regarding the association between PM/DM and injectable collagen. A causal relationship between collagen injections and the onset of PM/DM, or the other connective tissue diseases listed, has not been established

Also, an increased incidence of cell-mediated and humoral immunity to various collagens have been found in systemic connective tissue diseases such as rheumatoid arthritis, juvenile rheumatoid arthritis, and progressive systemic sclerosis (scleroderma). 4-9 Patients with these diseases may thus have an increased susceptibility to hypersensitivity responses and/or accelerated clearance of their implants when injected with bovine dermal collagen preparations. Therefore, caution should be used when treating these patients including consideration for multiple skin testing

Patients with a history of dietary beef allergy should be carefully examined before injectable bovine collagen therapy, since it is possible that the collagen component of the beef may be causing the allergy. More than one skin test is highly recommended prior to treating these patients

The Collagen Test Implant must not be implanted into blood vessels. Collagen can initiate platelet aggregation, and implantation of Collagen Implant into dermal vessels may cause vascular occlusion, infarction, or embolic phenomena

PRECAUTIONS

The implantation of the Collagen Test Implant carries an inherent, yet minimal, risk of infection, as does any transcutaneous procedure

Results of the test implant may be inaccurate if patients are on immunosuppressive therapy.

Injectable bovine collagen should be used with caution in patients who are atopic or have a history of allergies. This class of patient has a greater potential of ultimately exhibiting an allergic reaction to bovine collagen than do other patients.

Use of Collagen Test Implant at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present should be deferred until the underlying process has been controlled

Since it has been reported that host collagen may be deposited at the site of collagen implantation, the patient should be informed that part or all of the correction may last for 2 years or more

ADVERSE EVENTS

Rare anaphylactoid responses have been reported with Zyderm® collagen implant, including acute episodes of hypotension, difficulty in breathing, tightness in chest, and/or shortness of breath.

On rare occasions, the hypersensitivity response has progressed to a cystic reaction which may drain purulent material. The incidence and severity of this type of hypersensitivity response reported to date has been greater with Zyplast® collagen implant than with ZYDERM collagen implant. These reactions develop weeks to months following injections and may result in scar formation, rarely requiring medical revision to correct. This type of reaction can occur as multiple and/or recurrent sterile abscesses which tend to be persistent and resistant to drug therapy; careful incision and drainage has been a useful treatment

Systemic complaints have been reported by fewer than 0.5% of Collagen Implant patients. During clinical testing and subsequent monitoring of patient complaints following exposure to ZYDERM collagen implant, a variety of systemic complaints have been reported. These reports included flu-like symptoms (fever, myalgia, neuralgia, headache, nausea, malaise, or dizziness), pruritus; rash; transient visual disturbances including blurred vision, tingling and numbness, transient polyarthralgia; and various systemic diseases including immune-mediated diseases.

To report an adverse reaction, phone the Medical Monitoring Department, INAMED Corporation, toll-free: 800.624.4261

DIRECTIONS FOR USE

Note: The Collagen Test Implant should be stored at standard refrigerator temperatures. **DO NOT FREEZE**

Prior to the test implantation with Collagen Test Implant, the patient should be provided with a copy of the Collagen Test Implant Card. The patient should be fully apprised of the purpose of and evaluation criteria for the test implant.

- 1 After verifying that contraindications to the proposed injectable collagen treatment do not exist, a Collagen Test Implant is administered. At the time of the initial evaluation, a complete medical history should be obtained
- 2 After cleaning the site, 0.1 cc of material from a Collagen Test Implant Syringe should be implanted intradermally into a volar forearm surface.
- 3 **The results of the test implantation must be carefully evaluated for a four-week period prior to the initiation of treatment with injectable collagens. Patients should be instructed to notify their physicians of any untoward test response observed within the four-week period.** An untoward test site response is defined as erythema of any degree, induration, tenderness, or swelling at the test site, with or without pruritus, which persists for more than six hours or appears more than 24 hours following implantation. Patients with such responses are ineligible for treatment with Collagen Implants. In addition, the onset of rash, arthralgia or myalgia should be brought immediately to the attention of the treating physician in order that he might evaluate its possible relationship to the test implant. Approximately 3.0% of the patients tested have had one or more of the above-described reactions to the test implantation
- 4 **TREATMENT WITH INJECTABLE COLLAGEN IMPLANT IS CONTRAINDICATED IN ANY PATIENT EXHIBITING AN UNTOWARD TEST RESPONSE DURING THE FOUR-WEEK EVALUATION PERIOD.**

Occasionally, a normal skin test will exhibit a palpable bead of collagen in the absence of inflammation, swelling or pruritus. If the test implantation response is equivocal, it is recommended that a second test implantation be administered in the opposite arm and evaluated prior to the initiation of treatment. The majority of retest responses will occur within 72 hours, however, the repeat test also should be observed for the full 4 weeks

Clinical experience has shown that screening of the collagen test implant cannot be overemphasized. However, a negative skin test does not preclude the possibility of the patient subsequently developing a delayed hypersensitivity response to the implant material following treatment exposures

5. Discard the syringe after administration of the test implantation

HOW SUPPLIED

The Collagen Test Implant is supplied sterile in syringes, in 0.1cc volumes. The test syringes are packaged with sterile needles, ready for implantation

Collagen Test Implant syringes are appropriate for testing prior to treatment with ZYPLAST collagen implant (cross-linked collagen), and ZYDERM collagen implant

To place an order, phone toll-free
In USA: 800.624.4261
In Canada 800.336.3793

STORAGE DIRECTIONS

Collagen Test Implant syringes should be stored at standard refrigerator temperatures. **DO NOT FREEZE**

Collagen Test Implant has a whitish, opaque or semi-opaque appearance. In the event that a syringe contains material that is clear (like water), do not use the syringe and notify INAMED Corporation immediately at 800.624.4261. In Canada, notify INAMED Canada Inc. immediately at 800.336.3793

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