

## Summary of Safety and Effectiveness Data

### I. GENERAL INFORMATION

Device Generic Name: Injectable Collagen Filler for Aesthetic Use  
Device Trade Name: EVOLENCE® Porcine Collagen Dermal Filler  
Applicant: ColBar LifeScience Ltd.  
9 Hamenofim Street  
Herzlyia, 46733  
Israel  
  
c/o Hogan & Hartson, LLP  
Mr. Jonathan S. Kahan  
555 Thirteenth Street, NW  
Washington, District of Columbia 20004

PMA Number: P070013  
Date of Panel Recommendation: None. An Advisory Panel meeting was not required for this submission.  
  
Date of Notice of Approval: June 27, 2008  
Expedited: Not Applicable

### II. INDICATIONS FOR USE

**EVOLENCE®** Collagen Filler is an injectable product indicated for the correction of moderate to deep facial wrinkles and folds such as nasolabial folds.

### III. CONTRAINDICATIONS:

**EVOLENCE®** Collagen Filler is contraindicated in the following:

- Patients with known hypersensitivity to any collagen products or planning to undergo desensitization injections to porcine products, as these injections can contain porcine collagen.
- Patients with a history of anaphylactic reactions or history or presence of severe recurrent allergic reactions.
- **EVOLENCE®** Collagen Filler should not be implanted in spaces other than the dermis of the face.
- **EVOLENCE®** Collagen Filler should not be implanted in patients with bleeding disorders.

### IV. WARNINGS AND PRECAUTIONS:

The warnings and precautions can be found in EVOLENCE® Collagen Filler physician's labeling.

## WARNINGS

- Local necrosis is a rare event which has been observed following other collagen implantation and may occur following injections to the glabella. It is thought to result from the injury, obstruction, or compromise of blood vessels.
- Patients with a history of dietary porcine allergy should be carefully examined before porcine collagen injections, since it is possible that the collagen component of the porcine material may be causing the allergy.
- Avoid injecting EVOLENCE® into blood vessels as collagen can initiate platelet aggregation and may cause vascular occlusion and localized infarction or embolic phenomena.
- Use of EVOLENCE® at specific sites in which infections or active inflammatory reaction is present, should be deferred until the underlined process has been controlled.
- Injection site reactions (*e.g.*, swelling, redness, tenderness, or pain) to EVOLENCE® have been observed as consisting mainly of short-term minor or moderate inflammatory symptoms starting early after treatment and with less than 7 days duration. Refer to the adverse reactions section for details.
- Delayed onset inflammatory papules have been reported following the use of dermal fillers. Inflammatory papules (solid, raised skin lesions less than 1 cm in diameter) that may occur rarely should be considered and treated as a soft tissue infection.

## PRECAUTIONS

The following precautions must be observed:

- **STERILE CONTENT.** The prefilled syringe is intended for single patient use. Do not resterilize. Do not use if the package is opened or damaged.
- As with all transcutaneous procedures, injection of EVOLENCE® carries a risk of infection. The usual precautions associated with injectable material should be followed.
- Bruising or bleeding may occur at EVOLENCE® injection sites. Patients using substances which may reduce coagulation, such as aspirin and non-steroidal anti-inflammatory drugs, , may experience increased bruising or bleeding at injection sites as experienced with any injection.
- The safety and effectiveness of EVOLENCE® for the treatment of anatomic regions other than facial wrinkles and nasolabial folds have not been established in controlled clinical studies.
- The safety and efficacy of EVOLENCE® for lip augmentation has not been established.
- The safety of usage in breast augmentation or injection into bone, tendon, ligament or muscle has not been established in controlled clinical studies.
- EVOLENCE® should be used with caution in patients on immunosuppressive therapy.
- The safety of EVOLENCE® in pregnant or breastfeeding females, as well as in patients under 18 years of age has not been established.
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- The safety of EVOLENCE® with concomitant dermal therapies such as epilation, UV radiation, or laser, mechanical or chemical peeling procedures has not been evaluated in controlled clinical trials, therefore there are no data available on the potential for site inflammatory reaction.

- Injection of EVOLENCE® into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- Patients should minimize exposure of the treated areas to excessive sun, UV lamp exposure and extreme hot or cold weather for the first 24-48 hours following treatment.
- Based on preclinical studies the use of EVOLENCE® in individual patients should be limited to 10 ml over a one year period. The safety of injecting greater amounts has not been established. In clinical trials using a split face design, patients were injected with up to approximately 4 mL of EVOLENCE® in a single injection site over a one year time period.
- The safety of EVOLENCE® in patients susceptible to keloid formation, hyperpigmentation and hypertrophic scarring has not been established.
- Long term safety and effectiveness of EVOLENCE® beyond one year have not been investigated in clinical trials.
- After use, treatment syringes and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local, state, and federal requirements.
- EVOLENCE® should not be mixed with other products before implantation of the device.
- EVOLENCE® is a yellowish, homogenous, opaque gel. In the event that a syringe contains material exhibiting phase separation between solid and liquid, or change of color, do not use the syringe and notify OrthoNeutrogena division of Ortho-McNeil-Janssen-Pharmaceuticals, Inc. at 1-800-EVOLENC (386-5362).

## V. DEVICE DESCRIPTION

EVOLENCE® Collagen Filler is a sterile, non-pyrogenic device stable at physiological pH that is a yellowish, homogeneous, opaque gel, prepackaged in a syringe. It is composed of 35 mg/ml ( $\pm$  5 mg/ml) biodegradable Type 1 fibrillar porcine collagen crosslinked using d-ribose suspended in phosphate-buffered saline (PBS). Various antigenic portions of the collagen molecule have been removed. EVOLENCE® Collagen Filler is available in two sizes – 0.5 ml and 1.0 ml – pre-filled into a 1.0 ml glass syringe with a Luer-lock adaptor that is packaged in a unique sealed blister and placed into a rigid plastic container.

The filled syringe in the plastic container is packaged in a transparent polypropylene box and includes the IFU insert. The blister is sealed with a Tyvek® lid. The final product presentation is packaged with 2, 27G, 0.5 inch needles.

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternate methods of soft tissue augmentation for aesthetic purposes include injectable dermal fillers, such as bovine collagen, human collagen, or cross-linked hyaluronic acid (HA). Other methods for treatment of facial rhytids include injection of botulinum toxin, topical creams, chemical peels, laser skin resurfacing, dermabrasion and surgical intervention.

## VII. MARKETING HISTORY

EVOLENCE® Collagen Filler initially obtained CE mark in 2004 and is currently marketed in most European countries, Canada, Israel, Singapore and South -Korea. EVOLENCE® has not been withdrawn from marketing for any reason. Approximately 35,000 units have been distributed to date.

## VIII. POTENTIAL ADVERSE EFFECTS ON HEALTH:

### Clinical Evaluation of EVOLENCE® Collagen Filler

Under a US Investigation Device Exemption (IDE), a randomized, comparative trial to evaluate the safety and efficacy of EVOLENCE® Collagen Filler was conducted at 6 clinical centers, 149 subjects were injected with EVOLENCE® into one nasolabial fold (NLF) and Hyaluronic Acid-based dermal filler (Restylane®) into the contralateral NLF.

Each subject recorded treatment symptoms up to 14 days following initial injection and up to any event resolution following the touch up facial injection in the subject's diary. Subjects were instructed to rate each common treatment response listed in the diary as Mild, Moderate, Severe or None. Injection site responses (symptom related AE) reported by >5% of subjects in either treatment group are summarized in tables 1 and 2.

Table 1: Number & (%) of Subjects with AEs at the Injection Site\* by Maximum Severity – for Adverse Events Occurring in >5% of Subjects, as Reported in Subjects' Diaries and Physician Case Report Forms

|                            | EVOLENCE®<br>(Total N = 149) |            |          | Restylane®<br>(Total N = 149) |                   |            |           |         |
|----------------------------|------------------------------|------------|----------|-------------------------------|-------------------|------------|-----------|---------|
|                            | Overall Incidence            | Mild       | Mod      | Severe                        | Overall Incidence | Mild       | Mod       | Severe  |
| Injection Site Conditions† | 123 (82.6)                   | 111 (74.5) | 11 (7.4) | 1 (0.7)                       | 130 (87.2)        | 113 (75.8) | 16 (10.7) | 1 (0.7) |
| Pain                       | 84 (56.4)                    | 77 (51.7)  | 6 (4.0)  | 1 (0.7)                       | 95 (63.8)         | 85 (57.0)  | 10 (6.7)  | 0       |
| Erythema                   | 86 (57.8)                    | 83 (55.7)  | 2 (1.3)  | 1 (0.7)                       | 89 (59.7)         | 84 (56.4)  | 5 (3.4)   | 0       |
| Swelling                   | 80 (53.7)                    | 74 (49.7)  | 5 (3.4)  | 1 (0.7)                       | 102 (68.5)        | 94 (63.1)  | 8 (5.4)   | 0       |
| Bruising                   | 54 (36.2)                    | 52 (34.9)  | 2 (1.3)  | 0                             | 71 (47.7)         | 63 (42.3)  | 7 (4.7)   | 1 (0.7) |
| Pruritus                   | 23 (15.4)                    | 23 (15.4)  | 0        | 0                             | 25 (16.8)         | 25 (16.8)  | 0         | 0       |
| Induration                 | 20 (13.4)                    | 17 (11.4)  | 3 (2.0)  | 0                             | 9 (6.0)           | 8 (5.4)    | 1 (0.7)   | 0       |

Mod = Moderate

\* Adverse events occurring after the first facial injection.

As detailed in Table 1, 123 of the 149 subjects who were treated with EVOLENCE and 130 of the 149 subjects who were treated with the HA Control product reported injection site reactions. Of those reported, in the EVOLENCE group 326 reactions were reported as mild, 18 as moderate and 3 severe. In the HA Control group, 359 reactions were reported as mild, 31 as moderate and 1 severe.

The following disorders at the injection site were reported as either EVOLENCE® -related or Restylane®-related in at least 5% of the subjects: pain, erythema, swelling, bruising, pruritus, and induration. Adverse events in this category that occurred more commonly (≥5% difference) for Restylane® vs. EVOLENCE®-treated subjects respectively, were injection

site pain (63.8% vs. 56.4%), swelling (68.5% vs. 53.7%) and bruising (47.7% vs. 36.2%). The only AE to occur more commonly in the EVOLENCE® treated group ( $\geq 5\%$  difference) was induration (13.4% vs. 6%).

No other device-related AEs were reported in more than 2 subjects (1.3%) per device. Serious AEs were reported in 2 subjects (Atrial septal defect and Metastatic colon cancer to ovaries).

**Table 2: Number (%) of Subjects with Skin Reactions (Occurring in >5% of Subjects) to Study Product by Injection and Maximum Duration, as Reported in Subjects' Diaries and Physician Case Report Forms**

|                  | After First Facial Injection*  |              |              |              |                      |              |              |             |
|------------------|--------------------------------|--------------|--------------|--------------|----------------------|--------------|--------------|-------------|
|                  | EVOLENCE® (N = 149)            |              |              |              | Restylane® (N = 149) |              |              |             |
| Duration (Days)  | ≤ 3                            | 4-7          | 8-14         | >14          | ≤ 3                  | 4-7          | 8-14         | >14         |
| No. of Subjects† | 96<br>(64.4)                   | 66<br>(44.3) | 17<br>(11.4) | 17<br>(11.4) | 99(66.4<br>)         | 70<br>(47.0) | 28<br>(18.8) | 13<br>(8.7) |
| No. of Episodes  | 200                            | 94           | 25           | 21           | 209                  | 124          | 34           | 21          |
| Erythema‡        | 52<br>(34.9)                   | 21<br>(14.1) | 4<br>(2.7)   | 3<br>(2.0)   | 48<br>(32.2)         | 27<br>(18.1) | 4<br>(2.7)   | 4<br>(2.7)  |
| Swelling‡        | 43<br>(28.9)                   | 21<br>(14.1) | 8<br>(5.4)   | 2<br>(1.3)   | 54<br>(36.2)         | 31<br>(20.8) | 5<br>(3.4)   | 7<br>(4.7)  |
| Induration‡      | 6 (4.0)                        | 2 (1.3)      | 1 (0.7)      | 7 (4.7)      | 2 (1.3)              | 3 (2.0)      | 1 (0.7)      | 2 (1.3)     |
| Bruising‡        | 19<br>(12.8)                   | 22<br>(14.8) | 7<br>(4.7)   | 1<br>(0.7)   | 16<br>(10.7)         | 31<br>(20.8) | 16<br>(10.7) | 4<br>(2.7)  |
| Pain‡            | 48<br>(32.2)                   | 24<br>(16.1) | 5<br>(3.4)   | 5<br>(3.4)   | 57<br>(38.3)         | 27<br>(18.1) | 7<br>(4.7)   | 3<br>(2.0)  |
| Pruritus‡        | 17<br>(11.4)                   | 2<br>(1.3)   | 0            | 1<br>(0.7)   | 17<br>(11.4)         | 3<br>(2.0)   | 1<br>(0.7)   | 0           |
|                  | After Second Facial Injection§ |              |              |              |                      |              |              |             |
|                  | EVOLENCE® (N = 74)             |              |              |              | Restylane® (N = 74)  |              |              |             |
| Duration (Days)  | ≤ 3                            | 4-7          | 8-14         | >14          | ≤ 3                  | 4-7          | 8-14         | >14         |
| No. of Subjects† | 32<br>(43.2)                   | 12<br>(16.2) | 4<br>(5.4)   | 6<br>(8.1)   | 35<br>(47.3)         | 20<br>(27.0) | 3<br>(4.1)   | 4<br>(5.4)  |
| No. of Episodes  | 57                             | 21           | 6            | 9            | 65                   | 29           | 4            | 5           |
| Erythema‡        | 14<br>(18.9)                   | 4<br>(5.4)   | 3<br>(4.1)   | 4<br>(5.4)   | 12<br>(16.2)         | 9<br>(12.2)  | 1<br>(1.4)   | 3<br>(4.1)  |
| Swelling‡        | 13<br>(17.6)                   | 8<br>(10.8)  | 0            | 1<br>(1.4)   | 17<br>(23.0)         | 6<br>(8.1)   | 2<br>(2.7)   | 1<br>(1.4)  |
| Bruising‡        | 5 (6.8)                        | 3 (4.1)      | 0            | 1 (1.4)      | 5 (6.8)              | 7 (9.5)      | 0            | 1 (1.4)     |
| Pain‡            | 14<br>(18.9)                   | 5<br>(6.8)   | 2<br>(2.7)   | 2<br>(2.7)   | 22<br>(29.7)         | 5<br>(6.8)   | 1<br>(1.4)   | 0           |
| Pruritus‡        | 4 (5.4)                        | 0            | 1 (1.4)      | 0            | 4 (5.4)              | 2 (2.7)      | 0            | 0           |
| Induration‡      | 3 (4.1)                        | 0            | 0            | 1 (1.4)      | 1 (1.4)              | 0            | 0            | 0           |

\* Reactions started between the day of first injection and 13 days after the day of first injection, or before touch-up injection.

† Number of subjects with at least 1 episode of specified duration.

‡ Duration = Maximum number of consecutive days with symptom from onset until resolution.

§ Reactions occurring from the day of injection through Day 13 after the second injection.

Note: The incidence of induration after the second injection was <5% for both devices.

The majority of the skin reactions at either the EVOLENCE® or the Restylane® injection sites were of <4 days duration and almost all of them were less than one week in duration.

Non Local Adverse events considered to be non-device related, occurred in 41/149 (27.5%) of the study subjects. Since each subject received both EVOLENCE and HA based control

treatment, the causality of these events could not be identified. These events included Infections and Infestation ( 10.1%) (upper respiratory infection, nasopharyngitis, sinusitis); Skin and Subcutaneous tissue disorder (5.4%) (actinic keratosis); Hypercholesterolemia (2%); Psychiatric disorder (2%)(anxiety).

#### **Use of EVOLENCE® in Skin of Color Patients**

Of the 149 subjects randomized in the US pivotal study, twenty two (22) had skin tones of light brown (Fitzpatrick skin tone IV), six (6) had skin tones of brown (Fitzpatrick skin tone V), and none of the subjects had skin tone of black (Fitzpatrick VI).

In a separate skin challenge study, two (2) subjects had skin tone of brown (Fitzpatrick skin tone V). Twenty nine (29) subjects in France, Canada and Germany (i.e., twenty eight (28) with FP skin tone V and one with FP skin tone VI had EVOLENCE® injected in a post marketing setting.

None of these subjects experienced hyperpigmentation or keloid formation.

#### **Skin Challenge Study - Hypersensitivity**

In an open-label, non-controlled, single-center study, 530 subjects were injected with two sequential intradermal EVOLENCE® skin test injections (two week intervals), to evaluate the risk of developing localized hypersensitivity. Subjects were observed for 6 weeks following the first skin test (4 weeks from the second injection).

Of the 519 subjects that completed the study period, there were no clinical observations of hypersensitivity, as measured by clinical and patient observation of local responses and laboratory measurement of immunological (antibody) responses. (Positive hypersensitivity reaction was defined as erythema persisting more than 72 hours plus positive histopathology biopsy assessment of the site biopsy).

In addition no serious adverse events or unexpected adverse events occurred during the study period. Overall, 62 subjects reported 95 adverse events over the course of the study. Seventeen of the 95 adverse events were considered related to the treatment.

No adverse events resulted in discontinuation from study participation. All reported adverse events with two or more occurrences in this study are listed in table 3.

**Table 3: All Adverse Events Reported on or after One Skin Test Injection in >1 Subject (n=530)**

| Description of AE         | Number | Frequency (%) |
|---------------------------|--------|---------------|
| Headache                  | 8      | 1.5           |
| Injection Site Erythema   | 5      | 0.9           |
| Injection Site Discomfort | 6      | 1.1           |
| Injection Site Pruritus   | 6      | 1.1           |
| Nasopharyngitis           | 5      | 0.9           |
| Pharyngeal Pain           | 3      | 0.6           |
| Nasal congestion          | 3      | 0.6           |
| Dizziness                 | 3      | 0.6           |
| Influenza                 | 3      | 0.6           |

|                     |   |     |
|---------------------|---|-----|
| Myalgia             | 2 | 0.4 |
| Sinusitis           | 2 | 0.4 |
| Cystitis            | 2 | 0.4 |
| Cough               | 2 | 0.4 |
| Pruritus            | 2 | 0.4 |
| Joint injury/sprain | 2 | 0.4 |
| Vomiting            | 2 | 0.4 |
| Contact dermatitis  | 2 | 0.4 |
| Contusion           | 2 | 0.4 |

Related adverse events occurring in a single patient included swelling, injection site discoloration and injection site irritation. Other events occurring in a single patient, included injection site anaesthesia, fatigue, tenderness, aches, pains, sprains, injuries, anxiety, heart rate increase, herpes zoster, hyperhidrosis, ear infection, bronchitis, tooth infection, nausea, migraine, rash, increased tear production, ocular redness, and outpatient non-related surgical procedures.

One subject experienced erythema, tenderness and induration at the second skin test site (right forearm) more than two months post the End of the Study (more than three months after dosing of the second skin test). Histopathology from site biopsied indicated that a positive hypersensitivity reaction was occurring. No sequelae were noted at the first skin test site (left forearm). Sera from this subject displayed positive titers for porcine collagen at study baseline prior to EVOLENCE®-Test injection and titers of sera from this subject remained positive through the end of the study.

**Other adverse event information** - In postmarket studies for EVOLENCE® use outside the US, the type, severity, and duration of adverse events has not varied from the adverse events reported in Table 3, above.

## IX. SUMMARY OF PRECLINICAL STUDIES

EVOLENCE® Collagen Filler has been extensively tested and characterized, through physical, chemical and bio-chemicals analyses. These studies, which are conducted on the collagen starting material as well as on the final product, demonstrate the purity, integrity and the physical appearance of the product to ensure its efficacy and safety during its clinical lifespan.

### **Biocompatibility and Animal Studies:**

The table below summarizes the animal implantation studies as well as the biocompatibility tests that were performed by ColBar with compliance to ISO 10993-1:2003 requirements.

| <b>Table 4: EVOLENCE® Biocompatibility and Animal Implantation Studies:</b>   |   |
|---|---|
| <b>Study Title</b>  | <b>Result/Conclusions</b>   |
| Cytotoxicity - Agarose Overlay Method   | The test article showed no evidence of causing cell lysis or toxicity.  |
| Genotoxicity: In vitro chromosomal aberration study in mammalian cells (extract)  | The test article extract was not genotoxic to Chinese Hamster Ovary cells in the presence or absence of S9 metabolic activation.  |
| Genotoxicity: Bacterial reverse mutation study (saline extract)   | The saline article extract was non-mutagenic to <i>Salmonella typhimurium</i> tester strains TA98, TA100, TA1535 and TA1537 and to <i>Escherichia coli</i> strain WP2uvrA.  |
| Genotoxicity: Mouse bone marrow micronucleus study  | The test article solution was not genotoxic to the mouse.   |
| ISO maximization sensitization study (solution)   | The test solution showed no evidence of causing delayed dermal contact sensitization in the guinea pig.   |
| Intracutaneous Reactivity (Rabbits, 72 hours)   | There was no evidence of significant irritation from the test article. The Primary Irritation Index Characterization for the test article was negligible.   |
| ISO Subcutaneous Implantation Study (Rabbits, 4 weeks)  | The macroscopic reaction was not significant as compared to the negative control implant material. Microscopically the test article was classified as a non-irritant as compared to the negative control article.             |
| ISO Muscle implantation study (Rabbits, 4 weeks)  | The macroscopic reaction was not significant as compared to the negative control implant material. Microscopically, the test article was classified as a non-irritant as compared to negative control article.                |
| ISO Muscle implantation study (Rabbits, 12 weeks)   | The macroscopic reaction was not significant as compared to the negative control implant material. Microscopically, the test article was classified as a non-irritant as compared to negative control article.                |
| USP and ISO Modified systemic toxicity study (Mice, 1 week)   | There was no mortality or evidence of systemic toxicity from the test article injected into mice.   |
| Sub Chronic systemic Toxicity following intracutaneous injections with histology (Rats, 13 weeks and 26 week)           | There was no mortality or evidence of systemic toxicity from the test article injected into mice. The microscopic evaluation of the selected tissues revealed no evidence of a treatment related response.                    |
| Intracutaneous implantation in the rabbit ear (up to 24 months) in comparison to bovine collagen derived dermal fillers | The histopathological and physical examinations indicated that the test article was well tolerated and preserved its shape over a period of 24 months. The comparator has almost completely degraded by 24 months.            |
| Intracutaneous Implantation in the Rat (up to 18 months) in comparison to a hyaluronic acid based dermal filler         | The test article was well tolerated and showed only little change in its original dimensions after 18 months, whereas the surface and height of the hyaluronic acid based product were significantly reduced after 18 months. |

#### **EVOLENCE® Collagen Filler Viral Inactivation/Removal Study**

Laboratory viral recovery studies were conducted to verify the capacity and efficacy of the EVOLENCE™ manufacturing process to remove or inactivate model viruses corresponding to four classes of viruses (DNA- and RNA- enveloped or non-enveloped). The study demonstrated the very high efficiency of inactivation of viruses during the manufacturing

process, sustaining the overall capacity of the process to generate a very safe product by exceeding the minimum threshold for reduction and/or inactivation of each of the model viruses.

## X. SUMMARY OF CLINICAL STUDIES

### **Pivotal Study**

#### **Study Design:**

A randomized, comparative, multi-center, within subject (split-face) clinical trial was conducted to compare the safety and efficacy of EVOLENCE® Collagen Filler versus HA based filler (Control) for the correction of soft tissue contour deficiencies.

Subjects were screened and tested for hypersensitivity to porcine collagen by injecting 0.1 mL of EVOLENCE®-Test. Subjects with a positive reaction within approximately 4 weeks of the injection were to be discontinued from the study. Blood samples were collected prior the treatment and during follow up visits for determination of collagen antibody titers.

Eligible subjects meeting all inclusion/exclusion criteria were randomized and received injections of investigational device and comparator into their nasolabial folds.

Each subject was injected with EVOLENCE® into one nasolabial fold (NLF) and Hyaluronic Acid-based dermal filler (Control) into the contralateral NLF.

Treatment was considered to be complete when Optimal Cosmetic Result (OCR) was achieved, as determined by the judgment of the Principal Investigator. Subjects could receive one touch-up injection with either EVOLENCE® or the Control 2 weeks later in order to achieve OCR.

The OCRs evaluation was performed on both sides at the same time. Routine follow up visits for safety and effectiveness occurred at 3 months interval post OCR visit thought 12 months after the last treatment.

Adequacy of masking of the subject and the Blinded Evaluating Investigator (BEI) was checked following each facial injection, and at 6 and 12 months post OCR visit. Standardized facial photography was taken prior to treatment and during the study follow up. The BEI evaluated the severity of the subjects NLF's using a validated 7-point photographic grading scale Modified Fitzpatrick Wrinkle validated Scale (MFWS) ranging from 0=no wrinkle to 3=deep wrinkle. BEI and subject self satisfaction with the overall treatment response using the Global Improvement Assessment scale (GIA), ranging from 1=much better to 4=worse, after each injection session and at each follow-up visit was conducted. Subjects maintain a preprinted diary of their treatment responses and severity form 14 days after each treatment. Treatment site responses and other adverse events were monitored throughout the study.

#### **Study Endpoints:**

The primary efficacy endpoint for the study of EVOLENCE® for the correction of the nasolabial folds was compared to the control, as determined by BEI's live evaluation of the NLF severity score (utilizing MFWS) at the 6-month post-OCR visit. The statistical objective was to demonstrate non-inferiority of EVOLENCE® to the control.

Safety was evaluated by comparing the incidence and severity of local and systemic adverse events reported by the treating investigator from the pretreatment skin testing through the 6-month post-OCR visit.

Additional analysis (secondary) included BEI and subject satisfaction (utilizing GIA) with the overall treatment response; measurements of anti-porcine collagen antibodies and comparison of total volume of EVOLENCE® injected to the NLF to achieve OCR vs. the study control.

**Effectiveness Assessment:**

The BEI examined the subject’s face and rated the depth of the nasolabial fold using the Modified Fitzpatrick Wrinkle Scale (MFWS), as defined below:

**Table 5: Modified Fitzpatrick Wrinkle Scale**

| <b>Modified Fitzpatrick Wrinkle Scale</b> |  |
|---|--|
| <b>Score</b>                              | <b>Description</b>   |
| 0   | <b>No Wrinkle.</b> No visible wrinkle; continuous skin line.                 |
| 0.5                                       | Very shallow yet visible wrinkle.  |
| 1   | <b>Fine Wrinkle.</b> Visible wrinkle and slight indentation.                 |
| 1.5                                       | Visible wrinkle and clear indentation, less than 1 mm wrinkle depth.         |
| 2   | <b>Moderate Wrinkle.</b> Clearly visible wrinkle, 1 mm to 2 mm wrinkle depth |
| 2.5                                       | Prominent and visible wrinkle; more than 2 mm and up to 3 mm wrinkle depth   |
| 3   | <b>Deep Wrinkle.</b> Deep and furrow wrinkle; more than 3 mm wrinkle depth   |

**Subject selection and main criteria for inclusion/exclusion:**

Male and female subjects  $\geq 18$  years of age of various ethnicities who had demonstrated clinical evidence of bilateral aging defects in the nasolabial area with wrinkles classified as Class 2 or greater using the validated MFWS and who presented a nasolabial wrinkle for at least 50% of the anatomical nasolabial area length.

Subjects who gave written informed consent prior to performance of any study related procedure and complied with all the inclusion and exclusion criteria. Subjects who agreed to comply with the requirements of the protocol and to receive investigational injections in areas of aging defects (wrinkles) as well as to undergo skin biopsy post-skin challenge if required.

Subjects were excluded if they had positive skin reaction to the pretreatment skin test, pregnant and/or nursing women, history of allergy and/or sensitivity to porcine collagen, gram positive bacterial proteins, hyaluronic acid (HA), local anesthetic products, natural rubber latex; history of autoimmune disease, bleeding disorders, collagen vascular disease or connective tissue disease, sensitivity to local anesthetics or a history of multiple severe allergies or history of anaphylactic shock, active skin disease (such as infection, psoriasis and herpes zoster near the injected area), clinically significant organic disease inflammation or related condition, or a previous usage of any alternative tissue augmentation /correction practices and procedures within specified wash out period as defined in the study protocol.

**Patient Enrollment**

The study was conducted in 6 study centers in the United States.

One hundred sixty-four (164) subjects were screened and tested for hypersensitivity to porcine collagen.

One hundred forty-nine (149) eligible subjects meeting all inclusion/exclusion criteria were randomized and received injections of investigational device and comparator into their nasolabial folds and followed up for 6 months post OCR. Accounting of the study subjects is presented in Table 6 below.

**Table 6: Subject Disposition – All Enrolled Subjects (Number (%) of Subjects)**

|  |                 |
|--|-----------------|
| <b>Total no. of subjects - n(%*)</b>           | <b>N = 164</b>  |
| Screened                                       | 200             |
| Received skin test injection                   | 164             |
| Received Initial injection into NLF            | 149             |
| Received Touch-up Injection into NLF (Visit 5) | 77 <sup>†</sup> |
| OCR (Visit 6)                                  | 149             |
| 3-months post-OCR (Visit 7)                    | 148             |
| 6 months post-OCR (Visit 8)                    | 148             |
| Completed Study <sup>‡</sup>                   | 148 (90.2)      |
| <b>Discontinuations – n(%*)</b>                |                 |
| Total discontinuations                         | 16 (9.8)        |
| <b>Reasons for discontinuation</b>             |                 |
| Positive skin test                             | 0               |
| Adverse event                                  | 0               |
| Enrollment criteria/Protocol violation         | 10 (6.1)        |
| Subject's request                              | 4 (2.4)         |
| Lost to follow-up                              | 1 (0.6)         |
| Investigator recommendation                    | 0               |
| Other  | 1 (0.6)         |

NLF = nasolabial fold; OCR = optimal cosmetic result.

\* The denominator is equal to the total number of subjects enrolled in the study.

<sup>†</sup> Number of subjects who received a touch-up with EVOLENCE® filler, Restylane®, or both devices.

<sup>‡</sup> At 6 months, all subjects who had not been discontinued remained ongoing in the study.

### Demographic Data

The randomized study population (n=149) was composed of 12 male and 137 female between the ages of 30-73 years of age.

The majority of subjects enrolled in the clinical study were Caucasian (92.6%) who most commonly represents skin type I-III and a minority population, who more commonly represent skin type IV-VI. The baseline demographics are displayed in Table 7 below:

**Table 7: Subject Demographics –ITT Population**

|  | Number (%) of Subjects |
|--|------------------------|
|  | ITT<br>(N = 149)       |
| <b>Gender – n (%)</b>                        |                        |
| Male   | 12 (8.1)               |
| Female                                       | 137 (91.9)             |
| <b>Age (yr)</b>                              |                        |
| Mean ± SD                                    | 55.7 ± 8.3             |
| Range  | 30.4 – 73.8            |
| <b>Race – n (%)</b>                          |                        |
| White  | 138 (92.6)             |
| Asian  | 1 (0.7)                |
| Native Hawaiian or other Pacific Islander    | 0                      |
| Black or African American                    | 4 (2.7)                |
| American Indian or Alaska Native             | 0                      |
| Other  | 6 (4.0)                |
| <b>Ethnicity – n (%)</b>                     |                        |
| Hispanic/Latino                              | 18 (12.1)              |
| Not Hispanic/Latino                          | 131 (87.9)             |
| <b>Skin Tone – n (%)</b>                     |                        |
| I to III Pale White/White                    | 121 (81.2)             |
| IV Light brown                               | 22 (14.8)              |
| V Brown                                      | 6 (4.0)                |
| VI Black                                     | 0                      |
| <b>Mean pretreatment MFWS Severity Score</b> |                        |
| <b>EVOLENCE®</b>                             | 2.38                   |
| Restylane®                                   | 2.37                   |

**Masking:**

The BEI and the subject remained masked throughout the study and were not permitted to refer to their own previous assessment, each others previous or current assessment or any of the Principle Investigators assessment. The subject wore blindfolds during treatment.

At the injection visit and the touch-up visit, neither the BEI nor the subject could distinguish between the EVOLENCE® injection and the control. At the 6-month post-OCR visit, one subject (who had no previous esthetic treatments) correctly distinguished between the EVOLENCE® and the control. Otherwise, the 2 treatments were indistinguishable.

**Effectiveness Results**

EVOLENCE® Collagen Filler was found to be non inferior to the control in the correction of NLF. During the 6 month follow up there was no statistically significant difference between EVOLENCE® and the control with regard to the measure of improvement at any time point. The change in the MFWS is presented in Table 8 below:

**Table 8: Change in Modified Fitzpatrick Wrinkle Scale (MFWS) – Blinded Evaluating Investigator’s Assessment – ITT Population (n=149)**

|  | <b>EVOLENCE®</b> | <b>Control</b> | <b>Difference</b> |
|--|------------------|----------------|-------------------|
| <b>Screening</b>                         |                  |                |                   |
| N  | 149              | 149            | 149               |
| Mean ± SD                                | 2.38 ± 0.36      | 2.37 ± 0.36    | 0.01 ± 0.30       |
| <b>OCR Visit</b>                         |                  |                |                   |
| Mean ± SD                                | 0.53 ± 0.52      | 0.50 ± 0.48    | 0.03 ± 0.35       |
| <b>Change from Screening at OCR</b>      |                  |                |                   |
| Mean ± SD                                | -1.85 ± 0.50     | -1.87 ± 0.45   | 0.02 ± 0.41       |
| <b>Observed Value at 3 months</b>        |                  |                |                   |
| Mean ± SD                                | 0.76 ± 0.65      | 0.71 ± 0.62    | 0.05 ± 0.48       |
| <b>Change from Screening at 3 months</b> |                  |                |                   |
| Mean ± SD                                | -1.62 ± 0.56     | -1.66 ± 0.55   | 0.04 ± 0.48       |
| <b>Observed Value at 6 months</b>        |                  |                |                   |
| Mean ± SD                                | 0.92 ± 0.65      | 0.87 ± 0.69    | 0.05 ± 0.53       |
| <b>Change from Screening at 6 months</b> |                  |                |                   |
| Mean ± SD                                | -1.46 ± 0.57     | -1.50 ± 0.60   | 0.04 ± 0.52       |

SD= standard deviation; Ranged from 0=No wrinkle – 3=Deep wrinkle

**Safety Results:**

**Adverse Events:**

The reported adverse events are presented in section VIII.

**Antibody Testing:**

The ELISA results indicate that multiple injections of **EVOLENCE®** for test and treatment did not result in development of antibodies against porcine type I collagen during this study of any clinical significance. With respect to IgG titers, 117 (80%) of the subjects were negative at all time points. 13 (8.8%) of the subjects displayed positive titers at both the Enrollment and Follow Up Visits of the study. 10 (6.8%) of the subjects changed status from negative to positive titers during the study. 3 subjects (2%) were borderline at enrollment and remained borderline at the end of the study and 1 subject (0.7%) changed from borderline to positive..

Notably the 14 subjects with elevated titers of antibodies to porcine collagen did not display any unusual adverse events with respect to incidence or characteristics, or any evidence of clinical symptoms compared to the general patient population. Of the 14 subjects with elevated titers post treatment, 10 subjects experiences adverse events at the injection site. These injection site adverse events were reported for both the EVOLENCE injection site and the HA Control product injection site. This proportion of adverse events (10/14, 71%) is similar to that observed in the entire Evolence population (126/149, 84.6%). All reactions observed in the 10 subjects with elevated titers were mild in severity and transient.

**Skin Challenge Study of Hypersensitivity**

In clinical practice, skin testing provides a means of eliminating most, but not all, subjects at risk of experiencing hypersensitivity in the application of medical devices for aesthetic

indications. The determination of hypersensitivity to a collagen device is based on clinical signs and symptoms, sometimes supplemented by antibody evaluations and biopsy examinations. The utility of such pre-treatment skin testing is a function of its precision in eliminating those with hypersensitivity, relative to all those who might eventually experience hypersensitivity that is a clinically relevant reaction upon treatment with the device. While approximately 3% of subjects exhibit hypersensitivity to the intradermal skin test for bovine collagen implants, an additional 1.3% develop an allergic reaction to treatment after having no reaction to the skin test<sup>1</sup>. This level of irreducible hypersensitivity risk is deemed acceptable to allow elimination of pretreatment skin test requirements.

### **Study Design**

Prospective open label, non-controlled, single center clinical study with two sequential skin test injections were used to evaluate the risk of developing localized immune hypersensitivity.

In the initial visit a baseline blood sample for anti- porcine collagen type I antibodies was obtained. The second visit consisted of the first skin test (0.1mL of EVOLENCE<sup>®</sup>-Test injected intradermally in the mid-volar, left forearm) to produce a bleb. Subjects then returned in approximately 72 hours for an evaluation of the skin test. All subjects who proved non-reactive to the first skin test were injected with a second skin test in the contra-lateral volar forearm after approximately 14 days. Approximately 72 hours after second injection, subjects returned for evaluation of the skin test sites and they returned again after ~30 days for evaluation. A second and final blood sample for anti- porcine collagen type I antibodies was taken at the final visit. The tested sites were monitored daily by the subject for signs of systemic and local reactions.

Healthy volunteers (18 years of age or older) were enrolled. Main exclusion criteria were: pregnant and/or nursing subjects; subjects treated with chemotherapy agent or systemic corticosteroids within the past 3 months; subjects with known allergy to collagen; subjects with a history of autoimmune disorder; subjects with severe allergies manifested by a history of anaphylaxis; or subjects with a current disease state that can affect immune response.

### **Study Objectives**

The purpose of this study was to demonstrate that the risk of experiencing hypersensitivity to a double skin test with porcine collagen implants was less than 1.3%. A risk of 1.3% - 1.5% is the estimated risk of developing hypersensitivity complications during facial treatments with injectable bovine collagen for subjects who were initially negative to the bovine collagen skin test.

### **Study Population**

Five hundred thirty (530) subjects were enrolled into the study consisting of one hundred and four (104) males and four hundred twenty six (426) females. The subjects' ages ranged from 18 to 92. Five hundred nineteen (519) subjects completed the study and were included in the evaluable population. Five hundred thirty (530) subjects were included in the safety population evaluation. In this study two (2) subjects had skin tone of brown (Fitzpatrick skin tone V).

### **Results**

Of the subjects who received 2 sequential skin tests , no subject displayed a positive hypersensitivity response against EVOLENCE<sup>®</sup>-Test (erythema grade moderate or severe

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<sup>1</sup> Cooperman et al, 1985; Castro and Krull, 1983

reaction). All subjects who displayed mild and mild to moderate erythema and did not exceed the initial bleb size of the implanted **EVOLENCE**<sup>®</sup>-Test. No induration was observed.

**Post Study Observation:**

One subject displayed a delayed positive local hypersensitivity reaction of increasing redness, swelling and tenderness at the right volar forearm (2<sup>nd</sup> injection site) more than two months post the end of the study (more than 3 months after injection of the second skin test).

**XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION**

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

**XII. CONCLUSIONS DRAWN FROM THE STUDIES**

**1. Safety**

During controlled clinical studies in the US, patients were exposed to nasolabial fold, facial wrinkles and/or forearm (skin test) injections of EVOLENCE®.

Clinical studies included a Skin Test study, specifically intended to evaluate the hypersensitivity rate to a double skin test with EVOLENCE®. No instances of positive hypersensitivity were observed during the study period. The upper bound of the one-sided exact 95% confidence interval for zero subjects experiencing strong to severe reactions to the EVOLENCE® Collagen Filler skin test is 0.58%.

The findings with EVOLENCE® demonstrate a lower incidence rate than collagen dermal fillers which do not require pre-treatment skin testing.

Other clinical studies were a US controlled trial, and controlled European clinical trials, in which EVOLENCE® was injected into facial wrinkles and folds and forearms.

None of the treated patients showed positive hypersensitivity reactions nor severe reactions to the product during study period following skin testing or post facial wrinkle injection.

Consequently EVOLENCE® may be used without a screening skin test prior to injection.

**2. Efficacy**

EVOLENCE® was statistically noninferior to the control in the correction of the nasolabial folds, maintained for at least 6 months following the OCR visit. At the 6 months post-OCR visit, 91.2% of subjects continued to rate the nasolabial fold treated with EVOLENCE® as “better” or “much better” than pretreatment. . In this study, EVOLENCE® and Restylane® showed similar safety profiles, consistent with known risks of the product class. Most of the AEs were injection site conditions, including erythema, pain, swelling, bruising, pruritus, or induration. Almost all of these were mild and were of less than one week duration. None of the adverse events observed led to withdrawal from the study. There was no evidence for

positive hypersensitivity reactions neither during the treatment period nor during the pretreatment skin test phase.

### XIII. CDRH DECISION

CDRH issued an approval order on June 27, 2008. The final conditions of approval cited in the approval order are described below.

In addition to the periodic post-market report (often referred to as annual report) requirements outlined in the enclosure, you have agreed to the Condition of Approval requiring that the company conduct a post-approval study described below and that the study will be conducted and the final study report will be submitted to FDA within 24 months of the device approval.

You have agreed to conduct a clinical post-approval study as per the EVOLENCE Postmarket Study protocol submitted to FDA on June 17, 2008. The post-approval study consists of an open-label, multi-center, prospective study to assess the safety and effectiveness of EVOLENCE in facial augmentation of subjects with Fitzpatrick skin types IV, V, and VI seeking correction of both sides of facial wrinkles and folds of the nasolabial area.

The primary objective of this study is to assess the safety of EVOLENCE in subjects with Fitzpatrick skin types IV, V, and VI seeking correction of facial wrinkles in accordance with the approved device labeling. Safety will be evaluated by the rate of local and systemic adverse events and especially pigmentation changes and/or keloid formation at the injection sites throughout the study period.

The secondary objectives of this study are to assess the device effectiveness as determine by: (a) the reduction of wrinkle severity score at 1, 3 and 6 months post injection compared to pre-treatment score as assessed by the principal investigator using the validated Modified Fitzpatrick Wrinkle Scale (MFWS); (b) investigator's and subject's satisfaction of the overall treatment, using the Global Improvement Assessment (GIA) scale at 1, 3 and 6 months post injection.

The main effectiveness endpoint is an improvement of at least 0.5 on the MFWS at six months as compared with baseline. The effectiveness success criterion for the study is a demonstration that at least 50% of the subjects achieve an improvement of 0.5 or greater at six months.

The study will enroll and treat a total of 165 subjects with Fitzpatrick skin types IV, V and VI who have clinical evidence of moderate to deep bilateral wrinkles in the nasolabial area corresponding to a rating of at least 2 on the validated MFWS. The study will enroll an even distribution of the skin types and include 15 investigational sites in the United States. The Subjects will be followed for 6 months after the optimal cosmetic results have been achieved. The follow-up visits will be performed at 1, 3 and 6 months post optimal cosmetic result visit. The study treatment will consist of injection of EVOLENCE for correction of both sides of facial wrinkles and folds of the nasolabial area.

Every 6 months for the first two years, and then annually thereafter, you are to submit a progress report to FDA that includes, but is not limited to, the status of site enrollment, the status of patient enrollment, the status of patient follow-up, and other milestones as it

compares to the stated goals in the protocol and an explanation for a delay, if any, in meeting these goals. This requirement is in addition to the annual reporting requirement for the PMA.

Expiration dating for this device has been established and approved at 2 years.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

#### XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.