

**Mid-Cycle Review Memorandum
OBE/DE Review for Pharmacovigilance Planning**

BLA: 125348/0

Isolagen Therapy, Autologous Human Fibroblasts
Isolagen Technologies, Inc.

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Introduction

OBE/DE/TBSB has completed a review of STN 125348/0, an original BLA application for Isolagen Therapy (IT). The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety monitoring, studies, or other pharmacovigilance activities, should the product be licensed.

Product Background

Isolagen Therapy (IT) is an autologous cell therapy product composed of fibroblasts grown separately for each individual patient. These autologous cells are obtained through punch biopsy of the patient's post-auricular skin and then expanded *ex vivo* using standard tissue culture procedures (Isolagen BLA, Section 2.2, p 4). The final product, a fibroblast suspension, is administered via intradermal injection into the superficial dermis along the nasolabial folds (Isolagen BLA, Section 2.2, p 4). The product is indicated for the cosmetic treatment of moderate to severe nasolabial fold wrinkles in adults 18 years old or older (Isolagen BLA, Section 2.5.1.2, p 7).

Isolagen Technologies has -----(b)(4)---INDs for the use of autologous fibroblasts in the correction of:

- Dermal contour deformities (IND) (b)(4)
- -----(b)(4)-----
- -----(b)(4)-----
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Approval is currently sought only for the indication of treatment of nasolabial (NL) fold wrinkles (Isolagen BLA, Section 2.2, p 4).

Manufacturing (Isolagen BLA, Section 2.2, p 4)

Product manufacturing consists of three phases:

1. Collection and preparation of the post-auricular biopsy in an outpatient setting
2. Culture and expansion of the cells
 - cells cultured from biopsy in presence of antibiotics
 - cells passaged and expanded
 - cells harvested and cryopreserved
3. Processing of the cells for shipment
 - cells thawed, washed, changed to serum free media and formulated for injection
 - cells shipped at $5 \pm 3^{\circ}\text{C}$ to the physician for injection intradermally

Cosmetic Benefit and Similar Products

Several structural fillers are approved in the United States for the treatment of nasolabial folds such as Restylane, Juvederm, and Radiesse (Isolagen BLA, Section 2.5.1.1, p 7). Cosmetic fillers such as Autologen™, Alloderm™, Zyderm™, Zyplast™ and Fibrel™ have been used to correct rhytids, and other soft tissue defects. According to the sponsor, the filling effects of these products dissipate with time and require additional treatments approximately every six months.

Since 2003, the Food and Drug Administration (FDA) has approved nine dermal filler devices with the condition of approval that the sponsor conduct a post-approval study (PAS) in patients with Fitzpatrick skin types IV-VI (darker skin types), as persons with this skin type were underrepresented in pre-approval clinical trials (Executive Summary – FDA/CDRH/Office of Device Evaluation General and Plastic Surgery Devices Panel Public Advisory Committee Meeting – Nov. 18, 2008 – p 17).

Non-Clinical Studies

No formal animal studies were conducted with IT for the treatment of NL folds due to previous commercial experience in humans (Isolagen BLA, Section 2.4, p 3). The sponsor does, however, reference animal studies of autologous fibroblasts (mice, rabbits) in literature that showed no oncogenic potential (Isolagen BLA Section 2.5.3.1, p 14).

Market Experience

According to the sponsor, approximately 1,100 subjects received treatment with commercially marketed IT at 110 clinics in the US prior to regulation in 1999 (based on projections from treatments occurring between 1995 and 1999). The product was also available in the United Kingdom from 2002 to 2007 with an estimated 6,000 patients treated (Isolagen BLA, Section 2.5, p 3).

Clinical Studies

Information on the clinical studies and safety data in this review is derived from the clinical summaries presented in the Isolagen BLA, Sections 2.7.3 (Summary of Clinical Efficacy) and 2.7.4 (Summary of Clinical Safety). IT was evaluated in three Phase II studies and four Phase III studies. IT-R-005 and IT-R-006, Phase III trials performed under SPA, were the pivotal studies. Additional supportive Phase III trials include IT-R-003A and IT-R-003B. One other Phase III trial (IT-R-002) and two Phase II trials (IT-R-001 and IT-R-007) were also conducted.

Study Number	Number of Study Centers	Study Start Study Stop	Study Objectives	Study Title
IT-R-001	2	3Jan03 Completed: Feb04	Safety and Proof of Concept	A Double-Blind, Randomized and Placebo Controlled Study of Isolagen for the Treatment of Rhytids
IT-R-007	5	22Mar07 Completed: Jun08	Safety and Efficacy	A Phase II Open Label, Multicenter, Trial of the Safety and Efficacy of Isolagen Therapy™ in the Treatment of Facial Wrinkles and Creases
IT-R-002	10	19May03 Complete: Jun05	Safety, Efficacy and Proof of Concept	A Phase III Double-Blind, Randomized and Placebo Controlled Study of Isolagen™ Injection for the Treatment of Contour Deformities
IT-R-003A	3	20Jul04 Completed: May05	Safety and Efficacy	A Phase III Double-Blind, Randomized and Controlled Study of Isolagen® Injection for the Treatment of Contour Deformities
IT-R-003B	3	21Jul04 Completed: May05	Safety and Efficacy	A Phase III Double-Blind, Randomized and Controlled Study of Isolagen® Injection for the Treatment of Contour Deformities
IT-R-005	7	23Oct06 Completed: Jun08	Safety, Efficacy, Schedule and Dose Confirmation	A Phase III Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial of Efficacy and Safety of Isolagen Therapy™ in the Treatment of Nasolabial Fold Wrinkles
IT-R-006	6	1Nov06 Completed: Jun08	Safety, Efficacy, Schedule and Dose Confirmation	A Phase III Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial of Efficacy and Safety of Isolagen Therapy™ in the Treatment of Nasolabial Fold Wrinkles

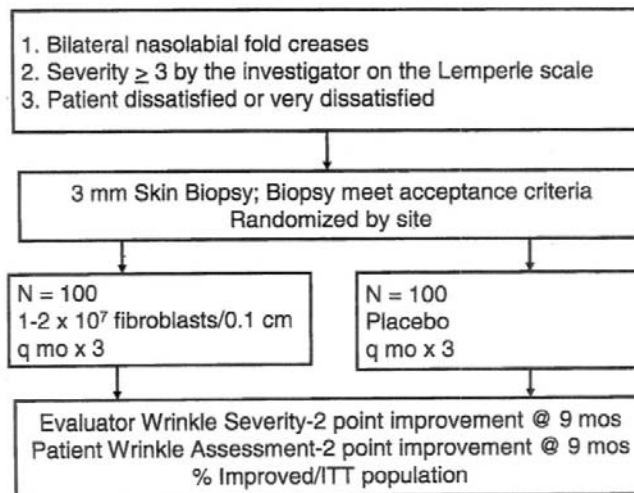
IT-R-005 and IT-R-006 (Pivotal Studies):

IT-R-005 and IT-R-006 were prospective, multicenter, randomized (1:1), placebo-controlled, double-blind Phase III studies of the efficacy and safety of IT. The subjects all had bilateral nasolabial folds with a severity of Grade 3 or higher on the Lemperle Wrinkle Severity Assessment scale. There were a total of 421 subjects enrolled, with 203 in IT-R-005 and 218 in IT-R-006 (see chart).

	IT-R-005		IT-R-006	
	IT	Placebo	IT	Placebo
Enrolled	100	103	110	108
Treated	83	92	98	99
Efficacy Evaluable	60	76	66	88

Study subjects were predominantly female (90%) and Caucasian (88%). Ten percent of subjects were Hispanic/Latino, and there were a total of 50 subjects from racial minority groups (25 received IT and 25 received placebo). The mean age of the subjects was 56.1 years with a range of 23 to 82 years. Of the 71 subjects that were 65 years or older, 29 received IT.

Each subject received three treatments at intervals of 4-6 weeks. The primary evaluation occurred six months after the final treatment and each subject had, on average a total of five visits. A long-term telephone follow-up 12 months after the primary assessment by is ongoing. The studies had two primary endpoints for efficacy, the Subject Wrinkle Assessment and the Evaluator Wrinkle Severity Assessment; they demonstrated efficacy on both endpoints. See diagram below for the flow of the study.

**IT-R-003A and IT-R-003B (Supportive Phase III Studies):**

The supportive Phase III trials, IT-R-003A and IT-R-003B, were identical, randomized, double-blind, placebo-controlled studies conducted to evaluate efficacy and safety of IT for the treatment of facial contour deformities. There were 100 subjects in the IT treated group and 113 in the placebo group. Study subjects had a mean age of 54.1 years and were 94% female and 95% Caucasian. The study had two primary endpoints – the subject's self assessment and the investigator's assessment using the Lemperle scale. Study IT-R-003B showed efficacy for both endpoints but Study IT-R-003A failed one endpoint (investigator's assessment).

Subjects in the IT-treated group received 3 treatments of IT containing 2.0×10^7 cells/mL. The primary evaluation was done at six months and there was long-term follow-up at nine to twelve months. Those adverse events considered possibly, probably, or definitely related to the use of IT were collected up to the 12-month study visit.

Summary of Safety from ITR-003A/B and ITR-005/006.

- Most events were common injection site reactions
- One instance of severe injection site ischemia after the third treatment in an IT-treated subject (IT-R-003B)
- Three subjects discontinued from the study due to an AE: injection site pain, breast cancer and fatigue syndrome

Other Studies:

Two Phase II studies (IT-R-001 and IT-R-007) and one additional Phase III study (IT-R-002) were also performed.

IT-R-001

IT-R-001 was a Phase II, double-blind, randomized, placebo-controlled study of IT for the treatment of rhytids in nasolabial folds, melolabial folds, perioral lines, glabellar lines, the forehead and acne scars. The study included 40 subjects randomized to four treatment groups (placebo and 3 groups with different doses of IT) with 10 IT-treated subjects per group. Each subject received three treatments, two weeks apart. Clinical laboratory testing and physical exams were performed at Visit 1 (day 0) and Visit 6 (month 6). Subjects who received either placebo or 0.5×10^7 cells/mL IT were eligible to receive re-treatment with 2.0×10^7 cells/mL IT after the acute phase of the study (four months after the first injection) was completed. All but one of the subjects in the 0.5×10^7 cells/mL IT group chose to get this additional treatment. Thirty subjects overall completed the long-term phase of the study, where they were followed for 12 months.

IT-R-002

IT-R-002 was a Phase III, double-blind, randomized, placebo-controlled study of IT for the treatment of facial contour deformities and scars. Out of the 158 subjects randomized, 111 subjects were treated with 3 injections of IT (2.0×10^7 cells/mL) and 40 received placebo. Additionally, after the acute phase of the study was completed (four months after the first injection), 31 of the placebo group subjects chose to receive open-label re-treatment with IT. In this longer term phase of the study all subjects were to be

followed for 12 months after their initial treatment. Of the 142 subjects in the long-term phase of the study, 122 completed the study.

IT-R-007

IT-R-007 was a Phase II, multicenter, open label, uncontrolled study of the safety and efficacy of IT in the treatment of facial wrinkles and creases. Fifty subjects were enrolled in the study and biopsied, while only 45 subjects were treated with IT. Each subject received two treatments of up to 6 mL of IT containing $1.0\text{-}2.0 \times 10^7$ cells/mL approximately five weeks apart. This study exposed subjects to a 3-fold higher dose of IT than in the 005/006 studies. All subjects were followed for six months after the final visit and then received a telephone call assessment of safety, 12 months after the final injection. Results of this long-term follow up will be submitted during the BLA review.

Summary of Safety from IT-R-001, IT-R-002 and IT-R-007

- Primarily injection site reactions such as pain, edema, or inflammation that resolved spontaneously.
- Majority of the reactions were considered mild or moderate.

Safety Database

The total safety database includes 508 subjects who received IT across all trials (including 41 placebo patients in IT-R-001 that were subsequently treated with IT) and 354 who received placebo (i.e., injection with the vehicle only). The subjects were >90% female, >90% Caucasian with fewer than 12% age 65 years or older. The only statistically significant demographic difference between the IT and control groups was the mean age, which was 52 years in the IT group and 54.2 years in the control group (p-value = 0.0009).

IT-treated subjects received a total dose between 2.5 and 3.5 ml of IT at $1\text{-}2 \times 10^7$ cells/ml, in one to three treatments, at intervals of one to six weeks. There was an average of 9.1 total injections per IT-treated subject and 8.2 injections per placebo subject (2.5.5.3, p 37).

Adverse Events

The sponsor conducted its primary analysis for safety using treatment-emergent adverse events (TEAE), which they defined as “any adverse medical occurrence that begins or worsens on the first day of treatment administration or any day thereafter during the study period” (2.5.5.4, p 38).

The most common TEAE reported by both subjects in the IT-treated and placebo groups were in the SOC General Disorders and Administration Site Conditions class. Sixty-

eight percent of IT-treated subjects and 40% of those treated with placebo reported at least one TEAE in this class. The most frequently reported TEAEs in this class (>1% of subjects) by PT in the IT-treated group versus the placebo treated group (respectively) were:

- Injection Site Erythema (16% vs. 9%)
- Injection Site Bruising (11% vs. 14%)
- Injection Site Swelling (14% vs. 4%)
- Injection Site Pain (6% vs. 2%)
- Injection Site Hemorrhage (3% vs. 5%)
- Injection Site Edema (4% vs. 0%)
- Injection Site Nodule (4% vs. <1%)
- Application Site Papules (2% vs. <1%)

Overall, the frequency of injection site reactions was somewhat higher in the IT-treated group than the placebo-treated group (BLA, Section 2.5.5.4, p. 39).

Severity of TEAEs

With regards to the severity of TEAEs, the Summary of Clinical Safety (Isolagen BLA, Section 2.7.4) discusses in detail only those TEAEs found in at least 1% of the study population. The majority of all TEAEs were classified by the sponsor as mild to moderate in both treatment groups.

There were six severe AEs overall reported in the General Disorders and Administration Site Conditions (GDASC) class. In the IT-treated group, one subject experienced severe injection site erythema, injection site swelling, and injection site pain immediately after injection. A second IT-treated subject reported severe injection site swelling. A placebo-treated patient reported severe injection site bruising. The other three severe GDASC AEs occurred in placebo-treated subjects and involved events with a frequency <1%.

Severe AEs were also reported in other SOC classes:

- Infections and Infestations (5 IT-treated vs. 3 placebo-treated)
- Skin and Subcutaneous Tissue Disorders (1 IT-treated)
- Musculoskeletal and Connective Tissue Disorders (7 IT-treated vs. 3 placebo-treated)
- Injury, Poisoning and Procedure Complications (3 IT-treated vs. 2 placebo-treated)
- Respiratory, Thoracic and Mediastinal Disorders (2 placebo-treated)
- Vascular Disorders (2 IT-treated subjects)

One life-threatening AE was reported in the Nervous System Disorders class in a placebo-treated patient.

Overall, IT-treated subjects more often reported moderate injection site-related TEAEs, while placebo-treated subjects more often reported mild TEAEs. More IT-treated subjects reported at least one severe AE than placebo-treated subjects and more of the

severe AEs reported by IT-treated patients were considered to be possibly, probably or definitely related to the study treatment.

The sponsor notes that they believe that IT is only slightly less well tolerated than placebo.

Relationship of TEAEs to the Study Treatment

When describing the relationship of TEAEs to the study treatment, the Summary of Clinical Safety discusses in detail only those TEAEs found in at least 1% of the study population. Overall, the majority of the TEAEs in the GDASC class, mainly localized injection site reactions, were considered possibly, probably or definitely related to the study treatment:

- Possibly (9% IT-treated vs. 1% placebo-treated)
- Probably (11% IT-treated vs. 4% placebo-treated)
- Definitely (33% IT-treated vs. 29% placebo-treated)

The sponsor concluded that TEAEs reported in other SOC classes were mainly considered unlikely or unrelated to study treatment with 1% or fewer of these events being considered possibly, probably, or definitely related to the study treatment. Additionally, they felt that IT-treatment showed a similar safety profile to placebo-treatment and that most events related to study treatment were those that would be expected from injection of any type of material.

Of the events considered possibly, probably or definitely related to the study treatment, the majority of those started less than one day from the administration of the IT or placebo (80% of IT-treatment and 89% of placebo-treated). Only eight IT-treatment events and two placebo-treatment events had an onset more than seven days after administration. These events included injection site reaction (1, IT-treated), injection site swelling (2, IT-treated), injection site erythema (2, IT-treated), injection site irritation (1, IT-treated), injection site anesthesia (1, placebo-treated), chapped lips (1, IT-treated), urticaria (1, placebo-treated) and basal cell carcinoma (1, IT-treated). The case of basal cell carcinoma had an onset 141 days after administration of IT and was considered by the investigator as possibly related to the study treatment.

Overall, there were more AEs considered treatment-related in IT-treated subjects (444 total events) than in placebo-treated subjects (207 total events). However, when the total number of subjects in each group is taken into account, the frequency of events was deemed to be similar by the sponsor (0.87 per IT-treated vs. 0.58 per placebo-treated).

All but 14% of IT-treatment reported events and 9% of placebo-treatment reported events resolved within seven days of onset. By the end of the study there were eight total IT-treatment reported events and two total placebo-treatment reported events that had not resolved (injection site swelling, injection site erythema (2), injection site reaction, alopecia areata, urticaria, hypoaesthesia oral and eyelid edema).

Other Safety Results:

Nodules:

- 23 across all studies – 20 (4%) in IT-treated subjects and 3 (<1%) in placebo-treated subjects.
- All nodules in placebo group and 19 of 20 nodules in IT-treated group were considered mild.
- One reported nodule (in an IT-treated subject) was considered moderate
- All resolved within 90 days with no treatment.

Ischemia:

- Three total across all studies – 2 (<1%) IT-treated and 1 (<1%) in the placebo group. Two of the ischemia events were considered severe (1 in an IT-treated subject).
- All resolved within one day with no treatment or sequelae.

Deaths:

Two deaths in study subjects occurred and were considered by investigators to be unrelated to study treatment.

- A 57-year-old female subject died from a myocardial infarction after three treatments with placebo
- A 77-year-old female subject died from heart failure after biopsy, but prior to study treatment

Study Terminations:

- Three subjects who received IT-treatment were terminated from the study for AEs
 - Two of these had moderate injection site pain that resolved without sequelae
 - One had severe injection site bruising that resolved in 10 days
- One subject discontinued treatment for an AE, but remained in follow-up
 - The subject experienced severe injection site erythema, swelling, and pain, which resolved in three to four days

Clinical Laboratory Investigations:

Laboratory investigations were performed in trials IT-R-001 and IT-R-002, but not in the other five studies. Chemistry, hematology and urinalysis parameters were included. None of the laboratory values were deemed clinically significant by the sponsor and they state that there were no discernable trends in the data.

Market Experience:

Between 1995 and 1999, approximately 1,100 patients were treated with IT in the U.S. by about 200 physicians in 110 clinics. IT was used to treat facial rhytids, scars, hypoplastic lips, burns and other problems. In non-regulated spontaneous reporting, there were no documented significant adverse events. Mild to moderate injections site reactions were reported: redness, swelling, rash, splotching and pruritus. There was one case of herpes outbreak after injection. The most significant AEs were a case of local redness/edema

that lasted more than three days and an instance of redness/induration that lasted for 10 days. In a U.S. retrospective study report from 2003, no serious AEs were observed in the 354 patients reviewed (Isolagen BLA, Section 2.4, p 3 and Section 5.3.5.4).

In the U.K., between 2002 and 2007, there were approximately 6,000 patients treated with IT. As in the U.S. market experience and clinical trials, most AEs were injection site reactions. All resolved in seven days to five months. Three severe AEs were reported:

- Angioedema
- Severe allergic reaction
- Lump requiring surgical removal (histology unknown).

Pharmacovigilance Planning

Proposed Pharmacovigilance Plan (PVP)

The BLA submission includes a PVP proposed by the sponsor (BLA Section 1.12.2). The plan states that the following types of data will be collected: serious and unexpected AEs from domestic and foreign sources, serious and expected AEs from domestic sources, nonserious AEs from domestic sources regardless of expectedness, reports of allogeneic cell administration of IT, IT utilization data (e.g., demographics), and reports of pregnancy during the treatment period. Active surveillance, passive surveillance, spontaneous report collection, literature reviews, and clinical trials will be used for adverse event reporting. Specific mechanisms or methodology for how “active surveillance” will be conducted is not provided.

Additionally, the sponsor proposes to conduct long-term safety follow-up by monitoring a subset of patients (100 patients) to gather additional safety data at six months and 12 months post completion of the last injection. This follow-up is to be via a patient registry or under protocol at certain treatment sites and will be conducted for the first two years that IT is in commercial distribution. The data collection will use a patient diary card.

A review of the sponsor’s proposed pharmacovigilance plan found it inadequate to address all of the safety concerns related to use of the product. Specifically, the description of active surveillance listed four possible types of data collection but lacked detail on the sponsor’s plans for this surveillance (periodicity of follow-up, content of questionnaires, methods for contacting patients/physicians, etc.). Regarding the proposed “Long-Term Safety Follow-Up”, the enrollment of 100 patients would be inadequate to detect uncommon adverse events and would not sufficiently expand the safety database beyond the 508 IT-treated patients already included in the clinical trials. In several of the clinical trials, patients have already been followed for 12 months; a longer follow-up period would be necessary to assess safety of IT beyond this period and to detect longer latency adverse events. The description also lacks essential details on the study methods.

Details on how the study will be conducted, how patients will be enrolled, how patients will be contacted and followed, or which study and demographic variables will be collected were not provided.

The sponsor plans to require physicians who will be receiving the product to attend training at a “Center of Excellence” established by the sponsor. Centers consist of Isolagen trained staff specializing in facial aesthetic treatments and will include training on:

- proper biopsy collection and shipment
- proper treatment preparation and injection technique
- proper logistics training from biopsy to injection
- the types and severity of AEs expected, and appropriate treatment and follow-up.

Only Isolagen certified physicians will receive the IT product. A copy of the training manual is included with the BLA submission (Isolagen BLA, Section 1.12).

Safety Concerns

Underrepresented Populations

(Isolagen BLA, Section 2.5.4.1 p 17, and 2.5.4.7 p 32)

Individuals with darker pigmented skin are underrepresented in the clinical trial study populations. More data needs to be collected to evaluate the potential relation of IT to keloids or hyper/hypopigmentation, as these patients are more likely to experience such skin conditions in association with skin trauma.

- Non-Caucasian subjects: Over 90% of the IT-treated subjects were Caucasian; only 1% were African-American and 1% were Asian.
- Subjects > 65 years of age: Less than 12% of study subjects were over the age of 65, a population that could reasonably be expected to receive the product routinely after licensure.
- Males - Over 90% of the study subjects were female.

Injection Reactions

(Isolagen BLA, Section 1.2.1)

Almost all of the TEAEs judged to be possibly, probably, or definitely related to IT-treatment were injection reactions. Local injection site reactions were very common – seen in over 60% of IT-treated subjects, although most were mild to moderate and resolved spontaneously.

- Keloid formation/pigmentation changes: darker-skinned individuals, who were underrepresented in clinical trials, may experience these AEs in response to skin/tissue trauma.
- Nodule formation was noted in several cases in the clinical trials and prior commercial experience. Most of the nodules resolved quickly, however, some persisted longer, with one requiring surgical removal. Additional post-licensure and longer term follow-up data will help further characterize the frequency of nodules, their duration, and if, in actual practice, demographic factors (e.g., skin pigmentation, age) or concomitant facial treatments (e.g., dermal fillers) influence their occurrence.
- Embolization: may be seen as ischemia or infarction.

Tumor formation

(Isolagen BLA, Section 1.2.2)

There is also the concern of malignancy related to IT treatment with the potential for overgrowth and malignant transformation of the implanted fibroblasts or for these fibroblasts to transform cells in their vicinity. Additionally, there exists the possibility of expanding cells from the biopsy that are already dysplastic or malignant and then implanting them with the IT injection. The sponsor includes these potential risks in the proposed labeling. The post-auricular region recommended for the biopsies is vulnerable to basal cell carcinoma, although nasal lesions are more common. Published case reports also describe other postauricular malignancies.

Other safety concerns:

- Allergic reactions – two cases in U.K.
- Long-term survival of transplanted cells – the long term survival of the transplanted fibroblasts and what might occur if they die after transplant is not fully assessed; none of the clinical trials followed patients for more than 12 months. Limited data from literature exists on the survival of transplanted cells.

Questions for Post-licensure Pharmacovigilance:

- What is the risk of keloid formation and pigmentation changes after IT treatment, particularly in non-Caucasian, dark-skinned individuals?
- What is the frequency of nodule formation, in particular nodules that do not resolve within a reasonable time period after injection, as the treated population increases?
- What adverse events might be expected over a long-term follow-up of greater than 12 months? How long do the transplanted cells survive? Does their survival or death provoke inflammatory or other specific risks?
- What is the risk of cancer from malignant transformation in implanted cells or from transplanted dysplastic or malignant cells from the biopsy location?
- How can injection site reactions be minimized and serious procedure-related adverse events, such as embolization, be avoided?

Assessment and Recommendations

1. Submit outstanding safety data

IT-R-005 and IT-R-006: 12 month safety assessment is ongoing and will be submitted in a safety update report during the BLA review.

2. Expand safety database, and collect long-term adverse event information

We recommend that the sponsor conduct a post-licensure registry study to:

- Enhance monitoring for tumor formation in IT-treated patients through follow-up of all consenting patients for several years.
- Address the limited safety information available for non-Caucasians.

- Detect AEs potentially associated with the end of the survival period of transplanted fibroblasts.
- Further assess the risk of certain AEs that were rarely observed in the clinical trials (nodule formation, allergic reactions, and ischemic events).

A registry study is a particularly feasible pharmacovigilance method for IT; information is already collected on each patient and provider due to the autologous nature of the product. While ultimately we may have to rely on spontaneous reporting to discover serious adverse events that are rare or have a long latency period, the registry study would likely provide earlier recognition of somewhat more common and shorter latency risks. This registry study could be completed as a post-marketing commitment (PMC), but assurance of diligent execution may be greater if it can be classified as a post-marketing requirement (PMR). Discussion is ongoing within CBER to evaluate if, under FDAAA, safety considerations may justify that the study be performed as a PMR.

3. Pharmacovigilance Study Planning

A detailed protocol should be developed, including planned enrollment size, follow-up schedule, data to be collected, and follow-up methodology:

- The study should enroll as many patients as feasible during the first years after licensure. Based on sponsor estimates of numbers of cell products to be processed after licensure, the study should plan to enroll a minimum of 1,000 distinct patients.
- Enrollment should include at least a certain proportion of non-Caucasian patients.
- Length of study time should be substantially longer than the 12 month follow-up period proposed in the sponsor's PVP long-term surveillance activity. We recommend a minimum of 5 years, however a longer follow-up period would increase the potential for detecting longer latency adverse events, particularly malignancies.
- Time points of office or telephone visits
- Data collected at each follow-up contact should, at a minimum, include any adverse events noted by the patient, their severity, duration, treatment required, and sequelae. Other information to record: dates of injections; patient demographics (age, race); concomitant related treatments/medications (e.g., dermal fillers, botulinum toxin injections, cosmetic surgery); AEs at the injected sites and the biopsy sites; keloid/scar/abnormal pigmentation at the injection or biopsy sites; tumor development both locally and distally.
- A plan for reporting to the FDA

4. Ensure safe application of the product

In certain instances, to ensure a favorable risk/benefit ratio for a product, the sponsor must prepare a Risk Evaluation and Mitigation Strategy (REMS). Discussion is underway to evaluate if, under FDAAA, a justification exists to require a REMS that would formally require the proposed training and restricted distribution described by the sponsor in the BLA. As stated in the pharmacovigilance plan, the sponsor will require each treating physician to receive certification from a "Center of Excellence," established by the sponsor, which verifies training in biopsy and administration techniques. Certification would be required prior to physician receipt of any IT product. Training would include the avoidance of pigmented or other lesions (which could be malignant or

pre-malignant) during the biopsy procedure and administration methods to minimize the frequency and severity of injection site reactions.

Reasons for requiring such training and restricted distribution include avoiding potentially malignant or pre-malignant lesions at the biopsy site, the potential for injection site reactions with improper technique, and the potential to cause occlusion/embolization if the product is injected into a vessel. These points are noted as risks by the sponsor (BLA Section 1.2.2, p 5). Injection site reactions, caused by the cell product and the invasive procedure itself, were frequent, occurring in over half of IT-treated subjects and considered related to the product. Although most injection site reactions were mild or moderate, it is reasonable to conclude that the potential for more severe reactions exists, particularly if physicians are not trained in proper techniques. IT administration is different from the administration of vaccine in many ways (e.g., biopsy site selection and technique, intra-dermal delivery, multiple injections at the treatment site) and warrants specialized training not necessary for vaccines.

Further, trial IT-R-003A failed one of its primary endpoints, and the sponsor noted that reasons include “insufficient investigator training and sub-optimal dosing” (2.5.1.4, p 10). According to the BLA, Section 2.5.4.4.1 (p 23), the sponsor held a meeting with investigators after the IT-R-003A/B trial was complete and observed the investigators’ injection technique. They noted large variability in technique among investigators. (Training was not provided for investigators prior to the 003 trials but was incorporated into the 005/006 trials.) The sponsor conducted additional training on injection technique at this meeting. “Investigators were expected to prove they could raise a wheal as expected for injection into the papillary dermis (BLA Section 2.5.4.4.1 (p 23)).” The sponsor concluded that “many inconsistencies between sites might be caused by a lack of common training in both injection site technique and assessment” (BLA Section 2.5.4.4.1 (p 23)). While these observations were made with regard to IT’s efficacy, it is reasonable to conclude that improper technique could result in increased risk of injection site adverse events. Finally, in the sponsor’s description of the four subjects terminating early from the clinical trials, it was noted that improved training in use of local anesthetic or administration techniques might minimize injection site reactions (BLA Section 2.7.4.2.1.7, p 53). Due to the cosmetic nature of IT, minimization of AEs, even mild ones, is important.

5. Training Components

To ensure the benefits outweigh the risks of Isolagen therapy, physicians need to be trained adequately to:

1. evaluate injection site and the biopsy site to identify any pre-existing skin lesions that should preclude use of that site or treatment with Isolagen Therapy.
2. handle live cells in a sterile manner – most health care providers have no experience in handling cell products, either in the laboratory or in clinical settings.
3. perform multiple (3) 3-mm punch post-auricular skin biopsies to obtain fibroblasts for manufacturing the final product

4. perform multiple injections of the product intradermally along the nasolabial fold wrinkle lines using proper technique to reduce the potential for injection-related local reactions (erythema, swelling, redness) and possible scarring.

Letter Ready Comments

1. To adequately address the missing data in certain populations (non-Caucasians, patients over > 65 years-of-age and males) and certain safety concerns, such as malignant potential and risk of other long-term adverse events, we recommend that you complete a post-licensure registry study. Please submit a detailed protocol, including planned enrollment size, follow-up schedule, data to be collected, and follow-up methodology.

Please consider the following recommendations in developing your study plan:

- The study should enroll as many patients as is feasible during the first years after licensure. Based on your estimates of numbers of cell products to be processed after licensure, the study should plan to enroll a minimum of 1,000 distinct patients.
- Enrollment should include at least a pre-specified proportion of non-Caucasian patients.
- Length of study time should be substantially longer than the 12 month follow-up period you proposed in the long-term surveillance activity included in the PVP. We recommend a minimum of 5 years, however, longer follow-up would increase the potential for detecting longer latency adverse events, particularly malignancies.
- Include active follow-up with enrolled patients or their physicians with specified time points of office or telephone visits.
- Data collected at each follow-up contact should, at a minimum, include any adverse events noted by the patient, their severity, duration, treatment required, and sequelae. Other information to record: dates of injections; patient demographics (age, race, gender); concomitant related treatments/medications (e.g., dermal fillers, botulinum toxin injections, cosmetic surgery); AEs at the injected sites and the biopsy sites; keloid/scar/abnormal pigmentation at the injection or biopsy sites; tumor development both locally and distally.
- A plan for reporting to the FDA

2. As you propose in your pharmacovigilance plan, each physician administering IT shall receive training in biopsy and subsequent administration techniques. This training would be required prior to physician receipt of the Isolagen product. Training should include the avoidance of pigmented or other lesions (which might be malignant or pre-malignant) during the biopsy procedure, as well as administration methods to minimize the risks of injection site reactions and blood vessel occlusion, infarction or embolization.

3. Submit outstanding safety update for studies IT-R-005, IT-R-006, and IT-R-007 as soon as possible.