

CLINICAL REVIEW  
P030032

HYLAFORM VISCOELASTIC GEL

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**INDICATION FOR USE:** Hylaform® is injected into the mid to deep dermis for correction of soft tissue contour deficiencies, such as wrinkles and acne scars.

Clinical studies were initiated on June 12, 2002 and continue under IDE G000315.

The CLINICAL STUDY that supports the safety and effectiveness of Hylaform for the correction of soft tissue contour deficiencies is titled “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”.

This clinical study was conducted at 10 centers in the US in two phases. These include:

- ?? An initial treatment phase evaluating safety and efficacy over a 12 week follow-up period, and
- ?? A repeat treatment phase to evaluate repeat treatment with Hylaform over a period of four (4) weeks. This study was extended to 12 weeks to allow an additional follow-up period to study the safety and efficacy of a new formulation, called Hylaform Plus, compared to Hylaform.

Note: The PMA is not requesting approval for Hylaform Plus at this time.

**DEVICE DESCRIPTION:**

Hylaform® (Hylan B) is a sterile, nonpyrogenic, viscoelastic, clear, colorless, transparent gel composed of cross-linked molecules of hyaluronan. Hylan is a derivative of hyaluronan (sodium hyaluronate) and consists of repeating disaccharide units of N-acetylglucosamine and sodium glucuronate. Hylan B is produced by chemically cross-linking hylan molecules to form an infinite molecular network. It is water-insoluble, viscoelastic and highly hydrated. The hydration fluid is isotonic physiological sodium chloride solution.

Hylan B gel slurry contains hylan B polymer at a concentration of 4.5 to 6.5 mg/ml, in a hydration fluid of 0.15 M NaCl. The osmolality of hylan gel is approximately 290 to 330

mOsm. The average size of particles in hylan gel slurry is 200-700 microns. The level of heavy metals is less than 2 ppm. Hylan B is susceptible to degradation by mammalian hyaluronidase, with production of low molecular weight oligosaccharides. Hylan B is also degraded by oxygen-derive free radicals.

Hylan B is derived from hyaluronan, present in all intercellular matrices of human connective tissue, where it acts as a tissue stabilizer and elastoviscous shock absorber.

Hyaluronan in the dermis, sub dermis and subcutaneous tissue contributes to space filling between the collagen and elastin fibers and cells, and stabilizes the collagen fibrous network. To prevent the rapid turnover of native hyaluronan, the cross-linking processes used in Hylaform manufacture produce an infinite molecular network of hyaluronan that forms a water-insoluble gel.

Hylan is a modified form of the naturally occurring hyaluronan, a glycosaminoglycan. The sodium salt of hyaluronan contains disaccharide units made of sodium D-glucuronate and N-acetyl-D-glucosamine linked together with beta-1,4 glycosidic bonds. These disaccharides are linked by beta-1,4 glycosidic bonds to form long unbranched polysaccharide chains. Hylan B is a polymer resulting from cross-linking reaction of hyaluronan with vinyl sulfone. Vinyl sulfone is a bifunctional molecule in which 2 vinyl groups are attached to a sulfonyl group. Each vinyl group can react with any chemical group containing an active hydrogen atom. The reaction with a hydroxyl group proceeds as follows, with the formation of an ether bond:



Hylan gel is a hydrogel of cross-linked insoluble hylan B hydrated in 0.15 M aqueous NaCl. The hylan B concentration in the gel is expressed in terms of concentration of the polysaccharide chains of hylan, and is found to be 4.5 to 6.5 mg/ml. The pH range is 6.0 to 7.5.

The hyaluronan in Hylaform is the cross-linked biological polysaccharide hylan B (also called hylan gel). Hylan B is a hydrated gel with the same polysaccharide chain and polyanionic characteristics as native hyaluronan; the viscoelastic properties of hylan B are enhanced as compared to those of native hyaluronan. The hyaluronan in hylan B is derived from the combs of domestic fowl and is chemically cross-linked and hydrated with a hydration fluid composed of water and a physiological concentration of sodium chloride. Hylan B remains in the dermal tissue for a considerably longer period of time compared to native hyaluronan, which diffuses away from the site of injection.

Hylaform® is contraindicated for use in breast augmentation, or for implantation into bone, tendon, ligament or muscle.

Hylaform® may not be injected into blood vessels; it may occlude the vessels and could cause infarction or embolization.

Hylaform is supplied as a 0.75 ml volume in a single-use 0.9 ml glass syringe with a protective sleeve, a needle-locking device and 2 sterile needles. Contents of the syringe are sterile and nonpyrogenic. Each 0.75 ml of Hylaform contains 4.1 mg of hylan B gel, 6.4 mg of sodium chloride, and USP water for injection to comprise a total volume per syringe of 0.75 ml. The units are to be stored at 2°C - 30°C and are not to be frozen. The syringe is a Hypak® glass syringe manufactured by Becton Dickinson and is a legally marketed device. The 30 gauge x ½” needles provided are also legally marketed medical devices. The syringe with the Hylaform and needles are provided in a polyethylene terephthalate glycol tray with a blister lid. These packages are placed into cardboard boxes.

**NON-CLINICAL LABORATORY STUDIES:** This is presented in Module 2 of the submission and has been reviewed by Dr. David Krause. Please see his review dated August 1, 2003.

### **CLINICAL STUDY**

Objectives: The primary objectives were (1) to evaluate the efficacy (non-inferiority) of Hylaform® viscoelastic gel for correction of nasolabial folds as compared to Zyplast collagen implant and (2) to evaluate the safety of Hylaform® as compared to Zyplast. The secondary objective was to evaluate the clinical utility of Hylaform® with respect to physician assessment and patient self-assessment

In the second phase (re-treatment phase) the primary objectives were to evaluate the safety of repeat treatment with hylan B viscoelastic products and 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 to determine safety through 12 weeks post treatment by the rates of adverse events associated with repeat treatment and by the presence of absence of a potential immune response to hylan B as measured by the development of hylan B antibody titers after repeat device implantation and to evaluate the clinical utility of Hylaform® Plus and Hylaform® with respect to physician assessment and patient self-assessment.

Inclusion criteria- For the main phase these include the following:

- ?? 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 candidates for correction by the procedure described in the protocol
- ?? 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, or was surgically sterile, or postmenopausal for at least one 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

Exclusion criteria- Initial phase:

- ?? 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 5,6 on the 6-point grading scale at the areas to be treated
- ?? Women who are pregnant or lactating
- ?? Received prior therapy (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 augmentation with permanent implants throughout the study
- ?? Previous tissue augmentation with permanent implants (eg, Softform, silicone)
- ?? 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 (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
- ?? Aspirin or nonsteroidal anti-inflammatory drugs within 1 week prior to treatment
- ?? Concomitant anticoagulant therapy, antiplatelet therapy, or history of bleeding disorders or connective tissue disorders
- ?? Over-the-counter wrinkle products or prescription treatments within 4 weeks prior to study; patients are restricted from using over-the-counter wrinkle products or prescription treatments throughout study duration
- ?? Immunocompromised or immunosuppressed
- ?? 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, preclude 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 on baseline clinical laboratory parameters

Inclusion criteria- Repeat Phase:

- ?? All of the above for the initial phase plus:
- ?? Hylaform® treatment during initial phase of study
- ?? Completed 12 week (no touch-up required) or 14 week (touch-up required) follow-up visit for initial phase

Exclusion Criteria- Repeat Phase:

- ?? Same as the initial phase

Methodology: The initial phase was a double-blind, randomized, multicenter study involving patients receiving treatment for cutaneous correction of nasolabial folds. The treatment plan is outlined below in chart form. Note that a “touch-up” was allowed at visit 5, week 2, and the follow-up period extended to week 14 for those patients needing this treatment. Touch-up was deemed necessary if there was a change of less than 1 point on the 6-point grading scale.

**Table 9-1 Schedule of Study Events for the Initial Phase**

Procedure	Initial Phase – All Patient Visits				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Week -6	Week -4 (±3 Days)	Day 0 (±3 Days)	Day 3 (±1 Day)	Week 2 (±3 Days)
Written informed consent	X				
Inclusion/exclusion criteria	X	X			
Randomization			X		
Demographics	X				
Vitals	X				
Pregnancy test (urine)	X		X		X <sup>a</sup>
Smoking history	X				
Sun exposure	X				
Medical history	X				
Physical examination	X				
Prior dermal treatments and medication assessment	X	X	X		
Skin test <sup>b</sup>	X <sup>c</sup>	X <sup>d</sup>			
Evaluation of skin test		X <sup>e</sup>	X <sup>f</sup>		
Facial photographs	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X
Adverse event and procedure-related event monitoring	X	X	X	X	X
Laboratory evaluations <sup>g</sup>		X			
Serum collection for antibody response			X <sup>h</sup>		
Investigator wrinkle assessment			X	X	X
Treatment			X		
Patient global assessment					X
Investigator global assessment					X
Evaluation for touch-up					X
Touch-up administration					X <sup>i</sup>

<sup>a</sup> Only if a touch-up was required

<sup>b</sup> Collagen Test Implant

<sup>c</sup> Administration of first skin test

<sup>d</sup> Administration of second skin test

<sup>e</sup> Evaluation of first skin test

<sup>f</sup> Evaluation of second skin test

<sup>g</sup> Hematology: WBC, RBC, hemoglobin, hematocrit, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils. Chemistry: Glucose, BUN, creatinine, SGOT (AST), SGPT (ALT), alkaline phosphatase, lactate dehydrogenase, total bilirubin, total protein, albumin, calcium, sodium, potassium, chloride.

<sup>h</sup> Collected before injection of study treatment

<sup>i</sup> Administration of touch-up to patients who did not achieve a 1-point improvement from baseline on the 6-point grading scale as determined by the investigator.

**Table 9-2 Schedule of Study Events for the Repeat Treatment Phase**

Procedure	Repeat Treatment Phase			
	Visit R1	Visit R2	Visits R3 and R5	Visits R4 and R6
	Day 0	Day 3	Weeks 2 and 8	Weeks 4 and 12
Written informed consent	X <sup>a</sup>			
Patient selection criteria	X <sup>a</sup>			
Medical history	X <sup>a</sup>			
Urine pregnancy test	X <sup>a</sup>			
Sunlight exposure and smoking history	X <sup>a</sup>			X
Physical examination	X <sup>a</sup>			X
Facial photographs	X <sup>a</sup>	X	X	X
Serum collection for antibody (ELISA)	X <sup>b</sup>			X
Clinical laboratory tests <sup>c</sup>	X <sup>b</sup>			X
Prior and concomitant medication review	X	X	X	X
Adverse events	X	X	X	X
Investigator wrinkle scores	X <sup>a</sup>	X	X	X
Repeat treatment administration	X			
Dispense patient diary	X	X		
Review patient diary		X <sup>d</sup>	X <sup>d, e</sup>	
Procedure-related event monitoring	X	X		
Global assessment (investigator and patient)			X	X

<sup>a</sup> Procedure performed prior to repeat treatment.

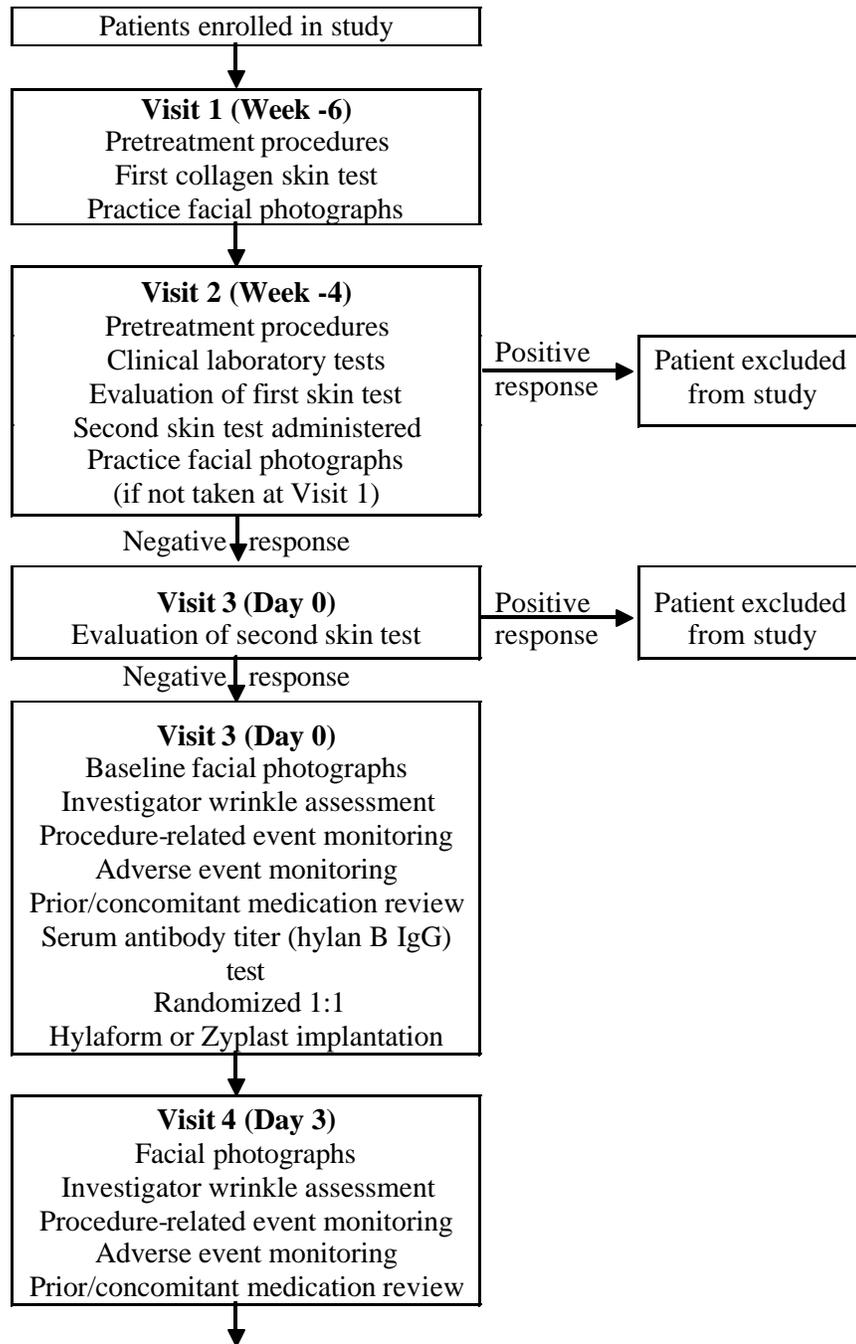
<sup>b</sup> Blood samples collected just prior to repeat treatment. When repeat treatment was performed on the same day as the blood sample collection for Visit 11 or Visit 12 of the initial phase, additional blood collection was not required.

<sup>c</sup> Hematology: WBC, RBC, hemoglobin, hematocrit, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils. Chemistry: Glucose, BUN, creatinine, SGOT (AST), SGPT (ALT), alkaline phosphatase, lactate dehydrogenase, total bilirubin, total protein, albumin, calcium, sodium, potassium, chloride.

<sup>d</sup> Patient diary was retrieved and reviewed for completeness and signs/symptoms of immunologic response or other adverse events.

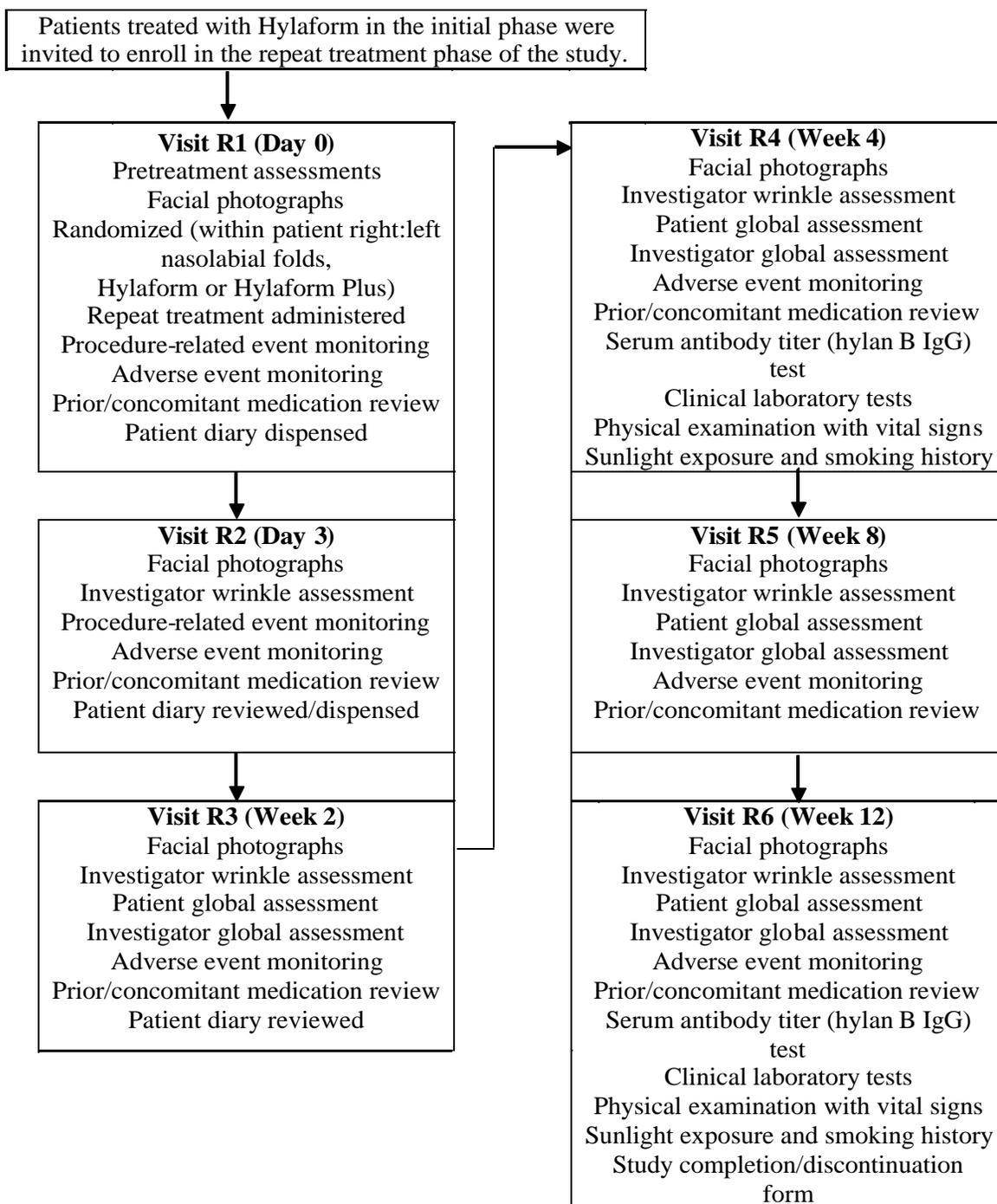
<sup>e</sup> Review of patient diary did not occur at Visit R5.

**Figure 9-1 Study Flowchart for the Initial Phase**



The follow-up phase allowed for the repeat treatment of all patients who completed phase one. The major difference in the repeat treatment phase was the introduction of Hylaform® Plus, a material identical to Hylaform® but with different size particles. Hylaform® particle size is 500 microns, Hylaform® Plus is 700 microns. Hylaform® was injected into one NLF, Hylaform® Plus into the other.

### Study Flowchart for the Repeat Treatment Phase



After treatment and follow-up were completed, a blinded independent panel of board-certified dermatologists reviewed, in random order, and scored the 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 time of the final visit. Clinical laboratory tests and serum antibody samples were collected at designated visits.

### **Primary and Secondary EFFICACY Parameters:**

The primary efficacy measure was the blinded Independent Panel Reviewer (IPR) Wrinkle Assessment Scores assigned to each patient's facial photographs taken at 12 weeks after the last implantation of the device for the ITT analysis. As described above, a panel of dermatologists scored each patient's week 12 or week 14 photo for both the left and right NLF.

Secondary efficacy was assessed by patient global self-assessments, Investigator global assessments, and Investigator wrinkle assessments. Assessments were done at baseline, 3 days, 2, 4, 8, and 12 weeks after the last implantation of the device.

Repeat treatment phase: As in the primary phase, efficacy was measured by the scores of the IPR at 12 weeks after implantation of the device. Secondary efficacy was similarly addressed, with a safety assessment at 4 weeks and again at 12 weeks.

### **SAFETY Endpoints:**

At each study visit the Investigator evaluated the patient for signs and symptoms of any potential AE's. Each event was assessed with regard to procedure, study device, and anesthetic agent.

Procedure related events will be coded according to the MedDRA coding dictionary and summarized by treatment group, body system, severity and relationship to device.

Procedure related events were analyzed separately.

Serum IgG antibody titers at baseline, visit 7 or 8, and week 12 or 14 were measured for each of the treatment groups.

Clinical lab parameters were assessed at designated times; descriptive statistics were provided for these parameters.

During the repeat treatment phase similar reporting occurred. There was a safety analysis at 4 weeks during the repeat treatment phase.

### **IPR- Evaluation Score:**

The following is the validated 6-point assessment score used by the evaluators of the photos taken during the study:

- 0 - None
- 1 - Minimal
- 2 - Mild
- 3 - Moderate
- 4 - Deep
- 5 - Very Deep

Each of the IPR panel members was trained in the evaluation of photos using this scale. Each panel member reviewed their photos independently from other panel members.

**Patient Demographics:**

A majority of patients in each group were Caucasian and female. The mean age was 46.6 years, mean weight 63.6 kg. The following chart outlines the ITT patient demographics for this study:

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

	<b>Hylaform N = 133</b>	<b>Zyplast N = 128</b>	<b>Total N = 261</b>
<b>Age (years)</b>			
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 <sup>a</sup>	30.0, 55.0	30.0, 56.0 <sup>a</sup>
<b>Sex [Number (%)]</b>			
Male	7 (5.3)	9 (7.0)	16 (6.1)
Female	126 (94.7)	119 (93.0)	245 (93.9)
<b>Ethnicity [Number (%)]</b>			
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 <sup>b</sup> (1.5)	3 <sup>c</sup> (2.3)	5 (1.9)
<b>Weight (kg)</b>			
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
<b>Height (cm)</b>			
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.

<sup>a</sup>Patient 07-10 entered the study at 55 years of age, but had a birthday before receiving the initial device implantation.

<sup>b</sup>Other was either African American/Native American or Lebanese.

<sup>c</sup>Other was Latina, Western European, or Bangladeshi South Asian.

Smoking and Sun exposure histories were monitored as part of the protocol. The following outlines the two treatment groups:

**Smoking and Sun Exposure History  
Intent-to-treat Patients**

	<b>Hylaform N = 133</b>	<b>Zyplast N = 128</b>	<b>Total N = 261</b>
<b>Smoking history [Number (%)]</b>			
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)
<b>Current smoker (cigarettes/day)</b>			
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
<b>Former smoker (years since quitting)</b>			
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
<b>Sun exposure (hours/day)<sup>a</sup></b>			
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.

<sup>a</sup>Exposure 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.

Concomitant medication use was also analyzed; there was no difference in the two groups. Ibuprofen was the most widely used medication in both groups.

**RESULTS:** The results that follow are of the initial phase 1 study. The sponsor has submitted only 4 week safety data for the repeat treatment phase, and no efficacy data has been presented. For this document, I will present only the results of the Phase 1 study and the safety results of the repeat phase.

**Analysis of Efficacy:**

The sponsor demonstrated that there was non-inferiority of Hylaform® as compared with Zyplast®; superiority was not demonstrated. The following table summarizes these findings:

**IPR Nasolabial Fold Assessment at 12 Weeks After Last Treatment  
Intent-to-treat Patients**

	<b>Hylaform N = 133</b>	<b>Zyplast N = 128</b>
Independent Panel Review (IPR) Median Score <sup>a</sup>		
n (number of nasolabial folds)	246 <sup>b</sup>	234 <sup>c</sup>
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) <sup>d</sup>		-0.38
Patients with =1-point improvement from baseline, n (%) <sup>e</sup>	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.

- <sup>a</sup> 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.
- <sup>b</sup> Ten patients in the Hylaform group had missing IPR median scores for the 12 weeks after last treatment assessment.
- <sup>c</sup> Eleven patients in the Zyplast group had missing IPR median scores for the 12 weeks after last treatment assessment.
- <sup>d</sup> Confidence interval constructed from a repeated measures analysis of covariance model with factors for treatment group, site, patient, nasolabial fold, and baseline score.
- <sup>e</sup> Patients showed an improvement of at least 1 point in both right and left nasolabial folds.

It should be noted that there were 10 patients in the Hylaform® group and 11 patients in the Zyplast® group whose 12 week IPR median scores were missing, and these patients were excluded from the analysis. A review of these data across the study centers (table 14.2.2) shows this treatment effect to be consistent.

Live assessments made by the investigators, and those of the IPR's were found to be similar; scores were higher in the Hylaform® group immediately after treatment but less so by the IPR than the live assessor. All the scores for the live assessment, IPR assessment and patient assessment are presented and reviewed, a summary follows:

**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)
<b>2 weeks after last treatment</b>				
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
<b>4 weeks after last treatment</b>				
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
<b>8 weeks after last treatment</b>				
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
<b>12 weeks after last treatment</b>				
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.

**Duration of Effect:** This parameter was measured as the proportion of Hylaform® treated nasolabial folds which returned to baseline scores at 12 weeks after last treatment, as assessed by the blinded IPR median score, using photographs. Of the 243 total Hylaform® treated folds, 178 (73.3%) returned to their baseline values. At 2 weeks the proportion was only 38.2%.

**Volume Administered:** To demonstrate the extent of exposure, the following table is presented.

**Exposure to Study Treatment  
Intent-to-treat Patients**

	<b>Hylaform N = 133</b>	<b>Zyplast N = 128</b>
<b>Initial treatment - Baseline (Day 0)</b>		
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
<b>Patients requiring touch-up, n (%)</b>	<b>22 (16.5)</b>	<b>9 (7.1)</b>
Difference in proportions of touch-up patients (Zyplast – Hylaform)	-9.5%	
95% confidence interval	-17.2, -1.7	
<b>Touch-up treatment (Week 2)</b>		
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.

Adequacy of Masking:

Patients were asked to assess which treatment they believed they received. The following summary is the patient's assessment of treatment group assignment:

	Hylaform® (n=133)	Zyplast® (n=128)
Patients Assessment		
Hylaform®	36 (27.1%)	25 (19.5%)
Zyplast®	18 (13.5%)	31 (19.5%)
Don't Know	76 (57.1%)	69 (53.9%)

## Summary of Adverse Events:

Classification of AE's was as follows:

- ?? Baseline- adverse events with onset time after signing of informed consent but prior to first implantation of the study device.
- ?? Treatment-emergent- adverse events with onset time on or after the first implantation of study device, or baseline findings that worsen in severity or frequency before the patients last initial phase visit.
- ?? Off-study- adverse events that occurred after patients last initial phase visit and prior to enrollment in the repeat treatment phase

Treatment-emergent adverse events were further classified as follows:

- ?? Procedure related events
- ?? Not procedure related

An overview of the AE's reported during the initial phase is presented:

In the Hylaform® group, 117 (88%) of 133 patients reported 342 treatment-emergent events; 281 were procedure related, 61 were not procedure related. Of these, three were considered device related (These events were injection site induration, injection site necrosis, and injection site pruritis). One serious unrelated adverse event was reported (Hemorrhoids).

In the Zyplast® group 112 (88%) of patients reported 322 treatment-emergent events; 259 were procedure related and 63 were not. Of these, 14 were considered device related (injection site bruising, erythema, necrosis, nodule, and pain). Two patients discontinued the study due to an adverse event (migraines and mobilization). Seven patients experienced 7 severe adverse events.

There were no trends noted. The following tables show the treatment and device related AE's in the treatment-emergent group. As noted in the charts, the majority of treatment related events are mainly the result of the injection of the material into the nasolabial folds. The severe adverse events noted above were baseline events unrelated to treatment.

**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
Local signs/symptoms	111	(84)	274	109	(85)	258
Systemic signs/symptoms	4	(3)	7	1	(1)	1
Other signs/symptoms <sup>c</sup>	0	0	0	0	0	0
Not procedure-related	39	(29)	61	43	(34)	63 <sup>a</sup>
Anesthetic-related	0	(0)	0	1	(1)	1
Local signs/symptoms	0	0	0	1	(1)	1
Systemic signs/symptoms	0	0	0	0	0	0
Other signs/symptoms <sup>c</sup>	0	0	0	0	0	0
Device-related	2	(2)	3	9	(7)	14
Local signs/symptoms	2	(2)	3	8	(6)	13
Systemic signs/symptoms	0	0	0	0	0	0
Other signs/symptoms <sup>c</sup>	0	0	0	1	(1)	1
Unrelated <sup>b</sup>	38	(29)	58	34	(27)	49
Local signs/symptoms	2	(2)	2	4	(3)	4
Systemic signs/symptoms	18	(14)	28	20	(16)	30
Other signs/symptoms	25	(19)	28	14	(11)	15
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

<sup>a</sup>One patient (Patient 02-25) had an adverse event that was considered both anesthetic-related and device-related.

<sup>b</sup>Unrelated to either procedure, anesthetic, or device.

<sup>c</sup>Other signs/symptoms refers to findings in the head and neck area that are not local events at the injection site

**Procedure-related Adverse Events by Maximum Severity Occurring in =2% of Patients**

[Number (%) of Patients]

Primary System Organ Class/Preferred Term <sup>a</sup>	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)
<b>General disorders and administration site conditions</b>	<b>105</b>	<b>(79)</b>	<b>6</b>	<b>(5)</b>	<b>0</b>	<b>(0)</b>	<b>105</b>	<b>(82)</b>	<b>2</b>	<b>(2)</b>	<b>2</b>	<b>(2)</b>
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)

Mod = Moderate.

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

**Device-related Adverse Events by Maximum Severity**

[Number (%) of Patients]

Primary System Organ Class/Preferred Term <sup>a</sup>	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)
<b>Gastrointestinal disorders</b>	<b>0</b>	<b>(0)</b>	<b>0</b>	<b>(0)</b>	<b>0</b>	<b>(0)</b>	<b>1</b>	<b>(1)</b>	<b>0</b>	<b>(0)</b>	<b>0</b>	<b>(0)</b>
Stomatitis	0	(0)	0	(0)	0	(0)	1	(1)	0	(0)	0	(0)
<b>General disorders and administration site conditions</b>	<b>2</b>	<b>(2)</b>	<b>0</b>	<b>(0)</b>	<b>0</b>	<b>(0)</b>	<b>6</b>	<b>(5)</b>	<b>2</b>	<b>(2)</b>	<b>0</b>	<b>(0)</b>
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)

Mod = Moderate; NOS = Not otherwise specified.

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

Note: Patients can have more than one adverse event, therefore, the numbers presented above do not all up to the total.

Analysis of Adverse Events in the Initial Treatment Group: There was a similar incidence of adverse events, and type of adverse events noted for each treatment group. Procedure related events were mild and did not require treatment. The most common treatment-emergent adverse event in both groups was local injection site reaction. Adverse events unrelated to the procedure or device were rare (38 Hylaform® and 34 Zyplast®). Other serious adverse events, unrelated to baseline serious adverse events, were reported. These are:

### 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	Foot fracture	Moderate	Not related	Recovered
04-10	-48	Nephrolithiasis	Moderate	Not related	Recovered

Of the significant adverse events reported two merit mention. Two patients in the Zyplast® group had significant adverse procedure/device related events; both were injection site necrosis which healed with treatment.

Laboratory determinations were taken serially throughout the protocol. There were no trends noted; six patients had clinically significant changes after treatment with Hylaform® (4) and Zyplast® (2). Five were definitely not device related; one patient had elevated AST and ALT with a low lymphocyte count at the 12 week visit. Follow-up continues with no trend noted. Other abnormalities (3) found in patients prior to device implantation were not clinically significant and were treated appropriately.

Serum IgG Antibody testing: Initially it was determined that, based on a large number of normal serum Hylan B antibody titers from a validated study had a serum IgG =50, suggesting prior exposure to avian proteins, a fourfold increase was (arbitrarily) set as the threshold for increased IgG levels in the treated patients. One patient had a greater than fourfold increase as compared to baseline; this patient had 2 AE's (injection site bruising lasting 11 days, and headache of severe intensity that lasted 2 days. I have reviewed the titers for all patients (titers per patient (table 16.2.8.1) and titers by visit (table 14.3.4.1) and found no trends or discrepancies.

Safety Conclusion: The majority of the treatment emergent events were reported as procedure related and minor (skin irritation, inflammation, etc.). Only two serious events were noted in patients who discontinued the study, skin necrosis at the injection site, and both were treated and these areas healed without complication. I have reviewed all the data presented for each patient (each lab test, Serum IgG levels, demographic data, and adverse events) and find no trends or concerns. I have no problems with patient accountability as each patient's course is presented in an easy to follow manner and all documentation is present.

IRB, CRF, and Informed Consent forms are included in the document. As these have been extensively reviewed in the IDE, and used for the study, they will not be reviewed again here.

### **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. All signed an IRB approved consent, had a repeat physical exam and nasolabial fold assessment, had facial photographs taken, and had blood samples taken for hylan B IgG antibody titers and routine clinical lab testing. Patients were randomly assigned to receive Hylaform® Plus in one nasolabial fold and Hylaform® in the opposite fold. Unlike the initial phase, a touch-up option was not offered in this phase; the investigator attempted to achieve optimal correction in a single repeat treatment session. 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 treatment. Patients maintained a diary of their observations of the treatment site for 7 days following treatment. Safety data was collected at 3 days, and at 2, 4, 8, and 12 weeks. Blood samples were collected prior to and at 4 and 12 weeks to detect the presence or absence of hylan B IgG antibody titers.

Hylaform® Plus is the same as Hylaform®; it is processed slightly differently to yield a slightly larger particle sizes (700 microns for Hylaform® Plus vs. 500 microns for Hylaform®). Hylaform® Plus is injected with a 27 gauge needle, Hylaform® with a 30 gauge needle.

At the time of this submission, the sponsor has submitted the initial 4 weeks of safety data for this repeat phase of the study; the second part, the results of the 12 week efficacy study for Hylaform® Plus compared to Hylaform®, will be reported as a supplement to the PMA and not be reviewed here.

In this phase, 96 patients were randomized and treated. Inclusion and exclusion criteria are noted on page 5 and 6 of this review. A review of the safety data for this part of the study reveals that 92 (96%) of the repeat treatment phase patients reported 589 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. There was a statistical difference in incidence rates favoring Hylaform®, possible attributable to the needles size used for delivery of the device. There were no clinically abnormal laboratory findings and no significant increase in hylan B IgG antibody titers up to 4 weeks after treatment.

**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 N = 96			Hylaform Plus Side N = 96			Non-NLF N = 96			Overall <sup>a</sup> N = 96		
	N	(%)	E	N	(%)	E	N	(%)	E	N <sup>b</sup>	(%)	E
<b>At least 1 adverse event</b>	<b>87</b>	<b>(91)</b>	<b>269</b>	<b>92</b>	<b>(96)</b>	<b>286</b>	<b>21</b>	<b>(22)</b>	<b>34</b>	<b>92</b>	<b>(96)</b>	<b>589</b>
<b>General disorders and administration site conditions</b>	<b>87</b>	<b>(91)</b>	<b>265</b>	<b>92</b>	<b>(96)</b>	<b>282</b>	<b>1</b>	<b>(1)</b>	<b>1</b>	<b>92</b>	<b>(96)</b>	<b>548</b>
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
<b>Infections and infestations</b>	<b>1</b>	<b>(1)</b>	<b>1</b>	<b>1</b>	<b>(1)</b>	<b>1</b>	<b>5</b>	<b>(5)</b>	<b>6</b>	<b>5</b>	<b>(5)</b>	<b>8</b>
Herpes simplex	0	(0)	0	0	(0)	0	2	(2)	2	2	(2)	2
<b>Skin and subcutaneous tissue disorders</b>	<b>2</b>	<b>(2)</b>	<b>2</b>	<b>1</b>	<b>(1)</b>	<b>1</b>	<b>3</b>	<b>(3)</b>	<b>9</b>	<b>5</b>	<b>(5)</b>	<b>12</b>
Contusion	0	(0)	0	0	(0)	0	2	(2)	8	2	(2)	8
<b>Gastrointestinal disorders</b>	<b>0</b>	<b>(0)</b>	<b>0</b>	<b>0</b>	<b>(0)</b>	<b>0</b>	<b>6</b>	<b>(6)</b>	<b>7</b>	<b>6</b>	<b>(6)</b>	<b>7</b>
Lip blister	0	(0)	0	0	(0)	0	2	(2)	2	2	(2)	2

Reference: Table R-14.3.1.1

E = Events.

<sup>a</sup>Overall 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.

<sup>b</sup>The number of patients who experienced a given adverse event in both NLF was calculated as the difference between the overall count and the sum of the counts for the Hylaform and Hylform Plus sides.

The injection site nodules noted above were documented on the repeat phase patient diaries; this AE was not on the investigator CRF for the initial phase of the study. Correlation with other AE's (swelling, edema) may account for these during the initial phase, but no data are available to make this comparison.

Twenty-one patients had 35 unrelated events, including lip blisters, herpes simplex, and contusion.

The majority of adverse events reported for either nasolabial fold were mild; moderate events were reported in approx. 3-4% of the cases, and severe events were 1%.

No patient in the repeat phase of the study had a greater than a four fold increase in the serum hylan B IgG antibody titer.

No patients discontinued due to an adverse event during the repeat phase of the study.

No deaths occurred during the study.

No clinically significant laboratory values were reported by the data cutoff date.

No trends in vital sign parameters were noted.

### 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 <sup>a</sup>			Hylaform Plus Side N = 96 <sup>a</sup>			Non-NLF N = 96 <sup>a</sup>			Overall N = 96 <sup>b</sup>		
	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	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 <sup>c</sup>	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.

<sup>a</sup>A total of 96 patients had completed Week 2 follow-up visits and 92 patients had completed Week 4 follow-up visits.

<sup>b</sup>Overall 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.

<sup>c</sup>Unrelated to either procedure, anesthetic, or device.

The device related events noted above are, for Hylaform, a single injection site abscess, and for Hylaform Plus, an injection site abscess and an episode of involuntary muscle contractions.

## **Review of European Data:**

Hylaform® has been commercially available since 1996 in several countries outside the U.S.

The sponsor has also provided a detailed listing of the worldwide AE's since 2001. There have been 319 events in 160 patients. The majority (276 of the 319) are general disorders (i.e., injection site bruising, pain, and erythema) which are similar to the distribution of AE's reported for the US clinical trial presented in this PMA. Over 278,000 units have been sold world wide.

### **Follow-up**

I have asked the sponsor to list the reported adverse events in groups, trying to separate those events which are truly device related from those secondary to the introduction of the device (Hylaform) into the nasolabial folds. To help with that determination, I have arbitrarily selected three days of duration of the event to separate these two possibilities.

### **Initial Phase**

#### **Incidence of Device and Procedure-Related Adverse Events For Events of Duration > 3 Days<sup>a</sup> Intent-to-Treat Patients**

Primary System Organ Class/ Preferred Term	Hylaform (N = 133)		Zyplast (N = 128)	
	Patients (%)	Events	Patients (%)	Events
AT LEAST 1 ADVERSE EVENT	61 (45.9)	100	72 (56.3)	117
95% Confidence Interval <sup>b</sup>	37.2, 54.7		47.2, 65.0	
Difference in Proportions (Zyplast-Hylaform) - %			10.4	
95% Confidence Interval <sup>c</sup>			-1.7, 22.5	
Gastrointestinal disorders	0 (0.0)	0	1 (0.8)	1
Stomatitis	0 (0.0)	0	1 (0.8)	1
General disorders and administration site conditions	61 (45.9)	100	71 (55.5)	116
Application site dryness	0 (0.0)	0	2 (1.6)	2
Application site papules	0 (0.0)	0	3 (2.3)	3
Application site scabbing	1 (0.8)	1	2 (1.6)	2
Injection site bruising	35 (26.3)	35	29 (22.7)	31
Injection site desquamation	2 (1.5)	2	4 (3.1)	4
Injection site erythema	31 (23.3)	35	27 (21.1)	32
Injection site induration	2 (1.5)	2	1 (0.8)	1
Injection site necrosis	0 (0.0)	0	2 (1.6)	3
Injection site nodule	0 (0.0)	0	3 (2.3)	6

Reference: Ad Hoc Listings 1 and 2.

<sup>a</sup>Including events with unknown duration.

<sup>b</sup>Exact confidence interval (CI) based on the binomial distribution.

<sup>c</sup>95% CI is based on the normal approximation of the binomial distribution.

Primary System Organ Class/ Preferred Term	Hylaform (N = 133)		Zyplast (N = 128)	
	Patients (%)	Events	Patients (%)	Events
General disorders and administration site conditions				
Injection site pain	3 (2.3)	3	7 (5.5)	9
Injection site pigmentation changes	0 (0.0)	0	1 (0.8)	1
Injection site pruritus	3 (2.3)	3	4 (3.1)	4
Injection site reaction NOS	1 (0.8)	1	1 (0.8)	1
Injection site swelling	16 (12.0)	16	15 (11.7)	16
Injection site tenderness	2 (1.5)	2	1 (0.8)	1

Reference: Ad Hoc Listings 1 and 2.

<sup>a</sup>Including events with unknown duration.

<sup>b</sup>Exact confidence interval (CI) based on the binomial distribution.

<sup>c</sup>95% CI is based on the normal approximation of the binomial distribution.

## Repeat Phase:

### Incidence of Device and Procedure-Related Adverse Events For Events of Duration > 3 Days Intent-to-Treat Patients

Primary System Organ Class/ Preferred Term	Hylaform Side (N = 96)		Hylaform Plus Side (N = 96)		Overall <sup>a</sup> (N = 96)	
	Patients (%)	Events	Patients (%)	Events	Patients (%)	Events
AT LEAST 1 ADVERSE EVENT	44 (45.8)	69	49 (51.0)	79	59 (61.5)	148
95% Confidence Interval	35.6, 56.3		40.6, 61.4		51.0, 71.2	
Difference in Proportions (%)			-5.2			
95% Confidence Interval <sup>b</sup>			-15.4, 4.9			
General disorders and administration site conditions	43 (44.8)	68	47 (49.0)	77	57 (59.4)	145

Reference: Ad Hoc Listings R-1 and R-2.

Note: Any adverse event occurring at a treatment site will be coded to a Preferred Term that is treatment site-specific. Conversely, the Preferred Term used for an event that does not occur at the treatment site will not include the words injection site or application site. Therefore, any row for a specific Preferred Term will include only treatment site-specific adverse events or only adverse events that are not treatment site-specific.

<sup>a</sup> Overall 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.

<sup>b</sup> Confidence interval constructed for the difference in dependent proportions.

Primary System Organ Class/ Preferred Term	Hylaform Side (N = 96)		Hylaform Plus Side (N = 96)		Overall <sup>a</sup> (N = 96)	
	Patients	Events	Patients	Events	Patients	Events
	(%)		(%)		(%)	
General disorders and administration site conditions						
Application site papules	2 (2.1)	2	1 (1.0)	1	3 (3.1)	3
Application site scabbing	0 (0.0)	0	1 (1.0)	1	1 (1.0)	1
Injection site bruising	17 (17.7)	17	22 (22.9)	22	28 (29.2)	39
Injection site dermatitis	1 (1.0)	1	1 (1.0)	1	1 (1.0)	2
Injection site desquamation	1 (1.0)	1	1 (1.0)	1	1 (1.0)	2

Reference: Ad Hoc Listings R-1 and R-2.

The following are added to show some of the specific events noted in the clinical summary.

**Incidence of Device and Procedure-Related Adverse Events  
For Events of Duration > 3 Days  
Intent-to-Treat Patients**

Primary System Organ Class/ Preferred Term	Hylaform Side (N = 96)		Hylaform Plus Side (N = 96)		Overall <sup>a</sup> (N = 96)	
	Patients	Events	Patients	Events	Patients	Events
	(%)		(%)		(%)	
General disorders and administration site conditions						
Injection site discoloration	2 (2.1)	2	1 (1.0)	1	2 (2.1)	3
Injection site erythema	18 (18.8)	18	17 (17.7)	18	25 (26.0)	36
<b>Injection site nodule</b>	12 (12.5)	12	13 (13.5)	13	19 (19.8)	25
Injection site pain	5 (5.2)	5	6 (6.3)	6	7 (7.3)	11
Injection site pruritis	1 (1.0)	1	2 (2.1)	2	2 (2.1)	3

Reference: Ad Hoc Listings R-1 and R-2.

Note: Any adverse event occurring at a treatment site will be coded to a Preferred Term that is treatment site-specific. Conversely, the Preferred Term used for an event that does not occur at the treatment site will not include the words injection site or application site. Therefore, any row for a specific Preferred Term will include only treatment site-specific adverse events or only adverse events that are not treatment site-specific.

<sup>a</sup> Overall 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.

<sup>b</sup> Confidence interval constructed for the difference in dependent proportions.

**Incidence of Device and Procedure-Related Adverse Events  
For Events of Duration > 3 Days  
Intent-to-Treat Patients**

Primary System Organ Class/ Preferred Term	Hylaform Side		Hylaform Plus		Overall <sup>a</sup>	
	(N = 96)		(N = 96)		(N = 96)	
	Patients (%)	Events	Patients (%)	Events	Patients (%)	Events
General disorders and administration site conditions						
Injection site swelling	7 (7.3)	7	10 (10.4)	10	12 (12.5)	17
Injection site tenderness	1 (1.0)	1	1 (1.0)	1	2 (2.1)	2
Injection site vesicles	1 (1.0)	1	0 (0.0)	0	1 (1.0)	1
Infections and infestations	1 (1.0)	1	1 (1.0)	1	1 (1.0)	2

Reference: Ad Hoc Listings R-1 and R-2.

**Incidence of Device and Procedure-Related Adverse Events  
For Events of Duration > 3 Days  
Intent-to-Treat Patients**

Primary System Organ Class/ Preferred Term	Hylaform Side		Hylaform Plus		Overall <sup>a</sup>	
	(N = 96)		(N = 96)		(N = 96)	
	Patients (%)	Events	Patients (%)	Events	Patients (%)	Events
Infections and infestations						
<b>Injection site abscess</b>	1 (1.0)	1	1 (1.0)	1	1 (1.0)	2
Nervous system disorders	0 (0.0)	0	1 (1.0)	1	1 (1.0)	1
<b>Muscle contractions involuntary</b>	0 (0.0)	0	1 (1.0)	1	1 (1.0)	1

Reference: Ad Hoc Listings R-1 and R-2.

Note: Any adverse event occurring at a treatment site will be coded to a Preferred Term that is treatment site-specific. Conversely, the Preferred Term used for an event that does not occur at the treatment site will not include the words injection site or application site. Therefore, any row for a specific Preferred Term will include only treatment site-specific adverse events or only adverse events that are not treatment site-specific.

<sup>a</sup> Overall 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.

<sup>b</sup> Confidence interval constructed for the difference in dependent proportions.

From the data presented above, it is clear that the adverse events presented are generally reflected in what the sponsor calls “treatment related” and are presented equally between the device and control groups. No concerns exist as to the number of events presented, or the severity of these reported events.

Conclusions: The sponsor presented a well designed and comprehensive protocol. They conducted the study within the set guidelines, and presented the data in a clear and concise manner.