

CLINICAL REVIEW

Division of Clinical Evaluation, Office of Cellular Tissue and Gene Therapy, Center for
Biologics Evaluation and Research

TITLE AND GENERAL INFORMATION

Medical Officers' (M.O.) Review Identifiers and Dates:

BLA/NDA #: 125348/0

Related IND #: IND (b)(4)

Reviewers: Agnes Lim, M.D.
Yao-Yao Zhu, M.D., Ph.D.
Changting Haudenschild, M.D.

Team Leaders: Bruce Schneider, M.D.
Changting Haudenschild, M.D.

Branch Chief: Wilson Bryan, M.D.

Office Director: Celia Witten, Ph.D., M.D.

Submission Received by FDA: March 6, 2009

Review Completed: December 9, 2009

Product:

Proper Name or Established Name: Autologous human fibroblast cells

Proposed Trade Name: azficel-T, formerly known as Isolagen TherapyTM (IT), is identified as IT in this clinical review

Product Formulation(s): A sterile suspension of each patient's own cultured living fibroblasts in Dulbecco's Modified Eagles Medium at a concentration of $1.0 - 2.0 \times 10^7$ cells/mL.

Placebo: Dulbecco's Modified Eagle's Medium (DMEM) without phenol red

Applicant:

Fibrocell Technologies, Inc., formerly known as Isolagen Technologies Inc., is identified as Isolagen in this review

Pharmacologic Class or Category:

Cell Therapy

Proposed Indication:

Clinical Review

BLA 125348

Isolagen Therapy™ is an autologous cellular product indicated for the treatment of moderate to severe nasolabial fold wrinkles in adults.

Proposed Population:

Adults

Dosage Form(s) and Route(s) of Administration:

Isolagen Therapy™ is available in a single dosage form of $1.0\text{-}2.0 \times 10^7$ cells/mL per 1.2 vial (sufficient to administer 1.0 mL). Up to 2 mL, administered as 0.1 mL per linear cm, are injected intradermally into the nasolabial fold area.

Documents Reviewed:

(See Section 4.1 in this review)

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY.....	6
1.1 Brief Overview of Clinical Program	
1.2 Efficacy Analysis of Studies IT-R-005 and IT-R-006	
1.2.1 Demographics	
1.2.2 Efficacy	
1.3 Safety	
1.3.1 Safety Database	
1.3.2 Safety Analysis of Studies	
1.3.3 Proposed Dosing Regimen and Administration	
1.3.4 Drug-Drug Interaction	
1.3.5 Special Populations	
1.4 Issues Raised at the Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC)	
1.5 Premarket Recommendations	
1.6 Postmarket Recommendations	
2. SIGNIFICANT FINDINGS FROM OTHER DISCIPLINES.....	11
2.1 Chemistry Manufacturing and Controls (CMC)	
2.2 Animal Studies	
3. CLINICAL AND REGULATORY BACKGROUND.....	12
3.1 Health-Related Conditions and Available Interventions	
3.2 Important Information from Pharmacologically Related Products	
3.3 Commercial Experience	
3.4 Regulatory Background Information	
4. CLINICAL DATA SOURCES, REVIEW STRATEGY, AND DATA.....	19
INTEGRITY	
4.1 Material Reviewed	
4.2 Summary of Clinical Studies	
4.3 Review Strategy	
4.4 Good Clinical Practices (GCP) and Data Integrity	
4.5 Financial Disclosure	
5. DESIGNS OF CLINICAL STUDIES.....	22
5.1 Studies IT-R-005 and IT-R-006	
5.1.1 Primary Endpoints	
5.1.2 Secondary Efficacy Endpoints	
5.1.3 Key Eligibility Criteria	
5.1.4 Study Schema	
5.1.5 Observation Period	
5.1.6 Randomization Procedure	

5.1.7	Re-Biopsy/Manufacturing Failure	
5.1.8	Blinding Procedure	
5.1.9	Treatment Regimen	
5.1.10	Concomitant Medications and Procedures	
5.1.11	Training for Study Investigators	
5.2	Statistical Analysis	
5.2.1	Sample Size Determination	
5.2.2	Efficacy Analysis Populations	
5.2.3	Efficacy Analysis	
5.2.4	Sensitivity Analysis for the Primary Efficacy Endpoints	
5.2.5	Secondary Endpoints	
5.3	Study IT-R-001	
5.4	Study IT-R-002	
5.5	Studies IT-R-3A and IT-R-3B	
5.6	Study IT-R-007	
6.	REVIEW OF EFFICACY.....	36
6.1	Study Results and Efficacy of Study IT-R-005	
6.2	Study Results and Efficacy of Study IT-R-006	
6.3	Comparison of Efficacy Outcomes Between the Two Studies	
6.4	Analysis of Secondary Endpoints	
6.5	Clinical Issues	
6.6	Efficacy Conclusions	
7.	OVERVIEW OF SAFETY ACROSS TRIALS.....	52
7.1	Safety Results of Study IT-R-005 and IT-R-006	
7.1.1	Method of Assessment	
7.1.2	Safety Results of Study IT-R-005	
7.1.3	Safety Results of Study IT-R-006	
7.1.4	Adverse Events in < 1% Safety Population in Studies 005 and 006	
7.1.5	Twelve-Month Long-Term Safety Assessment in Studies 005 and 006	
7.2	Safety Results of Study IT-R-001	
7.3	Safety Results of Study IT-R-002	
7.4	Safety Results of Studies IT-R-003A and IT-R-003B	
7.5	Safety Results of Study IT-R-007	
7.6	Analysis of Integrated Safety Information	
7.6.1	Overview, Extent of Exposure and Methodology of Assessment	
7.6.2	Adverse Events in > 1% Safety Population	
7.6.3	Adverse Events in < 1% Safety Population	
7.6.4	Severity of Adverse Events	
7.6.5	Duration of Adverse Events	
7.6.6	Comparison of Adverse Events in Pivotal Trials with Integrated Safety Data	
7.7	Significant Adverse Events	
7.7.1	Injection-Site Ischemia	
7.7.2	Injection-Site Nodules	

7.7.3	Basal Cell Carcinoma	
7.7.4	Allergic Reactions	
7.7.5	Herpes Simplex and Injection-Site Paresthesia	
7.7.6	Unresolved Adverse Events	
7.8	Safety Profiles in Subgroups	
7.9	Safety Conclusions	
7.10	Review of Commercial Training Manual (To be used in the labeling)	
8.	ADVISORY COMMITTEE MEETING.....	75
8.1	Summary and Discussion of Advisory Committee Meeting (bulleted texts summarizing the AC members' discussion)	
8.1.1	Efficacy	
8.1.2	Safety	
8.1.3	Product Safety	
8.1.4	Injection-Site Adverse Events	
8.1.5	Tumor Formation	
8.1.6	Race and Ethnicity	
8.1.7	Geriatric (> 65 years) and Male Population	
8.1.8	Physician Training	
8.1.9	Post-Treatment Biopsy	
8.1.10	FDA Considerations for Elements of Post-Treatment Biopsy Study	
9.	CLINICAL RECOMMENDATIONS.....	81
9.1	Recommendations for Pre-Approval Actions	
9.2	Recommendations for Labeling and Post-Approval Actions	
10.	APPENDICES.....	85
10.1	Appendix A: Abbreviations	
10.2	Appendix B: List of Documents Reviewed	
10.3	Appendix C: Photoguide Used with the Evaluator Wrinkle Severity Assessment (Lemperle Scale)	
10.4	Appendix D: Advisory Committee Meeting Questions	
11.	REFERENCES.....	90

1. EXECUTIVE SUMMARY

1.1 Brief Overview of Clinical Program

Isolagen Therapy (IT) is a cellular product consisting of autologous fibroblasts developed for the treatment of moderate to severe nasolabial fold wrinkles for up to six months in adults. The fibroblasts are derived from patients' post-auricular skin biopsies, expanded in culture, and suspended in proprietary isotonic medium. The final cell suspension is injected intradermally into patients' nasolabial folds. The treatment regimen comprises three sets of injections with a five-week interval between injections. IT is injected intradermally into the nasolabial fold wrinkles at the dose of 0.1 mL per linear cm, up to a total dose of 2 mL per treatment. The product has gone through three Phase 2 and four Phase 3 studies under IND.

The BLA application was submitted on March 6, 2009. The application included study reports of seven clinical trials. Of these seven trials, the Phase 3 studies IT-R-005 and IT-R-006 were conducted under US Food and Drug Administration (FDA) Special Protocol Assessment (SPA) agreements. Studies IT-R-005 and IT-R-006 were conducted at 13 study centers (seven in 005 and six in 006) in the U.S. from October 23, 2006 to June 26, 2008. The other five clinical studies varied in the injection sites, the cell doses and injection volumes, the interval between sets of injections, and study duration. Mechanism of action of IT was not examined in human or animal studies.

The data supporting efficacy claims were derived from the two trials, IT-R-005 and IT-R-006 (combined, n=421, 210 IT and 211 vehicle-control). Efficacy data from the other five trials were also reviewed. Conducted under an identical protocol, Studies IT-R-005 and IT-R-006 were multiple center, randomized, double-blind, vehicle-controlled trials to assess the efficacy and safety of IT. In these studies, the control subjects received injections of vehicle medium (proprietary isotonic) without cells. The studies were designed as double-blind. All investigators received special training by the sponsor in biopsy techniques, sterile handling of cells, and administration of IT. The evaluator who assessed wrinkle severity could not be the injector for that subject, and the evaluator was the same for each subject throughout the trial. The applicant helped maintain the blind by providing injectors with instructions on how to relate to subjects and administer study treatment. In addition, injectors were prohibited from discussing any of the subjects with other study staff members. The co-primary efficacy endpoints of these trials were:

- Proportion of subjects with at least two-point improvement from baseline to six-month post-treatment on both sides of face in Evaluator Wrinkle Severity Assessment.
- Proportion of subjects with at least two-point improvement from baseline to six-month post-treatment in Subject Wrinkle Assessment.

The safety analysis was derived from the two pivotal trials and the five other studies. These seven studies consisted of a total of 821 subjects, 467 treated with IT and 354 treated with vehicle only. Since the studies compared effects of injections of IT to those of an active vehicle-control (which has all the components of the final product except for the cells), the design precluded comparison of the safety of IT to that of a true placebo. The overall safety profile of IT treatment is derived from assessment of the totality of adverse events in both study arms.

1.2 Efficacy Analysis of Studies IT-R-005 and IT-R-006

1.2.1 Demographics

The intent-to-treat (ITT) population in Study IT-R-005 was predominantly female (88% of IT and 91% of vehicle-control), white (94% of IT and 96% of vehicle-control), with an overall mean age of 56.7 years (57.5 in IT and 55.9 in vehicle-control). Similarly, the ITT population in Study IT-R-006 was predominantly female (94% of IT and 88% of vehicle-control), whites (89% of IT and 88% of vehicle-control), and had an overall mean age of 54.6 years (53.9 in IT and 55.4 in vehicle-control).

1.2.2 Efficacy

- The two co-primary efficacy endpoints at six months were met in both IT-R-005 (n=203, 100 IT and 103 vehicle-control) and IT-R-006 (n=218, 110 IT and 108 vehicle-control), shown in Table 1.

Table 1. Results of Co-Primary Endpoints in Studies IT-R-005 and IT-R-006

Endpoints	Study IT-R-005			Study IT-R-006		
	IT n = 100	Vehicle n = 103	p-value	IT (n = 110)	Vehicle (n = 108)	p-value
Evaluator Wrinkle Assessment	33 (33%)	7 (7%)	< 0.0001	21 (19%)	8 (7%)	0.0075
Subject Wrinkle Assessment	57 (57%)	31 (30%)	0.0001	50 (45%)	19 (18%)	< 0.0001

- Efficacy beyond the 6-month post-treatment time point has not been demonstrated. No studies have been conducted evaluating the effects of repeating the treatment cycle.

1.3 Safety

1.3.1 Safety Database

The safety database included all seven clinical trials. The follow-up times for safety differed among the trials.

- 862 subjects received at least one injection in all seven trials. Safety data up to twelve months were available in a total of 436 subjects (Studies IT-R-001, n=40; IT-R-002, n=158; IT-R-003A, n=123; IT-R-003B, n=115)
- Twelve-month safety updates by a phone questionnaire from Studies IT-R-005 and IT-R-006 included an overview of 12-month safety assessment of subjects (combined; n=350, 167 IT and 183 vehicle control).

The applicant also provided descriptive information from commercial experiences in the U.S. and the U.K.

1.3.2 Safety Analysis of Studies

- Six-month safety data from Studies IT-R-005 and IT-R-006 demonstrated the following:
 - a. Common adverse events consisted of local injection-site reactions observed in both IT-treatment and vehicle-control groups. The incidence was higher in the IT treatment group than in vehicle controls.
 - b. Local reactions included the following: erythema (20% in treatment vs. 12% in controls), swelling (12% vs. 8%), bruising (5% vs. 13%), hemorrhage (6% vs. 8%), and papules (3% vs. 2%). There were two cases of nodules in each of the treatment arms (1%), which resolved within 30 days.
 - c. Most (74%) of the adverse events resolved spontaneously within seven days. There were three adverse events adjacent to injection sites remaining unresolved by the end of six months. These were puffiness and swelling in IT-treatment subjects and one event of numbness in one vehicle-control subject.
 - d. One case of basal cell carcinoma adjacent to the injection site was diagnosed at six months after injection of IT in a 73 year-old white female.
- Based on review of the 12-month safety data obtained from a total of 350 subjects in studies IT-R-005 and IT-R-006 via a telephone questionnaire, two cases of remaining adverse events were resolved and no new adverse events were reported. There were no cases of keloid and no additional cases of local tumor formation.
- Integrated safety analysis of all seven clinical studies demonstrated a safety profile similar to that of the pivotal trials. Injection-site reactions were common adverse events, most of which resolved spontaneously within 30 days. One occurrence of local puffiness and swelling remained unresolved in one IT treatment subject in Study IT-R-003A.
- The numbers of non-whites, males, and elders (>65 years) in clinical trials were small and the safety of IT treatment in these subgroups cannot be determined based on these studies.
- Safety beyond the 12-month post-treatment time point has not been evaluated.

1.3.3 Proposed Dosing Regimen and Administration

Isolagen Therapy™ is available in a single dosage form of $1.0\text{-}2.0 \times 10^7$ cells/mL per 1.2 mL vial (sufficient to administer 1.0 mL). Up to 2 mL, administered as 0.1 mL per linear cm, are injected intradermally into the nasolabial fold area at each of three treatment sessions at 5-week intervals.

Patients must undergo three 3-mm punch post-auricular skin biopsies as specified by Isolagen in order to produce the autologous fibroblasts for IT Therapy.

The needle is introduced into the papillary dermis with the bevel up and the needle threaded gently but firmly along the same plane staying parallel to the skin surface using a threading technique. All study investigators were physicians; over 90% were board certified dermatologists.

1.3.4 Drug-Drug Interaction

No data provided

1.3.5 Special Populations

Pregnant Women

The product is not recommended for use by pregnant women and pregnant subjects were excluded from the clinical studies. There are no data concerning use of IT in pregnancy.

Pediatric Population

In accordance with the Pediatric Rule (21 CFR 314.55 (c) and 601.27 (c)), the sponsor requested a pediatric waiver in IND (b)(4), amendment 110, received by FDA on October 24, 2008. The sponsor's rationale was that nasolabial fold wrinkles only occurred in adults and that IT would not be indicated for treatment in the pediatric group. The review division found the sponsor's rationale for the pediatric waiver to be acceptable and recommended granting a pediatric waiver. A full pediatric waiver was approved by the FDA Pediatric Evaluation Regulation Committee (PeRC) on December 2, 2009.

There is no data available concerning the use of IT in pediatric patients in this BLA submission.

1.4 Issues Raised at the Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC)

The safety and biological activities of IT, injected intradermally, and the post-injection tissue responses have not been evaluated in animal studies or in human tissues. At the Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC) on October 9,

2009, committee members raised serious concerns about the lack of any *in vivo* information on the following issues

- Lack of information on the fate of injected cells. It is unknown if the injected cells are alive and how long the cells remain alive. If the cells are dead, do they cause local inflammatory reactions or granuloma formation?
- If the cells are alive, what are their biological functions? Do they over-produce collagens that could lead to scar formation? Do these cultured cells transform into abnormal cells?
- What are the acute and chronic responses from the surrounding tissues to the injected cells?

One key question to answer in the field of cellular therapies is how to track and monitor the cells *in vivo*; however current cell tracking technologies are not sufficient for these purposes. Histopathological evaluations of biopsied samples after IT injection may reveal valuable information regarding the function of injected cells and potential safety concerns. Some CTGTAC members recommended that *in vivo* histopathological studies be performed to provide *in vivo* information before approval.

In addition, the CTGTAC raised questions concerning the characterization and purification of the final product. A detailed CMC review captured all issues in this regard. The final product contains a trace amount of fetal bovine serum albumin (BSA) as an expected residual impurity. The immunological response to FBS has not been evaluated; no systemic immunological reactions have been reported following the intradermal injection of IT in subjects in the clinical trials. It is however unclear whether the formation of antibodies to FBS or the level of antibodies plays a role in the severity and duration of local adverse events following injection. *In vivo* evaluation of the immunological responses may also be valuable in guiding the repeated IT application.

1.5 Premarket Recommendations

Complete Response is recommended for this BLA application. The following clinical comments are included in the Complete Response (CR) letter:

- Your application does not include sufficient data to determine whether azficel-T is safe for use under the conditions suggested in the proposed labeling draft (21 CFR §314.125(b)(4)). We note that there is essentially no information regarding the bioactivities of azficel-T and tissue responses to azficel-T, aside from that derived from visual inspection of the skin. The lack of such information limits our assessment of the safety of azficel-T. We are particularly concerned about the potential for scarring and inflammatory reactions following azficel-T injection. Additional data are needed to address these concerns. Such data should come from a histopathological study on biopsied tissue samples from patients following injection of azficel-T. We strongly recommend that you discuss the study design with FDA prior to initiating the study.

- Shipping errors during clinical development resulted in re-biopsy of several study subjects. Such errors may adversely impact the safety and/or efficacy of your product. To decrease the risk of errors and ensure product quality, your Clinical Support Center Policies and Procedures must specify your policies, procedures, and activities with regard to the commercial handling of biopsies and re-biopsies, and how shipping and post-release sterility testing failures will be addressed. These policies, procedures, and activities must comply with 21 CFR 1271.290 and ensure that each patient receives a product that is derived from his/her own cells. Please revise your Clinical Support Center Policies and Procedures accordingly and submit the revised document for our review

1.6 Postmarket Recommendation

If Isolagen TherapyTM (IT) is approved, we strongly recommend a register study to address the issuers concerning the safety of IT application. The postmarket register study should address the long-term safety concern beyond 12 months, including

- Tumor formation of transplanted cells
- Hypertrophic scars/keloid/pigmentation changes both at injection site and the biopsy site, especially in non-Caucasian population
- The incidences of severe and long-lasting injection-related adverse events

In addition, we recommend that serum antibody to BSA be measured at different time points to collect data regarding immunologic responses to BSA. The levels of antibodies should be analyzed with the clinical presentation to identify whether antibody levels are correlated with the clinical outcomes

2. SINGIFICANT FINDINGS FROM OTHER DISCIPLINES

2.1 Chemistry Manufacturing and Controls (CMC)

IT consists of a suspension of autologous fibroblasts at a defined cell concentration in a proprietary isotonic medium. The active ingredient is autologous cultured fibroblasts. The autologous fibroblasts are cultured, using standard methodologies, from three 3-mm punch biopsies (dermal and epidermal layers) taken from a patient's post-auricular skin. Following *in vitro* expansion, the fibroblasts are harvested, quality control tests are performed, and the cell suspension are cryopreserved in vials at a defined cell concentration. Fibroblasts represent greater than 98% of the final product. When required for clinical use, a dose of cells is thawed, washed, formulated and shipped to the clinical site at 2 to 8°C by overnight delivery. The cells are administered intradermally in three separate treatment sessions, five weeks apart.

The mechanism of action of IT has not been demonstrated. However, testing of each lot to determine that the product consisted of viable fibroblasts that produce collagen is performed.

2.2 Animal Studies

No preclinical studies were conducted by the applicant with the clinical product, IT, or with an animal cellular analog in support of early or late-phase clinical trials. The applicant provided five published articles of various *in vitro* and *in vivo* preclinical studies that they consider applicable to the administration of IT for the treatment of nasolabial fold wrinkles.^{1,2, 3, 4,5} The fibroblasts used in these articles were of human and animal origin. The cell isolation procedure, culture condition, passage number, and formulation for each experiment described in the various publications were different from those used for IT. The fibroblasts were administered to immune competent animals (animal analog cells) and to immunodeficient mice (human cells). General conclusions that can be made from the publications include the following:

1. Doses of $5-8 \times 10^7$ fibroblasts subcutaneously injected in mice, rats, and rabbits were functional, as evidenced by synthesis of type I collagen and elastin.
2. The long-term *in vivo* survival of the injected fibroblasts in the different animal models varied, with autologous rat fibroblasts surviving up to eight months post-administration, autologous rabbit fibroblasts surviving at least five months, and xenogeneic human fibroblasts surviving at least two months in nude mice.
3. Following injection of human fibroblasts in combination with collagen in nude mice, 80-90% of human cells were present in the injection site on Day ten, and 25% were present at Week 9.
4. Although not explicitly evaluated, no apparent adverse findings in the animals were cited.

3. CLINICAL AND REGULATORY BACKGROUND

3.1 Health-Related Conditions and Available Interventions

IT is indicated for the treatment of nasolabial fold wrinkles that result from the natural aging process, and therefore is considered treatment of a cosmetic condition rather than treatment of a disease. The visible appearance of aging, especially facial wrinkles and folds, are common effects that patients seek to reduce.

¹ Remmler D, Thomas JR, Mazoujian G, Pentland A, Schechtman K, Favors S, Bauer E. Use of injectable cultured human fibroblasts for percutaneous tissue implantation. An experimental study. Arch Otolaryngol Head Neck Surg. 1986; 115(7):837-844.

² Keller G, Sebastian J, Lacombe U, Toft K, Lask G, Revazova E. Safety of injectable autologous human fibroblasts. Bull Exp Biol Med. 2000; Aug; 130(8):786-9.

³ Yoon E, Han SK, Kim WK. Advantages of the presence of living dermal fibroblasts within Restylane for soft tissue augmentation. Ann Plast Surg. 2003; 51(6):587-592.

⁴ Solakoglu S, Tiryaki T, Ciloglu, SE. The effect of cultured autologous fibroblasts on longevity of cross – linked hyaluronic acid used as a filler. Aesthetic Surg J. 2008; 28(4):412-426

⁵ Zhao Y, Wang J, Yan X, Li D, Xu J. Preliminary survival studies on autologous cultured skin fibroblasts transplantation by injection. Cell Transplant. 2008; 17(7):775-783.

Options for the treatment of facial lines, wrinkles and folds include surgery, neurotoxins, structural dermal fillers, lasers, non-ablative therapies, microdermabrasion and chemical peels.

3.2 Important Information from Pharmacologically Related Products

Carticel is an autologous cellular product manufactured by in vitro expansion of cartilage obtained during arthroscopy from a non-weight bearing area of the knee.

Carticel is indicated for the repair of symptomatic cartilage defects of the femoral condyle (medial, lateral or trochlea, caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure (e.g., debridement, microfracture, drilling/abrasion arthroplasty, or osteochondral allograft/autograft).

3.3 Commercial Experience

Table 2 summarizes the commercial experience in the United States and United Kingdom. No data were provided for the commercial activity in Australia. More than 9,000 subjects were exposed to the Isolagen product during this period; however, the safety data collection was retrospective and limited in sampling size, documentation, and follow-up.

Table 2. Safety Database from Commercial Experience

Country	Market Period	Subjects	Safety Data Collection (Subjects)	Relate Adverse Events Subjects/total
US	12/1995 to 2/1999	1,200 in 110 clinics	Retrospective study: 354 subjects in 23 clinics	35/354 (10%)
UK	2002 to 2007	>7,877	1. Electronic system (2004-2006): 28 adverse event reports 2. International Registry (2003): 2 AE reports from sampling of 59 subjects (total of 400 subjects)	1. Electronic system: 28/7877 (0.35%) 2. International Registry: 2/59 (3.4%)
Australia	2003 to 2004	No data provided in the submission		
Total	1995 to 2007	>9,077	441/9,077(5%)	

More than 1,000 subjects received IT injection mainly for facial wrinkles in the US prior to its regulation under IND. As shown in Table 3, a retrospective safety study, based on chart review, was done on a subset of 397 subjects from 23 clinics in the US. There were 354 subjects who received at least one injection and were used as the safety population in the analysis. A total of 35 product-related adverse events were identified and tabulated.

The common adverse events were injection-site reactions, such as injection site inflammation, edema, contour change, ecchymosis and erythema. Most adverse events were graded as mild or moderate, whereas two cases of injection-site edema were graded as severe. No detailed information was available. There were four blacks, two Asians, and three Hispanics who were documented in the study. No keloid or hypertrophic scars were documented.

Table 3. Adverse Events in a Retrospective Study in the US

Adverse Events	Subjects (%) N=354	Adverse Events	Subjects N=354
Injection site inflammation	14 (4%)	Dizziness	2 (0.6%)
Injection site edema	13 (3.7%)	Pain	1 (0.3%)
Skin contour change	7 (2%)	Injection site hemorrhage	1 (0.3%)
Ecchymosis	3 (0.8%)	Numbness of skin	1 (0.3%)
Erythema	3 (0.8%)	Allergic reaction	1 (0.3%)
Rash	3 (0.8%)	Infection	1 (0.3%)
Urticaria	2 (0.5%)	Scarring	1 (0.3%)
Herpes simplex	2 (0.6%)	Acne	1 (0.3%)
Source: Module 5, Volume 66, Section 5.3.5.4 , page: 30/37			

From 2002 to 2007, in the UK, more than 7,000 subjects received IT injection mainly for facial wrinkles. In the UK, larger doses were used as compared to US experience. Each treatment of 3 mL containing $1-3.5 \times 10^7$ cells/mL was administered throughout the entire face for up to six treatments. The available safety data were derived from an electronic system instituted in late 2004, which was designed to monitor customer service and sales; a few AEs were documented. Of the 28 product-related adverse events, injection-site redness, swelling, and lumps were the most common. All the AEs resolved over a period of a few days to five months, as shown in Table 4.

Table 4. Adverse Events in the UK Commercial Experience

Adverse Events	Subjects	AE Duration
Injection site redness and swelling	9	4 days to 4 months
Injection site lump	5	5 days to 5 months
Injection site papules and acne	3	1 to 3 months
Injection site reaction	2	Several days
Angioedema	1	1 week
Anaphylaxis	1	7 days to several months
Injection site inflammation	1	12 days
Source: Module 5, Volume 66, Section 5.3.5.4, page: 12/37		

Table 5 lists three serious adverse events that were reported in the UK; two subjects had systemic allergic reaction with angioedema and respiratory distress; and one subject had a lump on the eyelid showing "fibrous overgrowth" in the biopsy and requiring surgical removal. The sponsor listed several possible contributing factors for these allergic reactions: -----(b)(4)----- used prior to November 2005 and residual -----(b)(4)----- used in the final freeze medium prior to July 2006.

Table 5. Three Serious Adverse Events - Reported in the UK Commercial Experience

Serious Adverse Events	Onset	Duration	Allergy	Medical History	Action
Severe swelling and itching followed 7 days later by throat restriction	Immediately post-injection	Injection-site redness for several months	Latex and lidocaine	N/A	Antibiotics and steroids
Full face swelling and redness (possible angioedema)	3 days post-injection	1 week	Asthma and atopy	Asthma and atopy	Steroids and antihistamine
Injection site lumps (injected into scar and granuloma on eyelid), bx: "fibrous overgrowth"	2-3 weeks post-injection	2-3 months	N/A	old scar with possible retained suture material in injection site	Surgical removal of lumps
Source: Module 5, Volume 66, Section 5.3.5.4 , Table 2, page 13 of 37					

Reviewer Comment: Although the safety population is large in the commercial phase with more than 9,000 subjects exposed to the Isolagen product, adverse event reporting and documentation are limited to a retrospective study based on chart review of 30% of subjects in the US and a commercial data registry in the UK, with 28 adverse events documented out of 7,000 subjects. However, the safety data that provided from both sources are valuable for the product as the safety data under IND. The adverse events that were reported from the US experience are similar to the current finding in the IND; in contrast, the UK data showed a more severe and longer-lasting AE profile. Factors such as larger dose, more injection areas, more repeated injections, and product impurity may contribute to the safety profile in the UK and need to be avoided in the application of the product in the future.

3.4 Regulatory Background Information

Autologous fibroblasts were initially evaluated for treatment of contour deformities by William K. Boss, M.D., Vice Chairman of the Department of Plastic Surgery at Hackensack University Medical Center. Autologous fibroblasts have been manufactured commercially and marketed in the United States (US) as a cosmetic treatment for wrinkles, burns, and facial contour deformities since 1992. Over 1,000 patients were treated in the US, and over 7,000 patients were treated in the United Kingdom (UK) and Australia prior to FDA's regulation of somatic cell therapies in the US.

In compliance with FDA's regulation of somatic cell therapies and the requirement to file

Investigational New Drug Applications (IND) and follow a formal approval process, clinical trials were initiated for the autologous product in 2003 under IND (b)(4). Seven clinical protocols have been conducted under this IND. To date, three Phase 2 studies (IT-R-001, IT-R-002 and IT-R-007) and four Phase 3 studies (IT-R-003A, IT-R-003B, IT-R-005 and IT-R-006) have been conducted. On October 12, 2006, the FDA approved a Special Protocol Assessment (SPA) for pivotal studies IT-R-005 and IT-R-006. These two Phase 3 studies were conducted under identical clinical protocols. The clinical regulatory history of IT is summarized below:

Isolagen Therapy™(IT): History of Clinical Regulatory Activities for IND (b)(4)

Date	Regulatory Activities
AUG 6, 1997	Isolagen manufacturing facility in New Jersey inspected to determine its activities and informed that an IND was required
JAN 27, 1999	Press release advertising Isolagen, stating that the product was not subject to FDA regulation
JAN 29, 1999	Isolagen requested to halt shipment until an IND is authorized by FDA
MAR 30, 1999	Pre-IND meeting - Isolagen indicated product shipment had ended
APR 20, 1999	Directed inspection - Isolagen continued to ship product
MAY 5, 1999	FDA letter sent, denying further treatment of patients
OCT 12, 1999	Submission of IND
DEC 9, 1999	Hold letter - IND placed on hold due to CMC for inadequate safety testing of the product. FDA's additional comments: <ul style="list-style-type: none"> • Separate INDs for treatments of rhytids and scars • Randomized, controlled, use of third-party blinded assessors • Efficacy for at least one year with magnitude of 75% • Efficacy of re-treatment Stated in informed consent (IC) form and investigator's brochure (IB) "no animal studies were conducted to study the toxicology"
APR 5, 2002	Complete Response to Clinical Hold Manufacturing facility now located in Houston, Texas
MAY 3, 2002	Clinical Hold lifted
JAN 3, 2003	Isolagen phase 2 study IT-R-001 began – "A double blind, randomized and placebo-controlled study of IT treatment of rhytids" (N=40)
APR 9, 2003	Meeting with FDA: to refine the clinical assessments for a pivotal study. Use of safety data from US and UK to support licensure depended on the data quality <ul style="list-style-type: none"> • Efficacy data from the US and UK will have limited usefulness because they were not blinded • Efficacy endpoints – <ul style="list-style-type: none"> ○ Co-primary endpoints ○ Lempere scale <ul style="list-style-type: none"> ▪ Concerns on intra- and inter-observer variability; Suggestion: to rate 100 photos twice ○ Isolagen should pre-determine the success rate • Training provided by Isolagen – for FDA review • Stratify subjects - age, gender, and ethnicity

Date	Regulatory Activities
JUNE 24, 2003	Isolagen submitted protocol for Phase 3 Study IT-R-002 – “A Phase III, double blind, randomized and placebo-controlled study of IT injection for treatment of contour deformities” (N= 151)
AUG 12, 2003	FDA informed Isolagen that IT-R-002 was insufficiently designed for a phase 3 trial. The study’s protocol contained multiple deficiencies, and did not contain information critical to assess the study’s procedural methodology. Enrollment in IT-R-002 had already been completed (N=151)
OCT 28, 2003	FDA informed Isolagen that results from Study IT-R-002 will be considered exploratory only, and was insufficient to support licensure.
DEC 18, 2003	<p>Pre-phase 3 meeting to discuss phase 2 data and phase 3 design. FDA informed Isolagen that Study IT-R-002 did not provide definitive safety and efficacy data and should begin designing other phase 3 studies that address these requirements. The sponsor was encouraged to submit these phase 3 protocols as SPA requests.</p> <ul style="list-style-type: none"> • IT-R- 001: (still blinded) - dose-determining study • IT-R-002 was insufficient to provide substantial evidence of efficacy due to deficiencies in the Statistical Analysis Plan (SAP) • At least two definitive studies demonstrating safety and efficacy would be required for approval <p>Sponsor was encouraged to re-evaluate the use of the 7-point photoguide system developed by Isolagen</p>
MAY 21, 2004	<p>Isolagen submitted protocol for phase 3 study IT-R-003A/B – A phase III, double-blind, randomized, placebo-controlled study of Isolagen injection for treatment of contour deformities. (N = 213)</p> <p>Letter: Phase 3 (003) protocol for SPA</p> <ul style="list-style-type: none"> • Adequate design to address the safety and efficacy to support a license • Agreed on the use of 2-point change on the 6-point validated photoguide (Lemperle); published data support its clinical utility
MAY 9, 2005	Type C meeting with DMPQ to discuss construction plans for a new commercial manufacturing facility in Exton, PA.
AUG 1, 2005	Isolagen reported that preliminary results from IT-R-003 A/B did not meet all of the primary endpoints and had failed to demonstrate statistical significance.
DEC 20, 2005	Isolagen implemented changes to the manufacturing process and changed location of manufacturing facility to Exton, PA. Isolagen planned multiple phases of comparability testing to demonstrate the equivalence of the new IT manufacturing process to the original Houston process.
JUN 9, 2006	Teleconference to discuss the Agency’s review of submitted CMC information related to the Exton manufacturing process.
JUN 2006	SPA for two identical phase 3 studies, 005/006 (N=400), submitted. SPA was withdrawn by sponsor due to numerous inconsistencies in the protocol and the SPA request
AUG 21, 2006	<p>SPA request for protocols IT-R-005 and IT-R-006 re-submitted in Amendment#72 – “A Phase III Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial of the Efficacy and Safety of IT in the Treatment of Nasolabial Fold Wrinkles” (N=400)</p> <p>Key SPA agreements:</p> <ul style="list-style-type: none"> • FDA response to applicant’s question regarding labeling claims: FDA cannot agree to labeling claims prior to review of trial data • FDA agreed that the co-primary endpoints as defined in the protocol were adequate to demonstrate a clinical response. • The Statistical Analysis Plan (SAP) was adequate; power calculation was also acceptable. However, the study may be under-powered if the effect size is substantially smaller than expected. FDA recommended incorporating a pre-specified interim analysis at 6 months or earlier, along with a plan to increase the size of the study if necessary.

Date	Regulatory Activities
	<ul style="list-style-type: none"> • Design is adequate to maintain blind if stated procedures were adequately implemented. Blinding will be determined in the review of the trials. • FDA agreed that the training instruction for the use of the product was adequate if properly implemented. The adequacy will be determined in the review of the trials • Regarding the additional of the safety database from an ongoing trial in the UK, the ability of the data to support safety depended on the nature of the study, the quality of the conduct of the trial, etc. • Additional FDA comments: <ul style="list-style-type: none"> ◦ FDA requested revisions to the Investigator's Brochure (IB) to include updated AEs from the UK studies ◦ FDA recommended inclusion of racial subgroups in study subject selection and analysis plan in order to draw conclusions from the safety and efficacy data
OCT 12, 2006	<p>Letter: Agency approved SPA protocols IT-R-005 and IT-R-006</p> <ul style="list-style-type: none"> • Agreed with the co-primary endpoints • Agreed with 6-month duration for efficacy study • Data from the US and UK commercial experience might be supportive for safety but not for efficacy
DEC 21, 2006	<p>New Protocol: IT-R-007 – “A Phase II Open Label, Multicenter, Trial of the Safety and Efficacy of Isolagen Therapy in the Treatment of Facial Wrinkles and Creases” (N = 50)</p> <p>Main objective: to demonstrate the efficacy of <u>two</u> treatments of IT compared to placebo control 6 months following study treatment 2.</p>
MAR 18, 2008	<p>Letter:</p> <ul style="list-style-type: none"> • Photos taken of all subjects • Subject assessment performed prior to Evaluator assessment
JUN 17, 2008	<p>Final Statistical Analysis Plan (SAP) for IT-R-005 and IT-R-006 submitted</p>
JULY 18, 2008	<p>Teleconference: addition of a modified intent-to-treat (MITT) population in data analyses was agreed upon with the FDA</p>
NOV 3, 2008	<p>Pre-BLA meeting</p>
NOV 13, 2008	<p>Isolagen submits Standardized Manufacturing Process Validation Protocol</p>
NOV 26, 2008	<p>Letter: Pre-BLA meeting</p> <ul style="list-style-type: none"> • Data from 005 and 006 were adequate to support a BLA • Safety data base to contain all 7 trials • Case report forms of 03A, 03B, 05 and 06; CRF of all on 01, 07, 02 that have SAEs or did not complete the study • Information on biopsy
MAR 6, 2009	<p>BLA submitted</p> <p>Currently in FDA review:</p> <ul style="list-style-type: none"> ▪ Mid-cycle review on August 13, 2009 ▪ Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC) meeting on October 9, 2009 ▪ Action due date January 4, 2010
SEPT 24, 2009	<p>Sponsor name changed from Isolagen to Fibrocell, effective 9/16/2009 (BLA Amendment#15)</p>
NOV 1, 2009	<p>Sponsor formally submitted long-term clinical study reports for Studies IT-R-05, IT-R-06, and IT-R-07 (BLA Amendment#21)</p>

4. CLINICAL DATA SOURCE, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Material Reviewed

The BLA application includes study reports of seven clinical trials (Table 6). The efficacy data to support this BLA submission are derived from two Phase 3 studies, IT-R-005 and IT-R-006. The two studies, conducted under identical protocols, were six-month, double-blind, randomized, vehicle-controlled trials in adults with moderate to severe nasolabial fold wrinkles. The safety data in this submission are derived from Studies IT-R-005 and IT-R-006 and five additional studies. These clinical studies are summarized in the Table 6 below.

All seven clinical trials were designed with an acute study phase and long-term study phase, and each of the study phases was summarized in a clinical study report. There are seven acute clinical study reports and seven long-term clinical study reports. However, long-term study reports for Studies 005, 006, and 007 were not available at the time of the original BLA submission. On September 4, 2009, the applicant submitted the preliminary long-term 12-month safety data for Studies 005 and 006 via email. On November 1, 2009, the applicant submitted Amendment 21 that include long-term clinical study reports for Studies IT-R-005, IT-R-006, and IT-R-007.

In addition, more than 9,000 subjects were exposed to the Isolagen product in a commercial phase prior to FDA regulation of cellular product. A summary of commercial experience in the US and UK was provided in Section 3.3. The safety data were mainly provided in two studies: (1) a retrospective study on 354 subjects who received at least one Isolagen injection in US commercial experience out of 1,200 exposed subjects; (2) an electronic system to monitor customer service, sales, product logistics and adverse events: 28 AE reports out of 7,800 subjects registered.

(See Appendix B for the complete list of documents reviewed)

4.2 Summary of Clinical Studies

Table 6. Summary of Clinical Studies

Study ID	Type of Study	Subjects enrolled (IT/control)	Study Length	Indication	Dose Range, Frequency of Exposure, # Facial Regions
IT-R-001	Phase 2, Randomized, double-blind, vehicle-controlled, parallel	40/0	Acute Phase: 1/3/03-2/20/04 Long-term: 1/3/03-6/3/05	Facial rhytids	0.5, 1.0, & 2.0 x 10 ⁷ cells/mL 0.1 mL/linear cm up to 1.0 ml, Every 1-2 weeks for 3 treatments 14 facial regions
IT-OR-002	Phase 2, Randomized, double-blind, vehicle-controlled, parallel	158 (116/42)	Acute phase: 5/19/03-6/3/05 Long-term: 5/19/03-6/10/05	Contour deformities	2.0 x 10 ⁷ cells/mL 0.1 mL/linear cm up to 2.0 ml, Every 2 weeks for 3 treatments 14 facial regions

Study ID	Type of Study	Subjects enrolled (IT/control)	Study Length	Indication	Dose Range, Frequency of Exposure, # Facial Regions
IT-R003A	Phase 3, Randomized, double-blind, vehicle-controlled, parallel	123 (61/62)	Acute Phase: 7/20/04-5/19/05 Long-term: 7/20/04-12/8/05	Contour deformities	2.0×10^7 cells/mL 0.1 mL/linear cm up to 1.0 ml, Every 1-2 weeks for 3 treatments 4 facial regions
IT-R-003B	Phase 3, Randomized, double-blind, vehicle-controlled, parallel	115 (58/57)	Acute Phase: 7/21/04-5/16/05 Long-term: 7/21/04-11/28/05	Contour deformities	2.0×10^7 cells/mL, 0.1 mL /linear cm up to 1.0 ml Every 1-2 weeks for 3 treatments 4 facial regions
IT-R-005	Pivotal, Randomized, double-blind, vehicle-controlled, parallel	203 (100/103)	Acute Phase: 10/23/06-6/26/08 Long-term: 8/14/07-10/27/09	Nasolabial fold wrinkles	$1.0-2.0 \times 10^7$ cells/mL 0.1 mL/linear cm up to 2.0 ml Every 5 weeks for 3 treatments 2 facial regions
IT-R-006	Pivotal, Randomized, double-blind, vehicle-controlled, parallel	218 (110/108)	Acute Phase: 11/1/06-6/9/08 Long-term: 5/31/07-10/27/09	Nasolabial fold wrinkles	$1.0-2.0 \times 10^7$ cells/mL 0.1 mL /linear cm up to 2.0 ml Every 5 weeks for 3 treatments 2 facial regions
IT-R-007	Phase 2, Multicenter, open-label, uncontrolled	50	Acute Phase: 3/22/07-6/23/08 Long-term: 6/23/08-10/27/09	Facial wrinkles and creases	$1.0-2.0 \times 10^7$ cells/mL 0.5 mL /linear cm up to 6.0 ml Every 5 weeks for 2 treatments 8 facial regions

Data of 857 ITT subjects from the seven (7) clinical studies have been reviewed for safety. Data of 421 ITT subjectss from the IT-R-005 and IT-R-006 studies have been used for the efficacy analysis. Intent-to-treat (ITT) is defined as all subjects who have been randomized regardless of whether they have received study injection (IT or vehicle-control) or not.

4.3 Review Strategy

Results from two randomized, double-blind, placebo-controlled Phase 3 Studies, IT-R-005 and IT-R-006, as well as summaries of additional preclinical, Phase 2 and Phase 3 studies were submitted in support of this BLA. The efficacy review of the BLA was primarily based on separate reviews of the data from Study IT-R-005 and Study IT-R-006. The safety review included analysis of the datasets supplied by the sponsor and was based on the safety dataset from Studies 005 and 006, earlier phase clinical studies, and was supplemented by previous commercial experience prior to FDA regulation of cellular products. The dataset was reviewed for potential study conduct issues such as eligibility, blinding, response assessment, imbalance between arms, dropout rates and missing data, protocol deviations, and efficacy and safety results across subgroups. In general, 20% of the Case Report Forms (CRFs) were reviewed. In some instances, all CRFs for particular

sites were reviewed when indicated. The sponsor's analyses were reproduced and additional FDA statistical analyses were performed using these datasets. The data provided on the CRFs were also assessed for recording accuracy and adherence to protocol stipulations by the FDA Bioresearch Monitoring (BiMO) review process and site inspections that were conducted at five selected study sites.

4.4 Good Clinical Practice and Data Integrity

The clinical studies were conducted according to Good Clinical Practice (GCP). The BiMO Branch of the Division of Inspections and Surveillance, Office of Compliance and Biologics Quality performed investigator and site inspections in support of this BLA. Pivotal study protocols, subject enrollment, geographic distribution, and serious adverse events were among the factors used to select the inspection sites.

Reviewer Comments:

1. *Withheld per Privacy Act*
2. *Withheld per Privacy Act*

4.5 Financial Disclosures

Certification of financial disclosure (Form 3454) was provided by the sponsor. The applicant certified that as the sponsor of the submitted studies, the applicant has not entered into any financial arrangement with the clinical investigators listed whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

Reviewer Comment: All investigators and sub-investigators for Study IT-R-005 and Study IT-R-006 have been declared by the applicant to have no financial agreements requiring disclosure, except for two investigators in Study IT-R-005 (sites 5300 and 5600) and one investigator in Study IT-R-006 (site 6600). Statements explaining the nature of the financial ties for these three investigators were submitted in the BLA. Analyses, particularly of the success rates in the Evaluator Wrinkle Severity Assessment, were performed to assess the impact of the sites involved on the efficacy assessments. The success rates for IT remained statistically superior to vehicle-control for Study 005 when sites 5300 and 5600 were deleted. The success rates for IT also remained statistically

superior to vehicle-control for Study IT-R-006 when site 6600 was deleted (See Section 6.5 of this review).

5. DESIGNS OF CLINICAL STUDIES

5.1 Studies IT-R-005 and IT-R-006

Studies IT-R-005 and IT-R-006 were prospective, multicenter, randomized (1:1), double-blind, vehicle-controlled, Phase 3 studies of the efficacy and safety of IT. The two studies were identically designed. Eligible subjects were adults with bilateral moderate to severe nasolabial fold wrinkles. Subjects were treated with either IT or vehicle-control in three separate treatment sessions at five-week intervals. The primary evaluation of efficacy was based on response assessment performed at Visit 6 that took place at month 6 following the last treatment injection. The acute period of observation in the study ended at the completion of Visit 6. The primary evaluation phases of the studies were conducted from October 23, 2006 to June 26, 2008 at seven US sites (IT-R-005) and from November 1, 2006 to June 9, 2008 at six U.S. sites (IT-R-006). The long-term safety evaluation was performed at 12 months by a telephone questionnaire.

The scale used for the Subject Wrinkle Assessment was based on the 5-point global wrinkle assessment scale, published by Cohen and Holmes.⁶ In the trial described in this article, the wrinkle grading scale was used by subjects to evaluate a collagen wrinkle filler. Subject assessment of satisfaction was recorded using the following scale: 1=very satisfied, 2=satisfied, 3=somewhat satisfied, 4=dissatisfied, and 5=very dissatisfied. These grading categories were similar to the Subject Wrinkle Assessment scale used in studies IT-R-005 and IT-R-006.

In Studies IT-R-005 and IT-R-006, subjects conducted a live comprehensive assessment of the wrinkles of the lower part of the face, first smiling and then at rest. Subjects were instructed to select one grade that best described their current feeling about the wrinkles on both sides of the lower part of the face. The 5-point scale was graded in response to the question, “How do you feel about the wrinkles in the lower part of your face today?” Subjects self-administered all assessments prior to evaluator assessment or study treatment. The grading categories were: -2 = very dissatisfied, -1 = dissatisfied, 0 = somewhat satisfied, +1 = satisfied, and +2 = very satisfied.

The Evaluator Wrinkle Severity Assessment was used with a photoguide to evaluate subjects’ severity of the bilateral nasolabial fold wrinkles on each side of the face in Studies 005 and 006. The scale was based on the Wrinkle Assessment Scale, published by Lemperle.^{7,8} In this article⁷, the Wrinkle Assessment Scale was examined as a

⁶ Cohen, S.R.; Holmes, R.E. Artecoll: A Long-Lasting Injectable Wrinkle Filler Material: Report of a Controlled, Randomized, Multicenter Clinical Trial of 251 Subjects. *Plast. Reconstr. Surg.* 2004, 114: 964.

⁷ Lemperle, G.; Holmes, R.E.; Cohen, S.R.; Lemperle, S.M. A Classification of Facial Wrinkles. *Plast. Reconstr. Surg.* 2001, 108: 1735-1750.

reference scale to enable clinicians to reliably classify deep facial wrinkles and folds. The correlation of the grade of wrinkles, classified from 0 to 5, with live judgment of wrinkles by evaluators was studied in 2 trials; both showed a significant correlation of 87% between subjective ratings and objective wrinkle depth measurement. For Studies IT-R-005 and IT-R-006, the 6-point ordinal scale had the following grading categories: 0= no wrinkle visible, 1= just perceptible, 2= shallow, 3= moderately deep, 4= deep and 5=very deep; and was used with a photoguide that showed a photographic example of each of the six wrinkle severity grading categories (see photoguide in Appendix C). Evaluators were trained in the assessment technique and were deemed by the Isolagen Medical Monitor to be competent.

5.1.1 Primary Endpoints

For efficacy evaluation in Studies 005 and 006, each study was declared as a success if IT was shown to be statistically superior to control with respect to each of the co-primary endpoints. The co-primary endpoints were the percentage of subjects who had at least a 2-point improvement from baseline to 6 months in the Evaluator Wrinkle Severity Assessment and in the Subject Wrinkle Assessment. Both primary endpoints must be statistically significant in the primary efficacy analysis for a successful trial.

Efficacy

Co-Primary Endpoints

- Subject Wrinkle Assessment: The subject's live comprehensive assessment of the wrinkles of the lower part of the face at Visit 6, using a 5-point wrinkle satisfaction scale with a response defined as a two-point or better increase in satisfaction compared to baseline
- Evaluator Wrinkle Severity Assessment: The blinded evaluator live assessment of each of the bilateral nasolabial fold wrinkles at rest, at Visit 6, using a 6-point ordinal wrinkle severity scale with a photoguide, with a response defined as a two-point or better reduction in severity compared to baseline

Safety

- Primary Safety Objective: To assess the safety of IT, given in three separate treatment sessions five weeks apart

5.1.2 Secondary Efficacy Endpoints

⁸ Lemperle, G et al. Avoiding and treating dermal filler complications. *Plast Reconstr Surg* 2006. 118(3 Suppl): 92S-107S.

1. Subject Wrinkle Satisfaction Assessment at Visits 3, 4, and 5, using a 5-point wrinkle satisfaction scale, where a response was defined as a 2-point or better improvement compared to baseline
2. Evaluator Wrinkle Severity Assessment at Visits 3, 4, and 5, using a 6-point wrinkle severity scale with a photoguide, where a response was defined as a 2-point or better decrease in wrinkle severity on both sides of the face compared to baseline
3. Subject Improvement Assessment performed at 6 months post-treatment, with a response defined as a 1-point or better improvement comparing baseline photo to photos taken at Visits 3, 4, 5, and 6
4. Evaluator Improvement Assessment performed at 6 months post-treatment, with a response defined as a 1-point or better improvement comparing baseline photo to photos taken at Visits 3, 4, 5, and 6

5.1.3 Key Eligibility Criteria

Inclusion

- ≥ 18 years old
- Subject requests cosmetic improvement of both nasolabial fold wrinkles and assesses the wrinkles of the lower part of the face as dissatisfied (-1) or very dissatisfied (-2)
- Bilateral nasolabial fold wrinkles with severities of \geq Grade 3 by the evaluator using a 6-point ordinal scale with a photoguide
- Non-scarred skin for biopsy on at least one side in the post-auricular space
- Expectations of possible benefit of IT treatment have been explained and subject indicates understanding that severe wrinkles may improve but may not disappear with IT, and that wrinkles will not immediately disappear, unlike filler therapy.

Exclusion

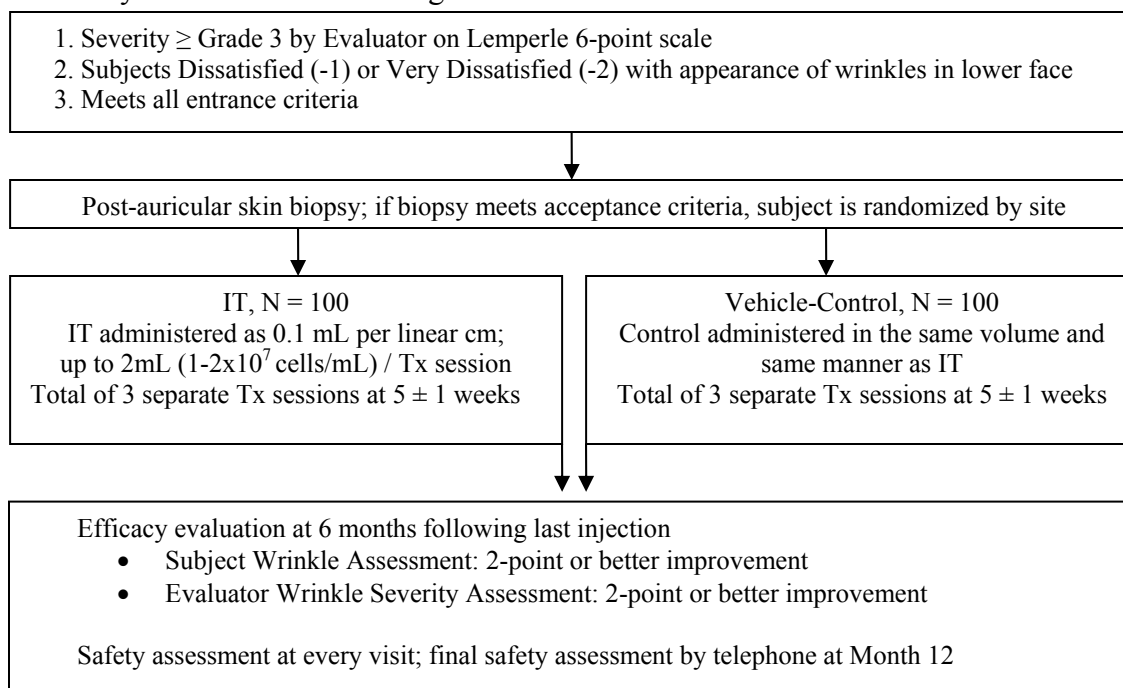
- Total treatment area > 20 cm in length
- Skin conditions that interfere with nasolabial fold wrinkle assessment/treatment (excessive dermatochalasis, inability to lessen the nasolabial fold wrinkles by physically spreading the area apart)
- Active or chronic skin diseases, including, but not limited to psoriasis, eczema, rosacea, blistering skin disease or local infection
- Excessive exposure to the sun, such as jobs requiring constant outdoor exposure
- Diagnosis of cancer, unless treated or in remission, with the exception of basal cell carcinoma which remains excluded
- Known genetic disorders affecting fibroblasts or collagen, such as achondroplasia, osteogenesis imperfecta, etc.
- Active systemic infection
- Requires chronic antibiotics or steroidal therapy
- Pregnant or lactating women
- Facial surgery in the lower 2/3 of the face or semi-permanent dermal fillers within 1 year prior to study enrollment

- Use of retinoic acid, microdermabrasion, Rx glycolic acid or similar treatment within 30 days prior to study enrollment
- Previous treatment with IT (vehicle-control is not excluded)
- Known allergy to collagen fillers, other bovine products, gentamicin, amphotericin B

Subjects were randomized following eligibility determination and were assigned to receive either IT or vehicle-control at three treatment sessions at 5 ± 1 week intervals. The vehicle-control was provided in the same volume as active product (2 vials of 1.2 mL). Both IT and vehicle-control have identical labeling and were packed, shipped, and stored under the same conditions. The study schema is shown in Figure 1.

5.1.4 Study Schema

The study schema is shown in Figure 1.



5.1.5 Observation Period

The total observation period was twelve months following the last treatment injection. The acute phase of the study ended six months (Visit 6) following the last injection. A twelve-month telephone assessment of adverse events was conducted for all subjects enrolled in these two studies. The study schedule is shown in Table 7.

Table 7. Study Schedule of Events

Procedure/Assessment	Screening	Baseline/ Biopsy	Visits						
			1	2	3	4	5	6	12-Mo
Eligibility	X	X							
Med Hx/Physical/Labs	X							X	
Subject Wrinkle Assessment	X	X			X	X	X	X	

Procedure/Assessment	Screening	Baseline/ Biopsy	Visits						
			1	2	3	4	5	6	12-Mo
Evaluator Wrinkle Severity Assessment	X	X			X	X	X	X	
Subject Improvement Assessment								X	
Evaluator Improvement Assessment								X	
Photograph		X			X	X	X	X	
Biopsy		X							
Randomization		X							
Study Treatment			X	X	X				
Adverse Events (AEs)		X	X	X	X	X	X	X	X
Concomitant Meds	X	X	X	X	X	X	X	X	
Concomitant Procedures	X	X	X	X	X	X	X	X	
Subject Blinding Assessment Postcard (to assess masking)			X	X	X				
Evaluator Blinding Assessment Postcards (to assess masking)					X	X	X		
<ul style="list-style-type: none"> Treatments were administered at Visit 1, Visit 2 and Visit 3. The time period between treatment visits was 5 ± 1 weeks. Visit 4 took place 2 months after Visit 3; Visit 5 took place 4 months after Visit 3; Visit 6 took place 6 months after Visit 3. The study was unblinded after Visit 6, the acute phase of the study, was completed. 									

5.1.6 Randomization Procedure

Prior to the start of the study, the randomization list was prepared and finalized by the Isolagen statistical group and provided to Isolagen Quality Assurance (QA). Once a biopsy was determined by Isolagen Quality Control to be acceptable, Isolagen QA representatives then randomized the subject to the next randomization slot on the site's list according to treatment assignment. Subjects were randomized by site, sequentially, as their biopsies were accepted. The sponsor's randomization procedure utilized a randomization block scheme and was stratified by study site. Subjects were randomized in a 1:1 treatment to vehicle-control ratio within each site.

5.1.7 Re-Biopsy/Manufacturing Failure

Re-Biopsy:

Acceptance of biopsies by Isolagen was determined according to pre-specified criteria. Subjects with unacceptable initial biopsies were not randomized and study sites were notified that re-biopsy was necessary. A total of two biopsies per subject were permitted prior to randomization. Criteria exceptions to this rule, such as forms not filled out correctly, may be allowed per Isolagen's Biopsy Acceptance protocol. Results of re-biopsies due to unacceptable initial biopsies by sites are shown in Table 8.

Table 8. Subject Re-Biopsied Due to Unacceptable Initial Biopsy

Study Site	Enrolled	Biopsied	Biopsy Unacceptable	Re-Biopsied	Reason for Re-Biopsy
------------	----------	----------	---------------------	-------------	----------------------

Study Site	Enrolled	Biopsied	Biopsy Unacceptable	Re-Biopsied	Reason for Re-Biopsy
5100	56	49	3	3	All 3 due to shipping error
5200	21	21	0		
5300	42	41	0		
5400	15	15	0		
5500	19	19	3	3	All 3 due to shipping error
5600	44	43	0		
5700	15	15	0		
6100	36	36	1	1	Vial not labeled
6200	29	29	0		
6300	44	44	1	1	Shipping error
6400	35	35	0		
6500	37	35	0		
6600	40	39	0		

The reasons for the shipping errors are further detailed in Table 9 below.

Table 9. Reasons for Unacceptable Biopsy that Required Re-Biopsy

Subject	Reason for Re-biopsy
-(b)(6)-	Shipping Error*
-(b)(6)-	Shipping Error*
-(b)(6)-	Shipping Error*
-(b)(6)-	Shipping Error*
-(b)(6)-	Shipping Error*
-(b)(6)-	Shipping Error*
-(b)(6)-	Vial not Labeled
-(b)(6)-	Shipping Error*
*Shipping Error: Biopsies must be received within a specified timeframe per Standard Operating Procedure (SOP); for these subjects, the timeframe for receipt of the biopsy material was exceeded so re-biopsy was necessary.	

Manufacturing Failure:

Since skin biopsy was necessary to grow cells for IT treatment, subjects were paired (IT and vehicle-control) to be withdrawn if the manufacturing process could not produce any IT or insufficient IT for all three treatments for subjects assigned to the IT group. As only biopsies from subjects who undergo active treatment were processed, Isolagen devised a procedure for selection of vehicle-group subjects to undergo a sham biopsy in the event of re-biopsies of actively treated subjects.

There were two types of IT manufacturing failures: no products produced and insufficient products. The manufacturing failure rates are shown in Table 10. The total IT manufacturing failure rate for Studies 005 and 006 was 11% (24/210). The total rate for not producing any IT product was approximately 6% (13/210). The total rate for producing an insufficient amount of IT was about 5% (11/210).

Table 10. Manufacturing Failure Rates for Studies 005 and 006

Type of Failure	IT-R-005 N=203		IT-R-006 N=218	
	IT n=100	Control n=103	IT n=110	Control n=108
No product produced, Total	5 (5%)	1 (1%)	8 (7%)	4 (4%)
Insufficient product, Total:	3 (3%)	0	8 (7%)	1 (1%)
• Enough for 1 treatment only	1 (1%)	0	4 (4%)	0
• Enough for 2 treatments only	2 (2%)	0	4 (4%)	1 (1%)

Manufacturing Timeline:

The time interval between baseline/biopsy and the first treatment injection at Visit 1 was approximately 90 days. Results of the biopsy/first treatment timeline are shown in Table 11.

Table 11. Interval (in days) between Baseline/Biopsy and Visit 1 for Studies 005 and 006

Study	Summary (in days)	IT	Vehicle-Control
IT-R-005	n	83	92
	Mean (SD)	123.9 (43.8)	116.9 (47.6)
	Min –Max	69 – 274	62 – 286
IT-R-006	n	98	99
	Mean (SD.)	117.9 (55.3)	108.5 (45.8)
	Min –Max	64 – 281	63 – 278

(Calculations are based on re-biopsy dates if the original biopsy did not meet the quality control prior to randomization)

Reviewer Comments:

1. *Biopsies for subjects randomized to vehicle-control were not processed; therefore no products were manufactured for subjects in the control group.*
2. *An IT/control pairing procedure to maintain randomization and study blind for manufacturing failure was initially used, but was later modified, which accounted for an imbalance in the manufacturing failure rates for IT vs. control.*
3. *Although subgroup analyses for smokers vs. nonsmokers were not performed, published articles have reported increased failure rates for cell expansion in cell transplantation in patients who used tobacco, as reported by Johnen, et al., in 2006 (Burns 32(2):194-200).*

5.1.8 Blinding Procedure

The studies were designed as double-blind studies. To help maintain the blind, the evaluator who assessed the subject for wrinkle severity could not be the injector for that subject, and the evaluator for each subject was constant. Maintenance of the study blind by injectors was accomplished by training investigators on how to handle subjects during treatment, and injectors were prohibited from discussing subjects with other study staff members. The injector could not be the evaluator for any given subject, and the injector

for each subject was constant. Both evaluators and injectors were instructed not to discuss patients' wrinkle severity or treatment assignment at any time. As an additional safeguard in maintaining the blind, adverse events were reported to the injectors, not the evaluators, when these events had to be reported to a physician.

Unblinding Procedure:

The study remained blinded until all subjects completed their 6-month visits and all data queries were resolved and locked prior to authorization of unblinding by the sponsor. A final open-label long-term safety assessment was conducted by telephone at 12 months following the last treatment injection.

Reviewer Comments:

1. *The clinical protocol does not clearly state whether the study will be unblinded after the 6-month or the 12-month visits. Section 6.2 states "The study will not be unblinded until all subjects have completed their 6-month visits and the data monitored and all data queries resolved. The database will then be locked prior to sponsor authorization of unblinding."; the protocol does not state the study will be unblinded after subjects have completed their 12-month visits, and no amendments were submitted to IND (b)(4) to clarify or change the unblinding rules for Studies 05/06. In this review, unblinding was interpreted to have taken place after the 6-month visits.*
2. *It is unclear whether evaluators conducting the 12-month safety follow-up telephone call were blinded. The questionnaire used in the follow-up calls was scripted.*

5.1.9 Treatment Regimen

The physician injector received two 2-mL vials containing 1.2 mL of IT or vehicle-control for injection. The vials were refrigerated at 2-8°C until 15-20 minutes prior to injection. Study treatment was administered within 24 hours of receipt. There were a total of three separate treatment sessions for administration of either IT or vehicle-control at 5-week intervals \pm 1 week. Treatment was administered at a dose of 0.1 mL per linear cm to treat up to a total 20 cm possible treatment area (up to 2 mL of product). Twenty-nine (29)-gauge, 1/2-inch needles were used for injection. The same areas were injected at each treatment session.

Vehicle-control was provided as proprietary isotonic medium in the same volume as IT and was administered in the same manner as IT.

Reviewer Comment: Since the injector and evaluator for any given subject were different investigators, blinding was maintained even if injectors were able to distinguish any difference in color, viscosity, etc., between the IT and vehicle-control suspensions.

5.1.10 Concomitant Medications and Procedures

In addition to enrollment criteria excluding use of steroids and antibiotics, the following medications and procedures were not permitted during the study:

- Dermatological treatments or procedures to the lower part of the face for the duration of the study
- Aspirin or NSAID for 7 days prior to each treatment
- Application of creams or cosmetics to the nasolabial fold wrinkles within 72 hours following each treatment

Facial washing and use of general cosmetics were allowed and sunscreen (SPF 30 or above) for the treated area were to be used by all subjects during sun exposure.

5.1.11 Training for Study Investigators

The training for study investigators for study-related procedures and assessments were described in the Appendix section of the clinical protocol for Studies 005 and 006.

Clinical Protocol Appendices:

B: Instructions for Evaluator Wrinkle Severity Assessment

C: Biopsy Procedures

E: Nasolabial Fold Wrinkle Injection Technique (Instruction for Use)

F: Subject and Evaluator Improvement Assessments

G: Blinding procedures

H: Training of Investigators-

- Background information
- Purpose of training discussed- evaluation, biopsy, injection, blinding, training of new investigators and study staff
- Description of Training: oral/slide presentation by the Medical Monitor or a trainer qualified by the Medical Monitor – Lemperle scale; photos demonstrating the nasolabial folds at all grades and what should or should not be included; evaluators then take an assessment knowledge test and a post-assessment photo test; tests scored by medical monitor; test scores compiled for all evaluators; post-assessment refresher testing performed a minimum of one week following the initial training - evaluators who did not demonstrate competency were retrained; therefore no assessments were performed by anyone who did not successfully complete assessment training
- Injection and biopsy training by slide presentation, DVD - demonstration of proper biopsy and injection techniques; discussion of blinding; completion of written skill assessments; live demonstration of injection technique; injectors who completed training and demonstrated proper technique were considered trained; those who cannot demonstrate proper knowledge or technique undergo retraining; following training, injectors were required to demonstrate proper injection technique to the Study Monitor - improper demonstration would trigger a new training program; investigators who passed training proceed to evaluate or inject subjects

- Additional site training – study coordinators ensure that subjects, injectors and evaluators do not discuss the trial, and ensure that techniques are properly performed, including subject assessment technique
- Training documentation – copies filed at investigative site; originals filed in master study file.

Reviewer Comments:

1. *The training method and proof of competency described in the protocol were adequate. The training was probably effective when all of the training modules were implemented as intended and described.*
2. *No significant deficiencies were found in the BLA review process or during the BiMO inspections.*

5.2 Statistical Analysis

5.2.1 Sample Size Determination

Based on previous study results and experience in non-randomized studies, the applicant estimated that the expected success rates for both endpoints would be somewhat higher than 40% for IT and no more than 20% for controls. A sample size of 82 subjects per arm per study was required to provide 80% power at a two-sided significance level of 0.05. At the IND stage, the applicant planned to enroll 100 subjects per arm or a total of 200 subjects for each study.

5.2.2 Efficacy Analysis Populations

The analysis populations were intent-to-treat (ITT), Efficacy Evaluable (EE) and safety populations. The FDA agreed to the addition of a modified intent-to-treat (MITT) analysis in July, 2008. The primary efficacy analysis was the ITT analyses; analyses based on EE and MITT populations were supportive. Safety analysis for studies 005 and 006 was based on the safety population. Definitions for the analysis populations are summarized below:

ITT = Randomized subjects. The ITT population was used to perform the:

- Primary analysis of the co-primary efficacy endpoints and
- Primary analysis of the secondary efficacy endpoints

MITT = Subjects who received \geq one treatment. The MITT population was used to perform the:

- Safety analysis
- Additional analysis of secondary endpoints

Efficacy Evaluable = Subjects who received all three treatments and did not have a major protocol violation

Safety = Subjects who received one or more IT or vehicle-control treatment

- Sample size powered for response rates $> 40\%$ of IT and $\leq 20\%$ for vehicle-control
- 80% power at a two-sided significance level of 0.05

- Missing data imputed as treatment failures
- Cochran-Mantel-Haenszel (CMH) test for the primary analysis, adjusted for site
- Efficacy analysis based on the ITT population was primary, and analyses based on the MITT and EE populations were secondary

5.2.3 Efficacy Analysis

The primary statistical analyses of the two co-primary endpoints were performed based on the ITT population. A CMH test was used to compare the overall success of IT vs. vehicle-control for the co-primary endpoints, adjusted for site. The alpha was 0.05, two-sided. Both primary endpoints must be statistically significant in the primary efficacy analysis for a successful trial. There were no interim analyses.

5.2.4 Sensitivity Analysis for the Primary Efficacy Endpoints

Fisher's exact test was used for comparisons. Sensitivity analysis was used for the primary endpoints by utilizing a repeat measures model to incorporate all relevant patient information with the assumption that data were missing at random. Additionally, a worst-case imputation was used where missing data in the vehicle-control group were treated as success while missing data in the IT group were treated as failures.

5.2.5 Secondary Endpoints

The principal analysis of the pre-specified secondary endpoints used the same approach as for analysis of the primary endpoints. The applicant used hierarchical testing (Table 12), as described in their Statistical Analysis Plan (SAP). For example, IT must be shown to be statistically superior to vehicle-control in the Subject Improvement Assessment at Visit 6 in order to proceed to test the success of the Evaluator Improvement Assessment at Visit 6. As a result, no multiplicity adjustment was needed.

Table 12. Hierarchical Order for Analysis of Secondary Endpoints

Hierarchical Order	Secondary Endpoint/Analysis
1	Success on Subject Improvement Assessment at Visit 6 (a score of +1 or +2)
2	Success on Evaluator Improvement Assessment at Visit 6 (a score of +1 or +2 on both sides of face)
3	Time-to-first improvement (2 or more points) on the Subject Wrinkle Assessment relative to Baseline
4	Time-to-first improvement (2 or more points) on the Evaluator Wrinkle Severity Assessment relative to Baseline

5.3 Study IT-R-001

- Title: "A Double-blind, randomized and placebo-controlled study of Isolagen injection for the treatment of rhytids"
- Study period: January 3, 2003 to February 20, 2004
- Study Phase: Phase 2

- Centers: 2 centers in Houston, Texas
- Objectives
 - Acute efficacy of three different doses at three months after the last injection
 - Safety of Isolagen
 - Long-term efficacy (open-label)
- Indication: 18 to 70 years old, 16 areas of facial rhytids and scars
- Primary efficacy endpoint
 - Change from the baseline of investigator 5-point ordinal scale defined by a photo guide at Month 4 (acute) and Month 12 (long-term), responder defined at one-point improvement
- Secondary efficacy endpoints
 - Change from baseline of subject Visual Analog and ordinal scales
 - Change in baseline of investigator Visual Analog
- Safety endpoints: incidence of adverse events, and change from baseline of laboratory assessments
- Study design
 - Prospective, randomized, double-blind, and placebo-controlled trial
 - 40 subjects, 10 in each of 4 arms: one control arm (carrier solution), three dosing arms (acute phase)
 - Three dose levels: (1) low: 5×10^6 cells/mL, (2) middle: 10×10^6 cells/mL, and (3) high: 20×10^6 cells/mL
 - Acute phase (4 months) three injections of either IT or vehicle-control, 1-2 weeks apart, followed by safety and efficacy evaluation at one and three months after the last injection.
 - Long-term phase: 6 months open-label follow-up for safety and efficacy, at office visits at Months 6, 9, and 12.
 - Long-term: 29 subjects in high-dose group (19 cross-over), 10 subjects in middle-dose group
 - Cross-over to high-dose: control and low-dose group

5.4 Study IT-R002

- Title: “A Phase 3 double-blind, randomized and placebo-controlled study of Isolagen therapy injection for the treatment of contour deformities”
- Study period: May 19, 2003 to June 3, 2005
- Study Phase: Phase 3
- Centers: 10 centers in US
- Objectives
 - Acute efficacy at Month 4
 - Acute safety
 - Long-term efficacy (open-label)
 - Long-term safety
- Indication: 18 years old and above, 16 areas of facial rhytids and scars
- Primary efficacy endpoint

- Change from the baseline of investigator 7-point ordinal scale at Month 4 (acute) and Month 12 (long-term); responder defined as one-point improvement (baseline score of 2) and two-point (baseline score of ≥ 3)
- Secondary efficacy endpoints
 - Change from baseline of subject Visual Analog and ordinal scales
 - Change from baseline of investigator Visual Analog Scale (VAS)
 - Blinded live assessment using ordinal scale
- Safety endpoints: incidence of adverse events, and change from baseline of laboratory assessments (chemistry, hematology, urinalysis, vital signs)
- Study design
 - Prospective, randomized (3:1), double-blind, and placebo-controlled trial
 - 158 subjects, 2 strata
 - 109 in stratum A for rhytids (3:1): 81 in IT, 28 in control
 - 49 in stratum B for facial scar (3:1): 35 in IT, 14 in control
 - IT dose: $1-2 \times 10^7$ cells/mL, vehicle control: carrier solution
 - Acute phase (4 months) three injections of either IT or vehicle-control, 1-2 weeks apart, followed by safety and efficacy evaluation at Month 2 and Month 4 after the last injection.
 - Long-term phase: 6 months open-label follow-up for safety and efficacy, office visits at Month 6, 9, and 12.
 - Long-term: 142 subjects (111 in IT from acute phase, 31 control-IT cross-over)
 - Cross-over: 31 control to IT-group after acute phase

5.5 Studies IT-R-003A and IT-R-003B

- Title: “A phase III Double-blind, randomized and placebo-controlled study of Isolagen therapy for the treatment of contour deformities”
- Studies 003A and 003B were conducted on an identical protocol
- Study period: July 20, 2004 to May 19, 2005
- Study Phase: Phase 3 (proposed)
- Centers: 6 centers in US (3 for each study)
- Objectives
 - Acute efficacy at Month 6 study visit
 - Acute safety
 - Long-term efficacy and safety (open-label)
- Indication: at least 18 years of age for treatment of nasolabial fold and glabellar wrinkles
- Primary efficacy endpoint
 - a. Co-primary efficacy endpoints: blinded assessor 6-point ordinal scale and subject visual analog to assess primary nasolabial fold deformity at Month 6
- Secondary efficacy endpoints
 - Secondary medical assessor 6-point scale for nasolabial fold at Month 6
 - Blinded assessor 6-point scale for glabellar line at Month 6
 - Subject VAS for glabellar at Month 6

- Secondary medical assessor 6-point scale for glabellar line at Month 6
 - Blinded assessor 6 point scale for all treated areas at Month 6
 - Subject VAS for all treated areas at Month 6
 - Secondary medical assessor 6-point scale for all treated areas at Month 6
 - Independent review panel 6-point scale on all treating areas using photos at Day 0 and Month 6
- Safety endpoints: incidence of adverse events, and measurement of vital signs
- Study design
 - Prospective, randomized, double-blind, and placebo-controlled trial
 - Treatment: nasolabial and glabellar lines, one to four areas, severity of 2 or greater
 - 100 subjects planned for each study with IT and control in 1:1 ratio
 - 003 A: 123 randomized: IT=61, Control=62; safety population (\geq one injection): IT=48, Control=59
 - 003 B: 115 randomized: IT=58, Control=57; safety population: IT=52, Control=54
 - Dose and mode of administration: 2×10^7 cells/mL in 1.2 mL, intradermally
 - Acute phase (6 months) three treatment of either IT or vehicle-control, 1-2 weeks apart, followed by safety and efficacy evaluation at Months 2, 4, 6.
 - Long-term phase: 6 months open-label follow-up for safety and efficacy, office visits at Months 9 and 12.
 - Long-term
 - 003A: IT=44, Control=9 (Month 9 Visit only)
 - 003B: IT=41, Control=17 (Month 9 Visit only)

5.6 Study IT-R-007

- Title: “A phase II multicenter, open-label trial of the safety and efficacy of Isolagen Therapy in the treatment of facial wrinkles and creases”
- Study period
 - Acute Phase: March 22, 2007 to June 27, 2008
 - Long-Term Phase: June 23, 2008 to October 27, 2009
- Study Phase: Phase 2
- Centers: 5 centers in US
- Objectives
 - Safety of two treatments of IT at 6 mL (of $1-2 \times 10^7$ cells/mL) for each treatment per subject
 - Efficacy of two treatments of IT in the treatment of multiple different facial regions 6 months after the last treatment using co-primary endpoints
 - Long-term: long-term safety and subject-reported appearance assessment in a telephone call survey
- Indication/eligibility: at least 18 years of age for treatment of facial wrinkles and creases on 8 different regions of the face
- Primary efficacy endpoint

- Safety endpoints: adverse events, serious adverse events, AE leading to withdrawal, and vital signs
- Efficacy endpoints:
 - Subject wrinkle assessment
 - Independent panel global improvement assessment
 - Investigator skin quality assessment
 - Subject skin quality assessment
- Subjects: Acute: 50, safety population (≥ 1 injection): 45; Long-term: 38
- Treatment/duration: two treatments of IT of 6 mL per each treatment at 4-6 week interval; office visits at 1, 3, and 6 months after the last treatment; follow-up with 1 phone call at 6 months after last observation.
- 12-month follow-up phone call questions
 - Resolution of unresolved AEs
 - Occurrence of new AEs
 - New cosmetic or medical procedures
 - Change of medications
 - Subject's opinion of treatment: same, worse or better

6. REVIEW OF EFFICACY

6.1 Study Results and Efficacy of Study IT-R-005

The primary efficacy analysis was based on the intent-to-treat (ITT) population, which consisted of all subjects randomized. A total of 203 subjects (100 IT, 103 vehicle-control) enrolled in IT-R-005 (Table 13).

Table 13. Study Population for Studies IT-R-005

Study Population	IT-R-005 n=203	
	IT	Control
Enrolled (ITT)	100	103
Treated (MITT)	83	92
Efficacy Evaluable (EE)	60	76

Populations Enrolled:

In the ITT population, subjects were predominantly female (88% of IT and 91% of control), white (94% of IT and 96% of control), with a mean age of 57.5 in the IT group and 55.9 in control. The demographics were balanced between arms and among the seven study sites. The demographics for Study 005 are shown in Table 14.

Table 14. Demographic Characteristics for ITT Population in Study IT-R-005

	IT n=100	Control n=103
Age (years)		
Mean (SD)	57.5 (8.32)	55.9 (7.87)
Median	57	56

IT-R-005

	IT n=100	Control n=103
Range	38-75	35-78
Baseline Age Group (years)		
> 40, ≤ 50	19 (19%)	25 (24%)
> 50, < 65	60 (60%)	62 (60%)
≥ 65	21 (21%)	16 (16%)
Gender		
Female	88 (88%)	94 (91%)
Male	12 (12%)	9 (9%)
Race/Ethnicity		
White	94 (94%)	99 (96%)
Black/African-American	1 (1%)	2 (2%)
Asian	2 (2%)	0
Hispanic/Latino	10 (10%)	7 (7%)
Am Indian/Alaska Native	0	1 (1%)
Other	3 (3%)	1 (1%)

Patient Disposition:

The majority of the discontinuations from the study were due to subject withdrawal (6 IT, 6 control; 6% overall) and sponsor request (5 IT, 1 control; 3% overall). The subjects who were discontinued due to sponsor request were withdrawn because product could not be manufactured within the timeframe required by the study. Four additional IT subjects were discontinued from study treatment after receiving at least one study treatment due to sponsor request because additional study product could not be manufactured within the timeframe required, these four subjects were included in the MITT population. Four subjects were discontinued from the study or withdrew consent due to adverse events; two subjects were diagnosed with a new medical condition, terminal adenocarcinoma and trigeminal neuralgia, both of which occurred after the baseline biopsy but prior to the first treatment visit. One subject in the control group died from a myocardial infarction after Visit 5. The disposition of subjects for Study 005 is summarized in Table 15 below.

Table 15. Patient Disposition in the ITT Population for Study IT-R-005

	IT-R-005		
	IT n=100	Control n=103	TOTAL n=203
Study Completion Status			
Completed Study	80 (80%)	88 (85%)	168 (83%)
Early Termination	20 (20%)	15 (15%)	35 (17%)
Reason for Termination			
Subject Withdrawal	7 (7%)	6 (6%)	12 (6%)
Sponsor Request	5 (5%)	1 (<1%)	6 (3%)
Adverse Event	1 (1%)	1 (<1%)	3 (2%)
Protocol Non-Compliance	3 (3%)	1 (<1%)	4 (2%)
Lost to Follow-up	1 (1%)	3 (3%)	4 (2%)
Others	3 (3%)	3 (3%)	6 (3%)
“Other” includes history or diagnosis of basal cell carcinoma and history of prolactin secreting tumor			

IT-R-005 Efficacy Results:

IT was statistically superior to vehicle-control in each of the co-primary endpoints in the primary ITT analysis for Study 005. The success rates in Subject Wrinkle Assessment were 57% IT vs. 30% control; and the success rates of IT vs. vehicle-control in the Evaluator Wrinkle Severity Assessment were 33% vs. 7% (see Table 16). The treatment effect was 27% (57% - 30%) for the Subject Assessment success rate and 26% (33% - 7%) for the Evaluator Assessment success rate.

Table 16. Success Rates at 6-Months in ITT Population for IT-R-005

Study	Study	IT-Treatment	Vehicle-control	p-value
IT-R-005 n=203	Subject Assessment	57/100 (57%)	31/103 (30%)	0.0001
	Evaluator Assessment	33/100 (33%)	7/103 (7%)	<0.0001

Investigators who participated in previous IT studies:

A potential clinical issue for Study 005 was that primary investigators at Sites 5100, 5300, and 5600 in Study 005 (as well as at site 6400 in Study 006) had participated in other Isolagen studies under the same IND (b)(4). The enrollment at Sites 5100, 5300, and 5600 accounted for 65.5% of the study population in Study 005. Efficacy evaluations, particularly the Evaluator Wrinkle Severity Assessment, were analyzed. For Study 005, the impact of the three sites (5100, 5300 and 5600) on efficacy results was not pronounced. Success rates of the Evaluator Wrinkle Severity Assessment at Sites 5100, 5300 and 5600 combined were 30% (20/67) and 4.5% (3/66) for IT vs. vehicle-control respectively; while the success rates at other sites were 39.4% (13/33) for IT and 10.8% (4/37) for control. The combined IT success rate for Sites 5100, 5300 and 5600 was less than for other sites (30% vs. 39.4%). However, the success rate of the Evaluator Wrinkle Severity Assessment in the vehicle-control group was lower at Sites 5100, 5300 and 5600 than at other sites (4.5% vs. 10.8%). A sensitivity analysis performed with the 3 sites excluded showed that IT was statistically superior to vehicle (see Statistical Review's separate memo).

Reviewer Comment: One of the concerns regarding investigators who had participated in earlier trials is that previous participation may affect blinding because investigators may recognize the way IT-treated patients looked due to their prior experience with IT treatment. For Studies 005/006, the concern would be evaluators who participated in previous IT trials.

6.2 Study Results and Efficacy of Study IT-R-006

The primary efficacy analysis was based on the intent-to-treat (ITT) population, which consists of all randomized subjects. A total of 218 subjects (110 IT, 108 vehicle control) enrolled in IT-R-006 (Table 17).

Table 17. Study Populations for Study IT-R-006

Study Population	IT-R-006 n=218	
	IT	Control
Enrolled (ITT)	110	108
Treated (MITT)	98	99
Efficacy Evaluable (EE)	66	88

Populations Enrolled:

In the ITT population, most subjects were predominantly female (94% of IT and 88% of control), white (89% of IT and 88% of control), and had an overall mean age of 54.6 years (mean age was 53.9 in the IT group and 55.4 in control). The demographics were balanced between arms (Table 18), and among the six study sites in Study 006.

Table 18. Demographic characteristics for the ITT Population in Study IT-R-006
IT-R-006

	IT n=110	Control n=108
Age (years)		
Mean (SD)	53.9 (10.38)	55.4 (9.92)
Median	55	55
Range	23-75	26-81
Baseline Age Group (years)		
> 40, ≤ 50	39 (35%)	34 (31%)
> 50, < 65	56 (51%)	55 (51%)
≥ 65	15 (14%)	19 (18%)
Gender		
Female	103 (94%)	95 (88%)
Male	7 (6%)	13 (12%)
Race/Ethnicity		
White	98 (89%)	95 (88%)
Black/African-American	1 (1%)	1 (1%)
Asian	0	0
Hispanic/Latino	12 (11%)	12 (11%)
Am Indian/Alaska Native	0	0
Other	11 (10%)	12 (11%)

Subject Disposition:

The majority of the subjects who were discontinued from the study were due to the applicant's request (10 IT, 4 control; 7% overall) and subject withdrawal (3 IT, 4 control; 3% overall). Among the subjects who were discontinued from the study due to sponsor request, 12 were withdrawn because study product could not be manufactured within the required timeframe. Two subjects in the ITT population were discontinued from the study due to adverse events. One subject who received vehicle-control died of cardiac arrest prior to receiving study treatment. One subject who received IT was taken off the study after the second set of injections due to mild bruising associated with the injections; the investigator considered this event to be definitely related to treatment. The subject disposition for Study IT-R-006 is summarized in Table 19.

Table 19. Subject Disposition in ITT Population for Study IT-R-006

	IT-R-006		
	IT n=110	Control n=108	TOTAL n=218
Study Completion Status			
Completed Study	93 (85%)	98 (91%)	191 (88%)
Early Termination	17 (15%)	10 (9%)	27 (12%)
Reason for Termination			
Subject Withdrawal	3 (3%)	4 (4%)	7 (7%)
Sponsor Request	10 (9%)	4 (4%)	14 (6%)
Adverse Event	1 (<1%)	1 (<1%)	2 (<1%)
Protocol Non-Compliance	2 (2%)	1 (<1%)	3 (1%)
Lost to Follow-up	0	0	0
Others	1 (<1%)	0	1 (<1%)
The subject terminated due to "Other" moved out of state			

IT-R-006 Efficacy Results:

IT was statistically superior to vehicle-control for each of the co-primary endpoints in the primary ITT analysis for Study 006. The success rates in the Subject Wrinkle Assessment were 45% IT vs. 18% control; and the success rates of IT vs. vehicle-control in the Evaluator Wrinkle Severity Assessment were 19% vs. 7% (Table 20). The treatment effect was 27% (45% - 18%) for the Subject Assessment success rate and 12% (19% - 7%) for the Evaluator Assessment success rate.

Table 20. Success Rates at 6-Months in ITT population for Study 006

Study	Study	IT	Control	p-value
IT-R-006 n=218	Subject Assessment	50/110 (45%)	19/108 (18%)	<0.0001
	Evaluator Assessment	21/110 (19%)	8/108 (7%)	0.0075

Sites with extreme results:

The success rates in the Evaluator Wrinkle Severity Assessment were lower for the IT group at Sites 6100, 6300, and 6600 (5%, 5%, and 10% respectively), as shown in Table 21. Enrollment at these three sites accounted for 55% of enrollment in Study 006. Since the three sites represented more than half of the study enrollment for Study 006, FDA examined the subject population for potential imbalances, such as age, baseline wrinkle severity, missing data rate, and product injection volume. No outstanding discrepancies were noted. Analyses excluding these sites gave a p-value of 0.0258 for success in the Subject Wrinkle Assessment and a p-value of 0.0081 for success in the Evaluator Wrinkle Severity Assessment.

Table 21. Results* of Co-Primary Efficacy Endpoints - Studies 005 and 006 (ITT)

	Subject Wrinkle Assessment		Evaluator Wrinkle Severity Assessment	
	IT	Vehicle	IT	Vehicle
Study 005 Sites:				
5100	15/25 (60%)	9/24 (37.5%)	5/25 (20%)	1/24 (4.2%)

	Subject Wrinkle Assessment		Evaluator Wrinkle Severity Assessment	
Study 005 Sites:	IT	Vehicle	IT	Vehicle
5200	6/10 (60%)	4/11 (36.4%)	2/10 (20%)	1/11 (9.1%)
5300	9/21 (42.9%)	5/20 (25%)	8/21 (38.1%)	1/20 (5%)
5400	7/7 (100%)	3/8 (37.5%)	4/7 (57.1%)	0/8
5500	5/9 (55.6%)	3/10 (30%)	3/9 (33.3%)	1/10 (10%)
5600	12/21 (57.1%)	6/22 (27.3%)	7/21 (33.3%)	1/22 (4.5%)
5700	3/7 (42.9%)	1/8 (12.5%)	4/7 (57.1%)	2/8 (25%)
Total	57/100 (57%)	31/103 (30.1%)	33/100 (33%)	7/103 (6.8%)
Study 006 Sites:	IT	Vehicle	IT	Vehicle
6100	11/19 (57.9%)	4/17 (23.5%)	1/19 (5.3%)	2/17 (11.8%)
6200	7/13 (53.8%)	2/16 (12.5%)	5/13 (38.5%)	2/16 (12.5%)
6300	13/22 (59.1%)	1/22 (4.5%)	1/22 (4.5%)	0/22
6400	6/18 (33.3%)	5/17 (29.4%)	5/18 (27.8%)	2/17 (11.8%)
6500	7/18 (38.9%)	3/17 (17.6%)	7/18 (38.9%)	2/17 (11.8%)
6600	6/20 (30%)	4/19 (21.1%)	2/20 (10%)	0/19
Total	50/110 (45.5%)	19/108 (17.6%)	21/110 (19.1%)	8/108 (7.4%)
*Missing data are treated as treatment failures.				

Reviewer Comment: The Evaluator Wrinkle Severity Assessment responses from all investigators in Studies 005 and 006 were examined. The Evaluator Wrinkle Severity Assessment scores at Sites 6300 and 6600 were lower in both IT and control groups, as compared to the scores from all other investigators in the two studies. However, the 13 data points (from the 7 sites in Study 005 plus the 6 sites in Study 006) were not large enough to derive any definitive conclusions (as compared to data from e.g. 100 sites) about the extreme outcomes. Given the extremely low response scores for both IT and control groups at Sites 6300 and 6600, evaluators' assessments at these two sites may be a factor for the extreme outcomes. It should be noted that all investigators in the two studies were trained and passed Isolagen's competency tests in all study procedures, including the assessment of nasolabial fold wrinkles.

Investigators who participated in previous IT studies:

In Study 006, the primary investigators at Site 6400 had participated in other Isolagen studies under the same IND (b)(4). The enrollment at Site 6400 accounted for 16% of the total enrollment in Study 006. The success rate of the Evaluator Wrinkle Severity

Assessment in the IT group at Site 6400 was 27.8% (5/18), a relatively low success rate, but higher than the success rates at Sites 6100, 6300 and 6600 (5.3%, 4.5% and 10% respectively). Because Study 006 generally had a relatively lower success rate in the Evaluator Wrinkle Severity Assessment as compared to Study 005 (19% vs. 33%), a sensitivity analysis excluding Site 6400 was performed; IT remained statistically superior to vehicle (see Statistical Reviewer's separate memo).

6.3 Comparison of Efficacy Outcomes Between the Two Studies

The success rates for IT vs. vehicle-control were generally robust, and results of the co-primary efficacy endpoints based on the ITT (primary) are shown in Table 22.

Table 22. Results* of the Co-Primary Efficacy Endpoints - Studies 005 and 006

No. of subjects (%)		Study 005			Study 006		
Type of Analysis	Endpoints	IT	Control	p-value	IT	Control	p-value
Primary (ITT) 005 – (100, 103) 006 – (110, 108)	Subject Wrinkle Assessment	57 (57%)	31 (30%)	0.0001	50 (45%)	19 (18%)	< 0.0001
	Evaluator Wrinkle Assessment	33 (33%)	7 (7%)	< 0.0001	21 (19%)	8 (7%)	0.0075
* Missing data are treated as treatment failures in all analyses.							

Subject enrollment was generally comparable between groups within each site for each study. Because results were similar among the three analysis populations (ITT, MITT, and EE), the efficacy review will focus primarily on the ITT outcomes, the primary analysis. IT is statistically superior to vehicle with respect to each of the co-primary efficacy endpoints in the primary ITT analysis. Analyses based on the EE and MITT populations were in agreement with the ITT analyses, and IT was statistically superior to vehicle with respect to each of the co-primary efficacy endpoints.

The success rates of IT vs. vehicle in the Evaluator Wrinkle Severity Assessment were 33% IT vs. 7% control for Study 005; and 19% IT vs. 7% control for Study 006. The success rates in Subject Wrinkle Assessment were 57% IT vs. 30% control for Study 005; and 45% IT vs. 18% control for Study 006. Although the results in both studies demonstrated a statistically significant difference between IT and vehicle-control for both the subject and the evaluator assessment in the ITT population, there was a difference between the two studies regarding the magnitude of benefit observed by the investigator (Table 23). The Evaluator Assessment success rate for Study 005 was 33% whereas the Evaluator Assessment success rate for Study 006 was 19%. This 14% difference in the evaluator response between the two studies is clinically significant and therefore **results for the two studies should not be pooled for the efficacy analyses.**

Table 23. Success Rates at 6-Months in ITT Population for Each Study

Study	Study	IT	Control	p-value
IT-R-005 n=203	Subject Assessment	57/100 (57%)	31/103 (30%)	0.0001
	Evaluator Assessment	33/100 (33%)	7/103 (7%)	<0.0001
IT-R-006 n=218	Subject Assessment	50/110 (46%)	19/108 (18%)	<0.0001
	Evaluator Assessment	21/110 (19%)	8/108 (7%)	0.0075

Since the subject demographic characteristics, product dose and regimen, and baseline wrinkle severity were similar between Studies IT-R-005 and IT-R-006, these factors were not likely to account for the differences in the primary efficacy results between the two studies. The study populations for Studies 005 and 006 were similar; each study was comprised mostly of whites (95% in 005 vs. 89% in 006), females (90% in 005 vs. 91% in 006), and subjects mostly between 50 and 60 years of age (mean age 57 years in 005, 55 in 006). Although the mean and median doses were slightly higher in Study 005 than in Study 006, there was a slight difference in the mean total treatment area defined by the Evaluator at Baseline (10.5cm in Study 005 and 9.3cm in Study 006) between the two studies. Similar numbers of subjects in the treatment and control groups in each study received 1, 2, or 3 total injections.

Conclusions based on different statistical methods for analyses were also in agreement – repeated measure, time to event (sustained success) up to 6 months, and missing data handling. No explanations were found to account for the extreme efficacy outcomes observed at three study sites in IT-R-006; evaluator assessment may be a factor. (See Statistical Reviewer’s separate memo).

Reviewer Comments:

- 1. The sponsor submitted pooled efficacy results from Studies 005 and 006. A 14% difference in the evaluator responder rate showed marked variability in the efficacy of IT. Pooling efficacy results from these two studies into a unified efficacy analysis gives a false impression of consistency in the evaluator response between the two studies.*
- 2. The investigators at the three “extreme” sites (Sites 6100, 6300, and 6600) did not participate in previous IT studies.*

6.4 Analysis of Secondary Endpoints

The analysis of the secondary efficacy endpoints was based on the ITT population. The pre-specified secondary endpoints in the protocols and the respective efficacy results for Studies IT-R-005 and IT-R-006 are as follows:

1. Subject Wrinkle Assessment at Visits 3, 4, and 5, using a 5-point wrinkle satisfaction scale, where a response was defined as a 2-point or better improvement compared to baseline. (Grading scale: Cohen)

Result: IT was superior to vehicle-control for patients with a 2-point or better improvement from baseline in the Subject Wrinkle Assessment on Visits 3, 4, and 5 in both studies.

2. Evaluator Wrinkle Severity Assessment at Visits 3, 4, and 5, using a 6-point wrinkle severity scale with a photoguide, where a response was defined as a 2-point or better decrease in wrinkle severity on both sides of the face compared to baseline. (Grading scale: Lemperle, with photoguide)

Results: IT was superior to vehicle-control for patients with a 2-point or better improvement from baseline in the Evaluator Wrinkle Severity Assessment on Visits 3, 4, and 5 in both studies.

3. Subject Improvement Assessment performed at 6-month post-treatment, with a response defined as a 1-point or better improvement comparing baseline photo to photos taken at Visits 3, 4, 5, and 6. (*see description of grading scale below)

Results: Compared to controls, a higher rate of patients in the IT group felt their appearance at six months was better (+1) or much better (+2) than before, based on the Subject Improvement Assessment in both studies. The response rates were 61% vs. 28.2% for IT vs. vehicle in Study 005; results were 54.5% IT vs. 18.5% control in Study 006.

4. Evaluator Improvement Assessment performed at 6-months post-treatment, with a response defined as a 1-point or better improvement comparing baseline photo to photos taken at Visits 3, 4, 5, and 6. (*see description of grading scale below)

Results: A higher percentage of patients in the IT group was evaluated as better (+1) or much better (+2) than before in the appearance of each side of the face at Month 6 in the Evaluator Improvement Assessment in both studies.

*The same wrinkle improvement grading scale was used for the Subject Improvement Assessment and the Evaluator Improvement Assessment (secondary endpoints 3 and 4). The photos taken at Visits 3, 4, 5, and 6 were compared to the photos taken at baseline, grading the photos consecutively in the order of visit and circling one of the grades that best described the appearance of the wrinkles on the lower part of the face: -2 = much worse than before, -1 = worse than before, 0 = same as before, +1 = better than before, and +2 = much better than before. The photo evaluation was done in one session at Visit 6, and no prior viewing of the photos was allowed.

Reviewer Comment: For secondary endpoints 1) and 2), the same response assessments were performed as the ones for the co-primary endpoints. The difference is that for the co-primary efficacy endpoints, assessment was performed only at Visit 6 (6 months after

the last treatment injection), whereas the same response assessment performed at Visits 3, 4, 5, and 6 were considered secondary endpoints.

The efficacy trends of the secondary efficacy endpoints were consistent with that of the co-primary efficacy endpoints. Results from a repeat measurement analysis support the superiority of IT vs. vehicle-control as shown in Tables 24 and 25 below:

Table 24. Secondary Endpoints - Proportion of Patients with Greater Than or Equal To 2-Point Improvement in Subject Wrinkle Assessment and Evaluator Wrinkle Severity Assessment over Visits in Studies 005 and 006

No. of subjects (%)		Study 005			Study 006		
ITT Analysis	Visit	IT (n=100)	Vehicle (n = 103)	p-value ¹	IT (n = 110)	Vehicle (n = 108)	p-value ¹
Subject Wrinkle Assessment	Visit 3	38 (38%)	23 (22.3%)	0.0133	34 (30.9%)	20 (18.5%)	0.0311
	Visit 4	49 (49%)	25 (24.3%)	0.0001	51 (46.4%)	25 (23.1%)	0.0003
	Visit 5	48 (48%)	26 (25.2%)	0.0006	47 (42.7%)	24 (22.2%)	0.0012
Evaluator Wrinkle Severity Assessment	Visit 3	14 (14%)	5 (4.9%)	0.0211	17 (15.5%)	4 (3.7%)	0.0022
	Visit 4	28 (28%)	10 (9.7%)	0.0005	22 (20.0%)	8 (7.4%)	0.0039
	Visit 5	27 (27%)	9 (8.7%)	0.0003	26 (23.6%)	7 (6.5%)	0.0002
<p>* Missing data are treated as treatment failures in all analyses. ¹ p-values are unadjusted and are based on CMH test stratified by study site. They are listed for reference purpose.</p>							

Table 25. Secondary Endpoints - Subject Improvement Assessment and Evaluator Improvement Assessment at Month 6 for Studies 005 and 006 (ITT)

No. of subjects (%)		Study 005			Study 006		
Available-Data Analysis		IT (n = 100)	Vehicle (n = 103)	p-value ¹	IT (n = 110)	Vehicle (n = 108)	p-value ¹
Subject Improvement Assessment							
No Information		22 (22%)	15 (15%)		17 (16%)	10 (9%)	
No change or worsening		17 (17%)	59 (57%)	< 0.0001	33 (30%)	78 (72%)	< 0.0001
≥ 1 pt. improvement		61 (61%)	29 (28%)		60 (55%)	20 (19%)	
Evaluator Improvement Assessment Right Side							
No Information		22 (22%)	15 (15%)		17 (16%)	11 (10 %)	
No change or worsening		26 (26%)	69 (67%)	< 0.0001	38 (35%)	75 (69%)	< 0.0001

No. of subjects (%)	Study 005			Study 006		
Available-Data Analysis	IT (n = 100)	Vehicle (n = 103)	p- value ¹	IT (n = 110)	Vehicle (n = 108)	p- value ¹
≥ 1 pt. improvement	52 (52%)	19 (18. %)		55 (50%)	22 (20%)	
Evaluator Improvement						
Assessment Left Side						
No Information	22 (22%)	15 (15%)		17 (16%)	10 (9%)	
No change or worsening	26 (26%)	69 (67%)	< 0.0001	41 (37%)	78 (72%)	< 0.0001
≥ 1 pt. improvement	52 (52%)	19 (18%)		52 (47%)	20 (19%)	
¹ p-values are based on patients who had data at Visit 6, and were derived using CMH stratified by site for ≥ 1 pt. better than before vs. no improved or worsening.						

Time-to-success analyses

In addition to the primary and secondary endpoint analyses, time-to-success analyses were included in the proposed BLA labeling: time-to-sustained-response of at least 2-point improvement from baseline. For example, if a patient had at least a 2-point improvement at 2 months post-treatment (Visit 4) and sustained until 6 months post-treatment (Visit 6), the patient's time-to-success is Month 2 post-treatment. On the other hand, if a patient had a 2-point improvement at Month 2, had less than a 2-point improvement or had no evaluation at Month 4, and had a 2-point improvement at Month 6 post-treatment, the patient's time-to-success is 6 months post-treatment. The sponsor proposed testing secondary endpoints in the hierarchical order shown in Table 12. Results of the time-to-sustained success for the Subject Wrinkle Assessment and Evaluator Wrinkle Severity Assessment supported outcomes of the co-primary endpoints. However, the time-to-sustained success for the Subject Wrinkle Assessment and Evaluator Wrinkle Severity Assessment were not pre-specified secondary endpoints.

Reviewer Comment: Although IT was statistically superior to vehicle-control in the secondary endpoints, the time-to-first improvement endpoints on the Subject wrinkle Assessment and on the Evaluator Wrinkle Severity Assessment were not pre-specified as secondary endpoints in the SAP, and therefore should not be included in the labeling if the BLA is approved.

6.5 Clinical Issues

- **Clinical issues in subgroups:** The demographics for studies 005 and 006 were similar. The following clinical issues were noted in the subgroups:
 - Female subjects accounted for 90% of the study population
 - 9.7% were male
 - Race was predominantly white, comprising 92% of the study population.
 - <1% was Black/African-American

- 1% was Asian
- Ethnicity was 10% Hispanic/Latino
- o The median age for the studies was 56 years (57.5 for IT, 55.9 for control in study 005; 53.9 for IT, 55.4 for control in Study 006)
 - approximately 6% were aged 40 and younger; with 1% aged < 35
 - 17% were age 65 and older
- o The efficacy trend favored IT for all age groups except for the elderly (age ≥ 65) subgroup for the Evaluator Wrinkle Severity Assessment in both Studies 005 and 006. Success rates for the Evaluator Wrinkle Severity Assessment were 5% IT vs. 13% control in Study 005; Subject Wrinkle Assessment success rates were 13% IT vs. 16% control in Study 006. The shaded areas in Table 26 show that efficacy trends in the wrong direction (i.e., control is numerically better), but the count difference is only one.

Table 26. Efficacy in the Elderly (age 65 and above) Subgroup

Age ≥ 65 years	Success in Evaluator Wrinkle Severity Assessment		Success in Subject Wrinkle Assessment	
	Isolagen	Placebo	Isolagen	Placebo
Study 005	1/21 (5%)	2/16 (13%)	11/21 (52%)	3/16 (19%)
Study 006	3/15 (20%)	1/19 (5%)	2/15 (13%)	3/19 (16%)

Reviewer Comments:

1. *The small subgroup size in the non-white, age ≤ 40, elderly, and male subjects may be inadequate to establish efficacy in these subgroups.*
 2. *Efficacy in the elderly subgroup has also been generally lower in previous IT studies.*
- Comparing the success rates for the Evaluator Wrinkle Severity Assessment, there is a 14 % difference between Study 005 and Study 006. The success rate of 19% (21/110) in the IT group in Study 006 was lower than the 33% (33/100) success rate for the IT group in Study 005. This 14% difference in the evaluator response between the two studies is clinically significant, and therefore results for the two pivotal studies should not be pooled for the efficacy analyses. The lower success rate for Study 006 was due to lower rates in the IT group at sites 6100, 6300 and 6600. A sensitivity analysis excluding these three sites showed IT remained statistically superior to vehicle-control. No explanations were found to account for the extreme efficacy outcomes; evaluator assessment may be a factor.
 - The efficacy of IT beyond 6 months has not been demonstrated.

- No studies have been conducted to assess the effects of repeating treatment cycles of IT.
- **Investigators with Financial Conflicts with Isolagen:**
Two investigators in Study 005 (sites 5300 and 5600) and one investigator in Study 006 (site 6600) had financial relations with the sponsor. When the evaluator results from these sites were excluded, IT remained statistically superior to vehicle-control for each study. The results are summarized in Table 27.

Table 27. Analyses Excluding Investigators with Financial Conflicts for Studies 005 and 006

Primary Endpoints		Isolagen	Vehicle	Comparison
	Study IT-R-005			
Evaluator Wrinkle Assessment	Sites 5300 + 5600	15/42 (35.7%)	2/42 (4.8%)	NA
	Sites excludes 5300 and 5600	18/58 (31.0%)	5/61 (8.2%)	0.0012
Subject Wrinkle Assessment	Sites 5300 + 5600	21/42 (50.0%)	11/42 (26.2%)	NA
	Sites excludes 5300 and 5600	36/58 (62.1%)	20/61 (32.8%)	0.0014
	Study IT-R-006			
Evaluator Wrinkle Assessment	Site 6600	2/20 (10.0%)	0/19	NA
	Sites exclude 6600	19/90 (21.1%)	8/89 (9.0%)	0.018
Subject Wrinkle Assessment	Site 6600	6/20 (30.0%)	4/19 (21.1%)	NA
	Sites exclude 6600	44/90 (48.9%)	15/89 (16.9%)	< 0.0001
The p-value in the comparison between Isolagen and vehicle is based on Cochran-Mantel-Haenszel test stratified by site (primary analysis method).				

- **Masking assessment:** The applicant assessed the adequacy of blinding, both for study subjects and for evaluators. Subjects were given a pre-printed postcard at Visits 1 through 3 to record their opinion as to which treatment they had received. The postcards were completed at home and mailed back prior to the next study visit. Evaluators were asked to record their opinion of which treatment each subject received at Visits 3 through 5 by a similar procedure. The results of the masking assessment are shown in Table 28.

Table 28. Assessment by Subjects and Evaluators of Treatment Received

	IT-R-005		IT-R-006	
	IT	Control	IT	Control
Subject's Assessment of Tx Received				
Visit 1				
Active	25/77 (33%)	17/87 (20%)	25/91 (28%)	8/91 (9%)
Control	6/77 (8%)	18/87 (21%)	6/91 (7%)	15/91 (17%)
Don't Know	46/77 (60%)	52/87 (60%)	60/91 (66%)	68/91 (75%)
Visit 2				
Active	31/74 (42%)	20/82 (24%)	36/83 (43%)	16/93 (17%)
Control	8/74 (11%)	21/82 (26%)	10/83 (12%)	27/93 (29%)
Don't Know	35/74 (47%)	41/82 (50%)	37/83 (45%)	50/93 (54%)
Visit 3				

	IT-R-005		IT-R-006	
	IT	Control	IT	Control
Active	41/71 (58%)	24/84 (29%)	43/79 (54%)	16/86 (19%)
Control	6/71 (9%)	31/84 (37%)	10/79 (13%)	30/86 (35%)
Don't Know	24/71 (34%)	29/84 (35%)	26/79 (33%)	40/86 (47%)
Evaluator's Assessment of Tx Received				
Visit 3				
Active	22/66 (33%)	9/88 (10%)	42/81 (52%)	19/91 (21%)
Control	8/66 (12%)	21/88 (24%)	18/81 (22%)	47/91 (52%)
Don't Know	36/66 (55%)	58/88 (66%)	21/81 (26%)	25/91 (28%)
Visit 4				
Active	26/73 (36%)	11/80 (14%)	39/77 (51%)	20/91 (22%)
Control	6/73 (8%)	19/80 (24%)	2/77 (29%)	35/91 (39%)
Don't Know	41/73 (56%)	50/80 (63%)	16/77 (21%)	36/91 (40%)
Visit 5				
Active	33/71 (47%)	14/77 (18%)	41/79 (52%)	21/91 (23%)
Control	10/71 (14%)	23/77 (30%)	17/79 (22%)	47/91 (52%)
Don't Know	28/71 (39%)	40/77 (52%)	21/79 (27%)	23/91 (25%)

A summary of success (2-point improvement) and failures in Subject Wrinkle Assessment and Evaluator Wrinkle Severity Assessment with respect to blinding assessment, where S = Success and F = Failure, is shown in Tables 29 and 30.

Table 29. Successes (2-Point Improvement) and Failures in Subject Wrinkle Assessment

		IT-R-005				IT-R-006			
		IT n=100		Control n=103		IT n=110		Control n=108	
Subject Blinding Assessment at Visit 1		S	F	S	F	S	F	S	F
	Active	20	5	9	8	13	12	2	6
	Control	3	3	2	16	1	5	2	13
	Don't Know	31	15	17	35	32	28	13	55
	No Info.	3	20	3	13	4	15	2	15
	Total	57	43	31	72	50	60	19	89

Table 30. Successes and Failures in Evaluator Wrinkle Severity Assessment

		IT-R-005				IT-R-006			
		IT n=100		Control n=103		IT n=110		Control n=108	
Evaluator Blinding Assessment at Visit 3		S	F	S	F	S	F	S	F
	Active	15	7	1	8	15	27	6	13
	Control	0	8	0	21	0	18	1	46
	Don't Know	13	23	5	53	4	17	0	25
	No Information	5	29	1	14	2	27	1	16

		IT-R-005				IT-R-006			
		IT n=100		Control n=103		IT n=110		Control n=108	
	Total	33	67	7	96	21	89	8	100

Reviewer Comments:

- 1. The responses were collected as information only and no formal analyses were proposed or performed utilizing this information. Based on the results shown, no definitive conclusions can be made.*
- 2. The blinding assessment questionnaires included a “don’t know” response, a category that is sometimes not allowed in masking assessment studies.*
- 3. According to the study schedule, subject blinding assessments were obtained for Visits 1, 2, and 3, whereas the evaluator blinding assessments were obtained for Visits 3, 4, and 5.*

- -----
-----Withheld per privacy act-----

-----Withheld per privacy act-----

[Withheld per privacy act; (b)(6)]

----- Withheld per privacy act -----

----- Withheld per privacy act-----

[Withheld per privacy act; (b)(6)]

- **Smoking**

Study results for smokers were not pre-specified, and no smoker subgroup analysis was performed by the sponsor. However, subjects' smoking history was obtained in the medical history and was documented in the Case Report Forms (CRF). FDA's subgroup analysis of efficacy regarding subjects' smoking status is shown in Table 33.

Table 33. Efficacy of Subjects Who Smoked in Studies 005 and 006

	Study 005		Study 006	
Evaluator Wrinkle Severity Assessment				
Smoking Status	IT	Vehicle	IT	Vehicle
Current smoker	0/5	1/12 (8.3%)	2/12 (16.7%)	0/13
Previous smoker	14/42 (33.3%)	3/35 (8.6%)	9/41 (22%)	4/49 (8.2%)
Non-smoker	19/53 (35.8%)	3/56 (5.4%)	10/57 (17.5%)	4/46 (8.7%)
Subject Wrinkle Assessment				
Smoking Status	IT	Vehicle	IT	Vehicle
Current smoker	1/5 (20%)	6/12 (50%)	7/12 (58.3%)	2/13 (15.4%)
Previous smoker	24/42 (57.1%)	8/35 (22.9%)	19/41 (46.3%)	7/49 (14.3%)
Non-smoker	32/53 (60.4%)	17/56 (30.4%)	24/57 (42.1%)	10/46 (21.7%)

The current smokers, previous smokers, and non-smokers accounted for 8%, 38%, and 54% of study enrollment respectively in Study 005; in Study 006, they were 11.5%, 41.3%, and 47.2% respectively for current smokers, previous smokers, and non-smokers. As shown in the bolded highlight in Table 33, the efficacy trend favored IT except for current smokers in both subject and evaluator assessments in Study 005.

Reviewer Comment: Data suggests smoking is an independent risk factor for the development of premature wrinkles. Kadunce et al. (Ann Intern Med. 1991;114:840-844) found wrinkled facial skin to be directly proportional to cigarette use (independent of age, sex, pigmentation, or sun exposure history). Specifically, persons with more than 50

pack-years history of smoking were almost five times as likely to be wrinkled as were nonsmokers. The pathophysiology for the increased wrinkling in smokers is unclear, but it is possible that tobacco use could affect smokers' response to wrinkle treatments.

6.6 Efficacy Conclusions

Results from two Phase 3 studies, IT-R-005 and IT-R-006, were submitted in support of the efficacy claim for IT for the indication of treatment of moderate to severe nasolabial fold wrinkles in adults. The studies were conducted under an FDA SPA agreement. The co-primary efficacy endpoints were 1) subjects who scored a 2-point or better improvement at 6 months after the last treatment injection from baseline in the live Evaluator Wrinkle Severity Assessment; and 2) subjects who scored a 2-point or better improvement at 6 months after the last treatment injection from baseline in the live Subject Wrinkle Assessment. Success for IT, as compared to a vehicle-control, was based on the ITT population. Both co-primary endpoints at six months were met in Studies 005 and 006. Results of the co-primary endpoints showed similar results over different statistical methods for data analyses. Efficacy results in the MITT and EE analyses were in agreement. Results of secondary endpoints were supportive of primary efficacy results.

A clinically significant difference in success rates for the Evaluator Wrinkle Severity was found between Study 005 and Study 006. Study 006 had a lower overall success rate for IT than Study 005 (19% vs. 33%), due to lower success rates for the IT group at Sites 6100, 6300, and 6600 (5%, 5%, and 10% respectively). Enrollment at these three sites accounted for 55% of the enrollment in Study 006. The reasons for the lower success rates at these sites could not be identified. The evaluator success rates for Study 006 and Study 005 for the IT group were similar when Sites 6100, 6300, and 6600 were excluded.

Although the overall results of IT were statistically superior to vehicle-control with respect to the primary endpoints, the following clinical issues were identified: 1) No information on the bioactivities of IT have been provided; 2) The mechanism of action for IT has not been studied; 3) The small subgroup size in the non-white, age forty and younger, elderly, and male subjects may be inadequate to establish efficacy in these subgroups; 4) The efficacy of IT beyond 6 months has not been demonstrated; and 5) No studies have been conducted for the effects of repeating treatment cycles of IT.

7. OVERVIEW OF SAFETY ACROSS TRIALS

7.1 Safety Results of Studies IT-R-005 and 006

7.1.1 Method of Assessment

The primary analysis of safety was conducted using treatment-emergent adverse events (TEAE), 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,” and classified by the System Organ Classes (SOC) General Disorder and Administration Site

Conditions. The safety population consisted of all subjects who received at least one injection of either IT or vehicle-control.

Reviewer Comment: The “placebo” used in these studies was a vehicle-control, which is a component of the test article, rather than a true placebo. Therefore, although the sponsor has derived the safety profile of IT from a comparison of IT with a vehicle-control, the safety profile of IT treatment is best appreciated from the scrutiny of the adverse events in each treatment group.

According to the study schedule for Studies IT-R-005 and IT-R-006, there was a 5 ± 1 week interval between treatment injections and assessment of AEs. The time interval between visits may impact the accuracy of recalling the onset and details of TEAE. The clinical protocol did not require subjects to report or record AEs between visits.

7.1.2 Safety Results of Study IT-R-005

One hundred seventy-five subjects (83 IT and 92 vehicle-controls) who received at least one treatment injection were analyzed for safety. The subjects were > 91% (159/175) female, 94% (165/175) white, with a mean age of 56 years (57.4 in IT, 55.6 in control group).

Common Adverse Events

Overall, 58% (112/193) of the TEAEs reported by IT-treated subjects and 37% (81/219) of TEAEs reported by vehicle-control subjects were considered by the investigator to be definitely or probably related to study treatment. The most commonly reported TEAEs in the IT-treated group were injection-site erythema (28% of subjects), injection-site swelling (22%), nasopharyngitis (7%), injection-site pain (6%), and injection-site bruising (5%). In the vehicle-control group, the most commonly reported TEAEs were injection-site erythema (19% of subjects), injection-site swelling (16%), injection-site bruising (13%), and headache (5%). The overall TEAE rates were balanced between groups; however, injection-site erythema (28% IT vs. 19% control) and swelling (22% IT vs. 16% control) occurred at a higher rate in the IT-treated group, as shown in Table 34.

Table 34. Adverse Events in IT-R-005 > 1% Safety Population

Preferred Terms	IT N=83		Control N=92	
	Subjects	Events	Subjects	Events
All treatment-emergent AE	51 (61%)	193	57 (62%)	219
Administration Site Conditions	31 (37%)	119	32 (35%)	94
(Related to Treatment)	28 (33%)	112	24 (26%)	76
Injection site erythema	23 (28%)	53	17 (19%)	28
Injection site swelling	18 (22%)	41	15 (16%)	27
Injection site pain	5 (6%)	6	4 (4%)	5
Injection site bruising	4 (5%)	5	12 (13%)	17
Injection site nodules	2 (2%)	3	2 (2%)	2
Injection site reaction	2 (2%)	2	2 (2%)	2
Application site papules	2 (2%)	2	1 (1%)	1

Table 35 summarizes the numbers of subjects who experienced at least one occurrence of adverse events.

Table 35. Number of Subjects Experiencing TEAEs in IT-R-005

	IT n=83		Control n=92	
	Subjects	Events	Subjects	Events
Any TEAE	51 (61%)	193	57 (62%)	219
Severe TEAEs	2 (2%)	4	5 (5%)	5
TEAEs, Definitely Related	24 (29%)	102	22 (24%)	73
TEAEs Leading to Early Termination	1 (1%)	1	1 (1%)	1
Treatment-Emergent Serious Adverse Events (TESAEs)	1 (1%)	1	3 (3%)	4
Deaths	0	0	1 (1%)	1

Early Termination due to a TEAE:

- One IT-treated subject withdrew consent after Treatment 1 due to moderate pain at injection site (resolved in 10 minutes).
- One vehicle-control subject (white female, age 57) died of a myocardial infarction after Visit 5.

Duration of TEAE

Table 36 presents the duration of injection-site adverse events. The majority of injection-site events resolved within three days. Of the 19 events that persisted beyond four days, 13 resolved by the end of seven days. Two related-TEAEs were ongoing at the time of data-lock at six months after the first injection. These were:

- An injection-site reaction termed a mild, probably related “ridge” at the right nasolabial fold
- A mild, probably related injection-site swelling at the left upper nasolabial fold.

Table 36. Duration of TEAE Related to Study Treatment in IT-R-005

Preferred Term	Duration in Days				
	≤ 1 Day	2-3 Days	4-7 Days	8-14 Days	>14 Days
Application site-papules	0	1	1	0	0
Injection-site bruising	1	8	4	3	1
Injection-site erythema	54	20	4	0	0
Injection-site extravasation	0	1	0	0	0
Injection-site irritation	0	1	0	0	0
Injection-site nodule	1	4	0	0	0
Injection-site pain	6	4	1	0	0
Injection-site pruritus	0	1	0	0	0
Injection-site reaction	0	1	2	0	1
Injection-site swelling	51	15	1	0	1
Post-procedural discomfort	1	0	0	0	0

Summary

Overall, 61% (51/83) of IT-treated subjects experienced 193 TEAEs and 62% (75/92) of vehicle-control treated subjects reported 219 TEAEs. The most commonly reported TEAEs (28%) in the IT group were injection-site erythema, injection-site swelling,

nasopharyngitis, injection-site pain, and injection-site bruising. In the vehicle-control group, the most common TEAEs (19%) were injection-site erythema, injection-site swelling, injection-site bruising, and headache. The occurrence rates of the various TEAE types were similar between treatment groups. Most injection-site reactions resolved within one week of injection. One IT-treated subject withdrew consent prior to study completion due to injection-site pain. Two related TEAEs were ongoing at the time of database lock; these were an injection-site reaction, termed a mild, probably related "ridge" at the right nasolabial fold and mild, probably related, injection-site swelling of the left upper nasolabial fold.

7.1.3 Safety Results of Study IT-R-006

Extent of Exposure

Of the 98 IT-treated subjects 86 (88%) received all three treatments, six subjects (6%) received two treatments, and six (6%) received one treatment. Of the 99 vehicle-control treated subjects, 97 (98%) received all three treatments and two (2%) received two treatments and no subjects received only one treatment.

Common Adverse Events

The most commonly reported TEAEs in the IT-treated group were injection-site erythema (14%), injection-site hemorrhage (10%), injection-site bruising (5%), and injection-site papules (4%) of subjects. In the vehicle-control group, the most commonly reported TEAEs were injection-site erythema (6%), injection-site hemorrhage (15%), and injection-site bruising (13%). The overall TEAE rates are balanced between groups, as shown in Table 37.

Table 37. Adverse Events in IT-R-006 > 1% Safety Population

Preferred Terms	IT N=98		Control N=99	
	Subjects	Events	Subjects	Events
All treatment-emergent AE	62 (63%)	161	56 (57%)	172
Injection-Site Reactions	32 (33%)	69	32 (32%)	84
(related to treatment)	29 (30%)	63	31 (31%)	80
Injection-site erythema	14 (14%)	19	6 (6%)	9
Injection-site hemorrhage	10 (10%)	30	15 (15%)	45
Injection-site bruising	5 (5%)	6	13 (13%)	20
Application-site papules	4 (4%)	4	2 (2%)	2
Injection-site irritation	3 (3%)	6	1 (1%)	3
Injection-site swelling	3 (3%)	3	0	0

Early Termination

One IT-treated subject withdrew consent due to an AE of mild injection-site bruising after the second IT treatment. No medical interventions were taken and the AE resolved in seven days. One subject (white male, age 77) was biopsied but did not receive study treatment. The subject died from cardiac arrest while he was in the ICU recovering from stomach cancer surgery.

Duration of TEAEs

The majority of related events resolved within three days. Of the 28 events that persisted beyond four days, 18 resolved by the end of seven days. One injection-site adverse event was ongoing at the time of data-lock. This consisted of an incidence of mild eye edema described as bilateral swelling of the upper eyelids. The applicant did not provide any additional details or the etiology for this event. The duration of TEAEs is shown in Table 38.

Table 38. Duration of TEAEs Related to Study Treatment in IT-R-006

Preferred Term	Duration in Days				
	≤ 1 Day	2-3 Days	4-7 Days	8-14 Days	>14 Days
Eye edema	0	0	1	0	1
Application site papules	0	2	1	1	1
Injection site bruising	1	13	10	1	0
Injection site erythema	6	19	1	1	1
Injection site hemorrhage	75	0	0	0	0
Injection site hypersensitivity	1	0	0	0	0
Injection site irritation	0	0	5	1	0
Injection site pruritus	1	0	0	0	0
Injection site swelling	0	2	0	1	0
Skin hyperpigmentation	0	0	0	0	2

Summary

The most commonly reported TEAEs in the IT-treated group were injection-site erythema (14%), injection-site hemorrhage (10%), injection-site bruising (5%), and injection-site papules (4%). The overall TEAE are balanced between groups, except injection-site erythema (higher in IT group) and hemorrhage that occurred at a slightly higher rate in the vehicle-control group.

7.1.4 Adverse Events in < 1% Safety Population in Studies 005 and 006

Table 39 lists less frequently-occurring adverse events in the two Phase 3 trials. These events were related to the product treatment by the investigators. The one case of basal cell cancer is discussed in Section 7.7.3. The adverse events were rare but expected for facial dermal injection. The case of recurrent eyelid edema may represent underlying skin hypersensitivity toward the product.

Table 39. Adverse Events < 1% in IT-R-005 and IT-R-006

Study	Group	Preferred Terms	Onset	Duration	Severity	Action
005	IT	Basal cell cancer	7 months after 1 st treatment	n/a	Moderate	Excision
005	IT	Herpes simplex of lip	5 days after 1 st treatment	4 days	Mild	meds
005	IT	Post-procedural headache	On 2 nd treatment	2 days	Mild	Meds
005	Control	Swelling under left eye	2 days after 1 st treatment	5 days	Mild	None
005	Control	Headache	On 1 st treatment	1 day	Moderate	Meds
005	Control	Injection site anesthesia	3.5 months after 3 rd treatment	5.5 months	Mild	none

Study	Group	Preferred Terms	Onset	Duration	Severity	Action
005	Control	Pain in jaw	On 1 st treatment	2 days	Mild	None
005	Control	Paresthesia right upper lip	2 days after 1 st treatment	3 days	Mild	None
005	Control	Post-procedural discomfort	On 1 st treatment	1 day	Mild	None
006	IT	Bilateral eyelid edema	1 day after each of 3 treatment	1 st , 2 rd : 1 week 3 rd : > 1 year	Mild	None
006	IT	Skin hyperpigmentation	1 day after 2 nd treatment	3 weeks	Mild	None
006	Control	Injection site hypersensitivity	On 1 st treatment	2 days	Moderate	None

7.1.5 Twelve-Month Long-Term Safety Assessment in Studies 005 and 006

On September 4, 2009, the applicant submitted the preliminary long-term 12-month safety data for Studies 005 and 006 via email. On November 1, 2009, the applicant submitted Amendment 21 that includes long-term clinical study reports for Studies IT-R-005, IT-R-006, and IT-R-007. In the submission, the applicant emphasized that the subjects in the long-term study of 005 and 006 had remained blinded during the telephone interview. Besides safety questions, the applicant also asked the subjects whether their facial appearance was better, worse or unchanged.

The following describes the telephone assessment regarding the safety data:

At Month 12 after the last injection, subjects were called by the investigator to collect safety information by asking the following two questions:

1. Our records show that you had the following unresolved medical problem at the time of your last study visit. Since this last visit, has the problem resolved? If so, when did it resolve?
2. Have you experienced any medical problems in the vicinity of the treatment area since your last study visit?

Safety summary of Month 12 telephone call:

- 167 subjects (79 IT and 88 vehicle) in IT-R-005 and 183 (88 IT and 95 vehicle) in IT-006 completed the 12-month safety evaluation.
- Two (injection site numbness and puffiness) of the four unresolved adverse events were resolved at 12 months, whereas one event of ridge above the right nasolabial fold and one event of bilateral eyelid swelling remained ongoing at 12 months, as summarized in Table 40.
- Three subjects with late-onset events near the injection sites were identified in Study 006. The AEs are (1) raised pustular bumps on cheeks and nose, (2) mild seborrheic dermatitis at the nasolabial folds, (3) injection site redness, peel and dryness. The three subjects all received vehicle-control injection.
- No cases of tumor were reported.
- No cases of keloid were reported.

Table 40. Outcome of the Four Unresolved AEs at Six Months

Subject#	Unresolved AE at 6 months	Time of Onset	Duration of AE	Outcome of AE at 12 months
-(b)(6)-	Numbness at right nasolabial fold	105 days after 3rd treatment	164 days	Resolved
-(b)(6)-	Puffiness at left nasolabial fold	8 days after 2rd treatment	208 days	Resolved
-(b)(6)-	Ridge above right nasolabial fold	8 days after 2rd treatment	+345 days	Ongoing
-(b)(6)-	Swelling on left and right upper eye lids	Third Treatment	+340 day	Ongoing

7.2 Safety Results of Study IT-R-001

Study Design

IT-R-001 was a Phase 2, double-blind, randomized, vehicle-controlled study in 40 subjects randomized to treatment with one of three dose levels of IT or vehicle. The subjects received three sets of injections at a one to two-week interval. The study was conducted at two US centers to determine the safety and efficacy of IT for improving rhytids at Month 4. Subjects who received the low dose of IT or vehicle-control in the acute phase elected to receive a high dose of IT for three treatments. All subjects who received IT were followed at 6, 9, and 12 months after their last treatment in a long-term, open-label study.

Results

All three IT dose levels were regarded as generally safe and showed no differences in safety compared to vehicle control. Twenty subjects experienced at least one injection-related adverse event. These events include injection-site edema, pain, inflammation, and injection-site ecchymosis. All the adverse events were judged as either mild or moderate in severity. One subject reported glabellar erythema and swelling that were ongoing at the end of 12-month follow-up.

7.3 Safety Results of Study IT-R-002

Study Design

IT-R-002 was a randomized, vehicle-controlled, double-blind Phase 2 study conducted in ten sites in the United States. The study was designed to assess the safety and efficacy of IT injection for the treatment of adults with rhytids (n=109) and facial scars (n=49), with IT to vehicle-control randomized in a 3:1 ratio. The subjects received three treatments at one to two-week intervals and were followed for safety and efficacy for four months from their first study treatment. The efficacy endpoint was the investigator assessment using a seven-point ordinal scale at the four-month visit. After unblinding for efficacy and safety analysis at four months, 31 of the control-group subjects elected to receive open-label treatment with IT. All the subjects who received IT were asked to participate in a long-term open-label study for efficacy and safety. The subjects were followed for 12 months after their first treatment with three visits at Months 6, 9 and 12.

Study Results

Acute Phase Study (4 months)

Of a total of 158 subjects enrolled, 139 completed the study. Nineteen subjects discontinued from the study for reasons other than adverse events. The primary endpoint assessment showed a statistically significantly higher responder rate in the IT group as compared to the vehicle-control group. The safety population included 151 subjects who received at least one injection, 111 IT subjects and 40 vehicle-control subjects. As shown in Table 41, injection-site edema and pain were reported only by IT patients. Injection-site ecchymosis occurred in both groups with higher frequency in the control group. Most events were mild to moderate in severity. One IT subject reported severe injection-site edema in glabellar and upper eyelid areas. The event resolved in two days without intervention. Of note, “injection-site edema” was reported from only one of the ten centers in Study IT-R-002.

Table 41. Treatment-Emergent Adverse Events in Study IT-R-002

Adverse Events	IT n=111 N=events (%)	Control n=40 N=events (%)
Injection-site edema	25 (22.5%)	0
Injection-site ecchymosis	18(16.2%)	11 (27.5%)
Injection-site inflammation	9 (8.1%)	3 (7.5%)
Injection-site pain	6 (5.4%)	0
Injection-site reaction	2 (1.8%)	2 (5%)
Subcutaneous tissue changes	4 (3.6%)	0
Total	64 (57.6%)	16 (40%)

Long-term Study (12 months):

Of the 142 subjects in the long-term phase of the study, 122 completed the study. Four subjects reported new adverse events during the period 6 to 12 months after the acute study (injection-site inflammation, joint disorders, and sinusitis). None of the AEs were considered to be related to the product by the investigator. One subject reported flare of alopecia, which was ongoing at the end of 12 months. The investigator listed this event as possibly related.

Reviewer Comment: Injection-site edema and pain were reported only by IT subjects (22.5% and 5.4%, respectively). One case of injection-site ischemia was reported in an IT-treated subject. The event resolved in two days without intervention.

7.4 Safety Results of Studies IT-R-003A and IT-R-003B

Study Design

IT-R-003A and IT-R-003B were identical, randomized, double-blind, vehicle-controlled Phase 3 studies conducted in six US centers (three in each study) to evaluate efficacy and safety of IT for the treatment of adults with nasolabial and glabellar deformities. Both studies were evaluated by FDA under Special Protocol Assessment.

Subjects received IT or vehicle control for a total of three treatments at one to two-week intervals. Outcomes of efficacy and safety were determined at Month 6 after the first treatment. The co-primary endpoints were measured by an investigator six-point ordinal scale (Lemperle) and subject visual analog scale (VAS). A total of 123 subjects were randomized (1:1) in Study IT-R-003A and 115 subjects were randomized (1:1) in Study IT-R-003B. The subjects who finished the acute study were asked to participate in a long-term, open-label study with visits at Month 9 and Month 12. The subjects who received vehicle-control during the acute phase were terminated from the long-term study.

Results

Study IT-R-003B showed treatment-related efficacy for both co-primary endpoints; however, Study IT-R-003A failed to attain the co-primary endpoint that was based on investigator assessment. More local adverse events were reported by IT patients as compared with vehicle-control group (Table 42). Two cases of local ischemia and five cases of local nodules were reported in these two trials.

Table 42. Treatment-Emergent Adverse Events

Adverse Events	IT-R-003A		IT-R-003B	
	IT N=48, n (%)	Control N=59, n (%)	IT N=52, n (%)	Control N=54, n (%)
Injection Site Erythema	15 (31%)	7 (12%)	3 (6%)	0
Injection Site Hemorrhage	9 (19%)	17 (29%)	1 (2%)	2 (3.7%)
Injection Site Pain	8 (17%)	2 (3%)	3 (6%)	0
Injection Site Edema	8 (17%)	0		
Injection Site Swelling	7 (15)	0		
Injection Site Nodule	4 (8%)	1 (1.7%)		
Injection Site Dermatitis	3 (6%)	1 (1.7%)	2 (3.8%)	0
Injection Site Induration	3 (6%)	0		
Injection Site Reaction	3 (6%)	0		
Injection Site Ischemia			2 (3.8%)	0

Reviewer Comment: Based on information from Studies 003A & 003B and prior studies, the applicant modified aspects of the study design for the next two Phase 3 trials 005 and 006 under Special Protocol Assessment. The changes were (1) increasing dosing, treatment intervals, and study observation time (two more months); (2) treatment of nasolabial folds only; (3) defining response as a two-point improvement in both nasolabial folds; (4) increasing baseline wrinkle severity; (5) changing subject assessment instrument from VAS to a 5- point ordinal scale; (6) limiting the number of injectors and evaluators per site, and defining a training program for injection technique as well as assessment of severity.

7.5 Safety Results of Study IT-R-007

Study Design (refer to Section 5.5 for detail):

IT-R-007 was a Phase 2, prospective, multicenter, open-label 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 approximately five weeks apart. This study exposed subjects to a 3-fold higher dose of IT than in the IT-R-005 and IT-R-006 studies. All subjects were followed for six months after the final treatment and then received a telephone call assessment of safety at 12 months after the final injection.

Safety Results:

Acute Phase: a total of 88 adverse events were reported by 46% of subjects; 49% of adverse events were related to the product. As shown in Table 42, common adverse events were injection-site erythema (12%), injection-site bruising (10%), injection-site swelling (10%), injection-site nodules (8%: 7 cases), pain (6%), and pruritus (4%). Ninety-three per cent of local AEs resolved within two weeks. One patient had injection-site pain for 32 days. One event of “slight numbness in upper lip” was ongoing at the end of the acute phase (Month 6), see Table 43.

Table 43. Injection Site Adverse Events in Studies 007, 005, 006 and Integrated Safety Population

Study	IT-R-007	IT-R-005		IT-R-006		Integrated Safety Population	
Adverse Events	IT N=50	IT N=83	Control N=92	IT N=98	Control N=99	IT N=508	Control N=354
Administration site conditions	11 (22%)	31 (37%)	32 (35%)	32 (33%)	32 (32%)	343 (67%)	144 (40%)
Injection site erythema	6 (12%)	23 (28%)	17 (19%)	14 (14%)	6 (6%)	81 (16%)	33 (9%)
Injection site bruising	5 (10%)	4 (5%)	12 (13%)	5 (5%)	13 (13%)	54 (11%)	48 (14%)
Injection site swelling	5 (10%)	18 (22%)	15 (16%)	3 (3%)	0	69 (14%)	15 (4%)
Injection site nodule	4 (8%)	2 (2%)	2 (2%)	0	0	20 (4%)	3 (1%)
Injection site pain	3 (6%)	5 (6%)	4 (4%)	0	0	31 (6%)	6 (2%)
Application site papules	2 (4%)	2 (2%)	1 (1%)	4 (4%)	2 (2%)	8 (2%)	3 (<1%)
Injection site pruritus	2 (4%)	0	0	0	0	5 (1%)	3 (<1%)

Long-Term Phase: as shown in Table 44, one ongoing adverse event at end of acute phase described as “slight numbness above right lip” resolved without sequelae at long-term telephone call with a total duration of about 10 months. The subject received IT treatment. Another subject, who received two IT treatments and reported no adverse

event in acute phase, gave information of an adverse event of discoloration in right eye fine line and scar at long-term telephone follow-up. This event resolved about 10 months later.

Table 44. Related-Adverse Events at Long-Term 12 Month Follow-Up in Study 007

Subject # Group	Race/Sex Age	Adverse Events	Treatment Regions	Onset	Duration	Severity & Relatedness	Action
-(b)(6)- IT	W. F 43 yo	Hypoaesthesia oral (“slight numbness in right upper lip”)	Bilateral Forehead Periorbital Cheek, Perioral	On 2nd treatment	10 months, resolved	Mild, possible	None
-(b)(6)- IT	W. F. 47 yo	Discoloration- right eye fine line scar	Forehead Periorbital Cheek Perioral	Unknown, reported at 12 Month telephone call	10 months, resolved	unknown	None

Source: BLA125348, Amendment 21, Section 12, page 556, 729

Reviewer Comment: Study 007 was designed to test the safety and efficacy of increased dose of IT (total volume doubled as compared to Studies 005 & 006) with increased areas of exposure (8 facial regions). As shown in Table 42, the local adverse events occurring in Study 007 are similar to those of the pivotal trials as well as the summation of the seven trials in terms of type and frequencies. Therefore, increased exposure areas with increased dosing demonstrated tolerability similar to the pivotal trials. The notable and significant adverse events include increased nodule formation (Table 44) along with two long- lasting events as shown in Table 45.

7.6 Analysis of Integrated Safety Information

7.6.1 Overview, Extent of Exposure and Methodology of Assessment

As shown in Table 45, the integrated safety population consists of the 862 subjects who received at least one injection of either IT or vehicle-control across the three Phase 2 and four Phase 3 trials. The population includes 508 subjects who received IT (including 41 subjects in control to IT cross-over) and 354 subjects in vehicle-controlled groups.

Table 45. Integrated Safety Information from Seven Trials

Study	Phases	Safety Observation (months)	Subjects IT/Control	Treatment Intervals (weeks)	Indications
IT-R-001	Phase 2	12	30/10	1-2	Rhytids and scar / 14 facial regions
IT-R-002	Phase 2	12	111/40	1-2	Rhytids and scar / 14 facial regions
IT-R- 003A	Phase 3	12	48/59	1-2	Nasolabial and glabellar / 4 facial regions

Study	Phases	Safety Observation (months)	Subjects IT/Control	Treatment Intervals (weeks)	Indications
IT-R-003B	Phase 3	12	52/54	1-2	Nasolabial and glabellar / 4 facial regions
IT-R-005	Pivotal	15	83/92	4-6	Nasolabial / 2 facial regions
IT-R-006	Pivotal	15	98/99	4-6	Nasolabial / 2 facial regions
IT-R-007	Phase 2	14	44/0	4-6	Forehead, periorbital, cheek, perioral / 8 facial regions
Total	7	12-15	862 (467+41*/354)	1-6	2-14 / facial regions

*subjects crossed-over from control group to IT group

The total length of safety observation includes the acute study observational phases, which varied from four to nine months, with the addition of long-term 12-month safety follow-ups from first or last treatment in all seven trials.

Both the amount of IT and facial regions that were exposed to the product varied among the seven clinical trials. As shown in Table 46 below, IT-treated subjects received an average of nine injections (range from 2 to 20), while vehicle-control subjects received eight injections (range 2 to 15). The average total dose per subject receiving IT was 3.7 mL (range from 0.7 to 12 mL). The number of treated facial regions differed across individual trials (2 to 14 injected regions) and included facial areas of forehead, glabellar line, periorbital line, nasolabial folds, melolabial folds, perioral lines, pock marks, and acne scars.

The schedules of safety data collection varied among seven trials, ranging from every one or two weeks up to every five weeks for a total of two to three treatments. During each visit, all adverse events collected from physician observation and patient spontaneous reporting as well as in response to questioning were assessed and classified by the investigator according to standard medical terminology of adverse events. The adverse events were documented with detailed description, including the time of onset, severity, and relationship to the product, medical intervention, and outcomes.

The frequencies of treatment-emergent adverse events from all seven clinical trials were pooled and tabulated for each preferred term in System Organ Class under IT and vehicle-control groups. The treatment-emergent adverse events are 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.

Table 46. Extent of Exposure for the Integrated Safety Population by Treatment

Extent of Exposure	# of subjects, Mean, Median, Range	IT	Control	IT (Crossover)
Number of Injections per	Number of subjects	467	354	50

Extent of Exposure	# of subjects, Mean, Median, Range	IT	Control	IT (Crossover)
Subject	Mean (SD)	9.1 (3.7)	8.2 (2.9)	10.0 (3.0)
	Median (range)	9 (2, 20)	6 (2, 15)	12 (3, 15)
Total Dose per Subject (mL)	Number of subjects	467	354	50
	Mean (SD)	3.7 (2.7)	2.9 (0.7)	2.9 (0.4)
	Median (range)	3.1 (0.7, 12.0)	3.0 (1.0, 6.0)	3.0 (1.0, 3.6)
Average Dose per Visit (mL)	Number of subjects	467	354	50
	Mean (SD)	1.5 (1.5)	1.0 (0.2)	1.0 (0.1)
	Median (range)	1.0 (0.2, 6.0)	1.0 (0.4, 2.0)	1.0 (0.3, 1.2)
Number of Subject Month on Study	Number of subjects	466	354	50
	Mean (SD)	8.2 (2.9)	8.3 (3.4)	7.8 (4.9)
	Median (range)	8.0 (0, 15.2)	7.9 (1.4, 20.9)	11.2 (0.5, 12.8)
Time from First to Last Treatment (Months) Subjects with < 12 injections	Number of subjects	279	250	23
	Mean (SD)	1.8 (1.4)	1.9 (0.8)	0.6 (0.2)
	Median (range)	1.9 (0, 9.8)	2.1 (0, 9.1)	0.5 (0.4, 1.0)
Time from First to Last Treatment (Months) Subjects with ≥ 12 injections	Number of subjects	187	104	27
	Mean (SD)	0.8 (0.3)	0.7 (0.2)	0.6 (0.2)
	Median (range)	0.9 (0.5, 1.7)	0.7 (0.5, 1.9)	0.6 (0.5, 1.4)
Source: Module 5, Volume 64, Section 5.3.5.3.2, Page 20 of 194, Table 2.				

Reviewer Comment: The treatment intervals increased from 1-2 weeks in early studies to 4-6 weeks in later studies for the purpose of decreasing adverse events and increasing the fibroblast growth in the injection site. Therefore, the accuracy of information collection based on patients' memory with regard to time to onset and duration, and other characteristics may be compromised when such adverse events occurred in the first hours or days post-treatment. In the absence of a formal mechanism for safety data collection such as patient diary, the spacing of the safety observation intervals may affect the accuracy of the safety data collection.

7.6.2 Adverse Events in more than 1% of Safety Population

Table 47 presents the frequencies of all the treatment-emergent adverse events in all the major organ systems occurring in at least 1% of subjects in either treatment group. Across seven clinical trials, 67% (343/508) of IT subjects reported injection-site adverse events, while 40% (144/354) of vehicle-control subjects reported those events. All adverse events occurring in other organ systems were approximately balanced between the two treatment groups and were mostly considered unrelated to the product. The

common treatment-related adverse events were injection-site erythema, bruising, swelling, pain, hemorrhage, edema, nodules, and papules.

Table 47. Frequencies of TEAE in Integrated Safety Population (>1%)

System Organ Class Preferred Term	IT (%) N=508	Control (%) N=354
General Disorders and Administration Site Conditions	343 (67%)	144 (40%)
(Related to treatment)	265/508 (52%)	119/354 (34%)
Injection-site erythema	81 (16%)	33 (9%)
Injection-site bruising	54 (11%)	48 (14%)
Injection-site swelling	69 (14%)	15 (4%)
Injection-site pain	31 (6%)	6 (2%)
Injection-site hemorrhage	13 (3%)	16 (5%)
Injection-site edema	22 (4%)	0
Injection-site nodules	20 (4%)	3 (<1%)
Application-site papules	8 (2%)	3 (<1%)
Injection-site irritation	6 (1%)	1 (<1%)
Injection-site dermatitis	5 (1%)	2 (<1%)
Injection-site pruritus	5 (1%)	3 (<1%)
Injection-site reaction	5 (1%)	2 (<1%)
Infections and Infestations (e.g., sinusitis)	80 (16%)	81 (23%)
Skin and Subcutaneous Tissue (e.g., acne)	47 (9%)	26 (7%)
Musculoskeletal and Connective Tissue (e.g., arthralgia)	33 (6%)	27 (8%)
Injury, Poisoning, and Procedural Complications (e.g., foot fracture)	24 (5%)	31 (9%)
Nervous System (e.g., headache)	24 (5%)	23 (6%)
Respiratory, Thoracic and Mediastinal (e.g., cough)	19 (4%)	15 (4%)
Vascular Disorders (e.g., hypertension)	12 (2%)	6 (2%)

Reviewer Comment: The control is not a true placebo. Subjects in the control group received a vehicle control injection. The adverse events in the control group were similar to those of the active group but at lower frequencies. Of all the injection site reactions, erythema, swelling) and pain were reported significantly higher in the IT subjects. Injection needle, volume, vehicle, cultured fibroblasts and its secreted factors, and media component all play a role for the local adverse events. These local adverse events occurred at high rates and are expected for any facial cosmetic dermal injection

7.6.3 Adverse Events in less than 1% Safety Population

Table 48 lists the adverse events that occurred in less than 1% of the safety population. The examples of adverse events are acne, rash, eyelid and facial edema, flare of herpes in lips, change in the skin sensations, and post-procedural discomfort, such as dizziness and headaches. These events occurred more frequently in the IT group.

Table 48. Adverse Events <1% Integrated Safety Population

Preferred Terms	IT N=508	Control N=354
Acne	4	0
Rash	2	0
Eye edema	2	1
Face edema	3	1

Preferred Terms	IT N=508	Control N=354
Herpes Labialis	3	0
Injection site vesicles	1	0
Hypoaesthesia	2	0
Injection site hypersensitivity	0	1
Lip paresthesia	0	1
Basal cell carcinoma	1	0
Injection site fibrosis	1	0
Injection site ischemia	2	0
Parapsoriasis	1	0
Alopecia areata	1	0
Hyperpigmentation	1	0
Pain in jaw	0	1
Headache	5	2
Post-procedural discomfort	0	1
Toothache	0	1
Chapped lips	1	0
Dizziness	2	0
Total	32	9

Reviewer Comments: (1) potential local allergic reaction: the description of a group of local events such as acne, rash, eye-lid/face edema implicates a skin hypersensitivity of IgE/histamine reactions or a hormonal effect. The potential allergens are likely derived from the cell product, its secreted factors and residual cell culture agents as most of such events only occurred in the IT group. (2) Altered immune response: another group of local events such as herpes flare, parapsoriasis, and alopecia flare may implicate an altered humoral or cellular immune status. (3) Changes of local circulation and peripheral nerve: a group of events such as hypoaesthesia, injection site hypersensitivity, lip paresthesia, and injection site ischemia (refer to Section 7.4.1): these events may indicate that needle injection, volume pressure, product/agents or anatomical location may compromise peripheral circulation or innervations.

7.6.4 Severity of Adverse Events

The severity of adverse events was graded based on Common Terminology Criteria for Adverse Events Version 3. For injection-site adverse events as shown in Table 49, 82% (283/343) of IT subjects were graded as mild (slight lesion or minimal symptoms), 16% (55/343) graded as moderate (marked or generalized lesion, symptomatic, simple medical intervention indicated), and 1% (5/343) graded as severe (interfering with activity of daily living, intervention indicated). Among subjects reporting severe events, five IT subjects reported injection-site erythema, pain, swelling, and ischemia, and one control subject reported injection-site bruising. All these severe events lasted from one to ten days and resolved without intervention except one case of ischemia (patient received aspirin and oxygen). None of the subjects with severe adverse events withdrew from the studies.

Table 49. Severity of injection-site adverse events in >1% integrated safety population

Injection-Site Reactions	IT N=343	Control N=144
Mild (slight lesion, minimal symptoms)	283 (82.5%)	131 (91%)

Injection-Site Reactions	IT N=343	Control N=144
Moderate (marked lesion, some symptoms, simple intervention needed)	55 (16%)	12 (8%)
Severe (interfering with activity of daily living, intervention indicated)	5 (1.5%)	1 (<1%)
Number of subjects reporting injection site adverse events		

Reviewer Comment: The majority of local events were mild or moderate in severity (98.5%). The product is generally tolerated. CTCAE is commonly used in oncological trials as well as other trials for grading adverse events; it was used by the applicant for Isolagen trials. However, the limited terminology in the cutaneous section may not provide precise definitions for the wide range of local adverse events occurring during these trials.

7.6.5 Duration of Adverse Events

Duration of treatment-related events is summarized in Table 50. Within seven days of onset, 85% (380/444) of injection-site adverse events in the IT group and 90% (187/207) of such events in the control group resolved. About 5% of such events lasted beyond 30 days. At the end of the study, five IT-related events were ongoing. Those five events were injection-site swelling, erythema, alopecia, skin numbness, and eyelid edema. Those events were graded as mild, and two events required medication treatment. The unresolved adverse events will be discussed in Section 7.3 Significant Adverse events.

Table 50. Duration of Injection-Site Adverse Events >1% Safety Population

Duration (days)	IT-Related Events=444	Control-Related Events=207
< 1 to 7	380 (85.5%)	187 (90%)
8 to 14	23 (5%)	13 (6%)
15 to 30	16 (3.6%)	1 (0.5%)
31 to 60	9 (2%)	2 (1%)
61 to 90	8 (1.8%)	2 (1%)
91 to 120	2 (0.4%)	0
Ongoing	5 (1%)	0

Reviewer Comment: The majority of injection-site adverse events was short-lived, without long-lasting sequelae, and is expected for any type of facial cosmetic dermal treatment. Therefore, the product is generally well tolerated. However, the longer-lasting events (>30 days) in 5% subjects and 1% persistent events may confer cosmetic concerns for a healthy individual seeking improvement of facial wrinkles.

7.6.6 Comparison of Adverse Events in Pivotal Trials with Integrated Safety Data

Table 51 presents the frequencies of injection site adverse events in Studies 005 and 006 as well as the integrated safety population. In comparison, subjects in Studies 005 and

006 reported lower incidence of injection site adverse events, about 30% vs. about 60% in the integrated safety population.

Table 51. Total injection site reactions in pivotal trials and integrated safety population > 1%

Study	IT-R-005		IT-R-006		Integrated safety population	
Subjects	IT N=83	Control N=92	IT N=98	Control N=99	IT N=508	Control N=354
Injection-Site Reactions	31 (37%)	32 (35%)	32 (33%)	32 (32%)	343 (67%)	144 (40%)

Reviewer Comment: The underlying reasons for decreased frequencies of adverse reactions may be due to one or more of the following factors: increased treatment intervals, enhanced physician training for injection techniques, and decreased exposed areas, as suggested by the applicant. The increased spacing of clinical safety observation intervals in the pivotal trials may play a role in decreased reporting of the adverse events.

7.7 Significant Adverse Events

7.7.1 Injection-Site Ischemia

Injection-site ischemia was described as “duskiness” and “purple mark”, and defined as “temporary interruption of blood supply” by the investigators in the case report forms. Three cases of ischemia were reported in Studies IT-R-002 and IT-R-003B. The three subjects were white females aged 51 to 54 years, who all received three IT treatments. One of the IT subjects in Study IT-R-003B reported a severe case of ischemia in the glabellar area at the third treatment. The patient was given aspirin and oxygen at the office, and the event resolved within one day. The other two subjects in Studies IT-R-002 and IT-R-003B reported mild ischemia at their second and third injection in the nasolabial area, which resolved within two days without intervention and without sequelae.

Reviewer Comment: Glabellar ischemia was a rare complication of bovine collagen implant (Zyderm and Zyplast). Evidence strongly suggested glabellar region is vulnerable to ischemia because of its unique vascular distribution. For this BLA, the three cases of ischemia all occurred in early trials, all of them received IT product, and one case was in the glabellar area. Enhanced injection technique training and avoidance of glabellar injection site may be related to the absence of ischemia in Studies 005 and 006.

7.7.2 Injection-Site Nodules

Injection-site nodules were reported in 20 subjects in the IT group and three subjects in the vehicle-control group. The subjects were all white females, average 51 years of age. All nodules were described as mild and resolved within one day to two weeks without medical intervention. The applicant did not describe how these nodules were defined,

and there were no histological data provided. More cases of nodules were reported in early studies IT-R-001, IT-R-002, IT-R-003 (16/283) than in later studies IT-R-005, IT-R-006, and IT-R-007 (7/226).

During the UK commercial phase, a serious adverse event of injection site lump was reported in a subject who received IT injection into an existing scar and granuloma on eyelid. The biopsy of the lump showed “fibrous overgrowth” after the lump was surgically removed. No detailed information was provided in the submission.

Reviewer Comment: There were no biopsy data describing those nodules because most of them were short-lived and mild. Some adverse events suggested a persistent nature of the nodules. For example, one subject had a persistent “ridge” and one subject had a “plumpness” on the injection sites (see unresolved AE) and the other had “injection site fibrosis” (see related AE in <1%). Post-treatment biopsy should target these early and late events of nodule formation. Biopsy data may clarify whether scar formation or inflammatory reaction is the underlying pathogenesis.

7.7.3 Basal Cell Carcinoma

Basal cell carcinoma was diagnosed in a 76 year-old white female who had a history of sun damage in the skin and received three IT treatments in Study IT-R-005 (Table 52). A 0.4 cm x 0.4 cm basal cell cancer was discovered immediately adjacent to the right nasolabial injection site seven months after the first IT treatment. A lesion of solar keratosis was found on the bridge of the nose at the same time. The basal cell cancer was excised and the subject did not have evidence of recurrence at the 18-month follow-up. For the assessment of wrinkle treatment, the patient was rated as a non-responder by the investigator. The investigator judged the event as possibly related to the product. Another subject was diagnosed with basal cell cancer in the shoulder area.

Table 52. Adverse Event Description: Subject --(b)(6)-- with Basal Cell Carcinoma

Demographics	76 yo, White, Female, ex-smoker						
Screening (1/8/07)	Skin: sun damage; eye: decreased vision acuity; Neuro: hand tremors						
Concomitant Medications	Primidone, sanctura, atenolol, vitamin c, multivitamin, loreal Brush powder, neutrogena anti-aging, sun screening, Ponds moisturizer cleanser						
IT #1 (4/11/07)	R+L nasolabial folds: 5+5.3 cm in length, total of 1.03 mL injection						
IT # 2 (5/18/07)	R+L nasolabial folds: 10.3 cm, 1.03 mL						
IT #3 (6/13/07)	R+L nasolabial folds: 10.3 cm, 1.03 mL						
Adverse Events	Onset	Resolution	Severity	Relation	Action	Outcome	SAE
Redness at injection site	4/11/07 5/18/07	4/14/07 5/20/07	Mild	Definite	None	Resolved	No
Swelling at injection site	4/11/07 5/18/07	4/14/07 5/19/07	Mild	Definite	None	Resolved	No
Solar keratosis at nasal dorsum	11/07	11/5/07	Mild	Unrelated	Liquid nitrogen	Resolved	No
Basal cell at right upper lip (pearly papule)	11/07	11/14/07	Moderate	Possible	Biopsy: 11/4/07 Mohs excision: 11/14/07	Resolved	No
Scar at right nasolabial fold	11/14/07		Mild	Unrelated	None	Unresolved	No

Scar at nasal dorsum	11/5/07		Mild	Unrelated	None	Unresolved	No
Seborrheic keratosis: back, forehead, neck,		11/5 – 11/21/07	Mild to moderate	Unrelated	Liquid nitrogen	Resolved	No
Wrinkle Outcomes	Subject Wrinkle Satisfaction Assessment: responder: -1 at baseline, +2 at Months 6						
	Evaluator Wrinkle Severity Assessment: non-responder: +3 at baseline and Months 6						
Source: Case Report Form --(b)(6)--							

Reviewer Comment: The safety profile of ex vivo expanded autologous fibroblasts is unknown with regard to tumor formation. There is theoretical risk of fibroblast transformation during the cultured conditions. It is inconclusive from this single case whether IT can promote the development of basal cell cancer. The investigator reported skin “sun-damage” during this subject’s screening physical examination. This patient was at increased risk of developing basal cell cancer, based on her age, location of the lesion, and sun exposure. To determine whether the product increases the risk of skin cancer formation requires a prolonged period of safety observation and a larger population.

7.7.4 Allergic Reactions

Two cases of anaphylactic reactions were reported as serious adverse events in the UK between 2005 and 2006. One subject developed severe swelling and itching immediately post-injection followed by throat restriction seven days later. Injection-site redness lasted for several months. The subject had known allergy to latex and lidocaine. The subject was treated with antibiotics and steroids. Another subject developed full facial swelling and redness (possible angioedema) three days post-injection, and the event lasted for a week. The subject was a smoker and had a history of poorly controlled asthma and atopy. The subject was hospitalized and treated with steroids and antihistamine. In addition, 9% of subjects were found to have rosacea-associated adverse events in the UK.

In the UK, --(b)(4)-- had been used to wash the biopsy and to treat the cells during manufacture until November 2005. -----(b)(4)----- had been used in the final freeze medium until July 2006, but has since been removed from the final product. Therefore, it is possible that IT injections before 2006 contained -----(b)(4)-----, which can cause local and systemic allergic reactions.

Reviewer Comment: --(b)(4)-- has not been used in the manufacturing process of IT in the US. (b)(4) was not used in the final freeze media. No systemic allergic reactions were reported in the integrated safety population for this BLA submission. However, some of the injection-site reactions resembled local immune hypersensitivity reactions. For examples, one subject in Study 006 reported bilateral mild eyelid edema on the next day following each of three IT treatments in the nasolabial area. There were many cases of acne, rash, facial edema and prolonged swelling and erythema. No pre-clinical, histology or laboratory data are available to define the pathophysiology of such injection-site reactions. The potential allergens may be from the fibroblasts in which some features may be altered after the manufacturing process or trace amount of DMSO and -----(b)(4)----- in the final cell suspension. As per FDA product review, -----(b)(4)----- and DMSO

----- (b)(4) -----

-----, DMSO (a
class 3 solvent) has a permitted daily exposure of ----- (b)(4) -----

-----, No further in vivo testing, such as
----- (b)(4) ----- in subjects who receive Isolagen, is needed in view of these
data.

7.7.5 Herpes Simplex and Injection-Site Paresthesia

As shown in Tables 53 and 54, in the integrated safety population, post-injection herpes labialis was reported in 3 subjects (0.59%, 3/508) who received Isolagen injection. During commercial experience in the US, three cases (0.56%, 2/354) of herpes simplex were also described in a retrospective study in a total of 354 subjects (see Section 3.3 Commercial Experience).

Table 53. Incidence of Herpes Labialis in Integrated Safety Population and US Commercial Experience

Study	Safety Population	#subjects with Herpes Labialis or blisters	Incidence
Integrated Safety Population	508	3 (herpes labialis)	0.59%
US Commercial Experience	354	2 (herpes labialis)	0,56%
<i>Dermal filler post-market 1/03-9/08</i>	<i>804</i>	<i>39 (blister/cyst)*</i>	<i>4.8%</i>

*herpes labialis is not listed as a category

There were four cases of injection-site hyper or hypoanesthesia, two in Isolagen and two in vehicle-control. Most cases occurred in the lips and eventually resolved (Table 53).

Table 54. Herpes labialis and injection site sensory changes in < 1% safety population

Study	Adverse Events	Location	Onset from treatment	Duration	Severity	Action
002 IT	Herpes labialis	Not specified	2 days post-1 st treatment	5 days	Mild	Antiviral med
002 IT	Herpes labialis	Left lip	One day post-2 nd treatment	2 weeks	Mild	Antiviral med
005 IT	Herpes labialis	Left lower lip	5 days post-1 st treatment	3 days	Mild	Antiviral med
007 IT	Hypoaesthesia	Right eyebrow	The day of 1 st treatment	24 days	Mild	None
007 IT	Hypoaesthesia	Right side of upper lip	The day of 2 nd treatment	10 months	Mild	None
005 Control	Injection site anaesthesia	Top of right nasolabial fold	3.5 month post-3 rd treatment	5.5 months	Mild	none
006 Control	Injection site hypersensitivity	nasolabial fold	The day of 1 st treatment	1 day	Moderate	none

Source: BLA 125348, Amendment 013, Table 2, Page 20 of 28; Case Report Forms

Reviewer Comment: The recurrence of herpes labialis was usually triggered by exposure to UV light, febrile illnesses, stress, premenstrual tension, and surgical procedures such as dental or neural surgery, lip tattooing, or derm-abrasion. In post-marketing adverse events reporting, blister/cyst was reported at 4.8% in dermal filler users. Any surgical procedure that disturbed the nerve roots and adjacent tissues may precipitate the reaction of the latent herpes virus. For example, about 10 to 15% of those having a tooth pulled develop oral-labial HSV infection an average of 3 days after that procedure. Therefore, the occurrence of herpes simplex flare in the injected area in Isolagen study appears to be a low-prevalent event. The recurrence can be further lowered and managed by prophylaxis using anti-viral medication. Injection site skin sensory changes may be related to the needle and injected volume as well as cellular or liquid component, causing temporal peripheral nerve injury.

7.7.6 Unresolved Adverse Events

Table 55 displays five events of local injection-site reaction, all in IT subjects, that were ongoing at the end of the 12-month safety follow-up. These events include injection-site swelling, erythema, alopecia, numbness, and eyelid edema. All these ongoing adverse events were graded as mild, and two of the events required medication treatment.

Table 55. Unresolved Adverse Events in Safety Population at the 12 months

Study	Ongoing Adverse Events	Treatment Areas	Onset Day	Duration Day	Severity	Action
001	Redness and swelling in glabellar area	Glabellar, perioral	Second treatment	357+	mild	Benadryl, Aleve
002	Flare of alopecia areata	Nasolabial, perioral	Third day after second treatment	354+	mild	Aldara, Kenalog
003A	Plumpness in upper lip	Nasolabial, glabellar	A month after third treatment	287+	mild	no
005	Ridge in right nasolabial fold	Nasolabial	A week after second treatment	409+	mild	no
006	Swelling on left and right upper eyelids	Nasolabial	Third Treatment	396	mild	no

Reviewer Comment: The prolonged erythema, swelling and induration appear to be related to the product. Whether those long-term sequelae represent a scar or granuloma or chronic inflammatory process is unknown without biopsies of those tissues.

7.8 Safety Profiles in Subgroups

As shown in Table 56, the geriatric (>65 years), non-white, and male subgroups each comprised only 10% of total subjects in the safety population. As demonstrated in Table 57, elderly subjects (> 65 years) had increased incidences of local erythema and swelling as compared to the younger subjects. Males had decreased incidences of injection-site reactions such as erythema, swelling, and bruising as compared to females. Overall, the

safety profiles in all subgroups were similar to that of the integrated safety population; however, the ability to draw firm conclusions regarding safety was limited due to the small sample sizes of all those sub-groups.

Table 56. Subgroup Distribution in Integrated Safety Population

Sub-groups	IT N=467	Control N=354	Total N=821
> 65 years	44 (9%)	41 (12%)	85 (10%)
Male	42 (9%)	34 (10%)	76 (9%)
Non-white	43 (9%)	35 (10%)	78 (10%)
41 cross-over subjects not included			

Among non-white sub-groups, there were three African-American subjects in the IT group and five in the vehicle-control group. For Asian subjects, six were in the IT and three in the control group. Review of the African-American sub-group of eight subjects did not reveal any cases of keloid formation, which occurs more frequently in dark-skin populations (Fitzpatrick skin type IV to VI) in response to skin injury, compared to individuals with lighter skin color.

Table 57. Treatment-Related Adverse Events in Subgroups of Safety Population

Sub-Groups		Erythema N (%)	Swelling N (%)	Bruising N, (%)	Hemorrhage N (%)	Pain N (%)
< 50 Years	IT n=210	26 (12%)	22 (10%)	21 (10%)	6 (3%)	0
	Control n=111	10 (9%)	4 (4%)	8 (7%)	5 (5%)	0
> 50 < 65	IT n=254	45 (18%)	37 (15%)	29 (11%)	5 (2%)	1 (<1%)
	Control n=202	19 (9%)	7 (3%)	35 (17%)	8 (4%)	1 (<1%)
≥ 65	IT n=44	10 (23%)	10 (23%)	4 (9%)	2 (5%)	2 (5%)
	Control n=41	4 (10%)	4 (10%)	5 (12%)	3 (7%)	0
White	IT n=465	76 (16%)	62 (13%)	50 (11%)	13 (3%)	27 (6%)
	Control n=319	30 (9%)	14 (4%)	46 (14%)	15 (5%)	6 (2%)
Non- White	IT n=43	5 (12%)	7 (16%)	4 (9%)	0	4 (9%)
	Control n=35	3 (9%)	1 (3%)	2 (6%)	1 (3%)	0
Female	IT n=465	75 (16%)	66 (14%)	53 (11%)	13 (3%)	
	Control n=320	31 (10%)	15 (5%)	46 (14%)	15 (5%)	
Male	IT n=42	6 (14%)	3 (7%)	1 (2%)	0	
	Control n=34	2 (6%)	0	2 (6%)	1 (3%)	

Reviewer Comment: Whether this product increases the risk of keloid is inconclusive from an extremely small sample size of African American population (8 subjects). The population with Fitzpatrick skin types IV to VI and a history of keloid should be warned for the risk of keloid formation. A larger-risk population and longer period of observation is required to draw firmer conclusions regarding the potential risk of keloid formation in dark-skin subgroups. Post-treatment biopsy study in this subgroup may shed light on the potential risk for scar formation and fibrous overgrowth in the dermis after the product injection.

7.9 Safety Conclusions

Injection-site adverse Events: Most adverse events were local, transient and expected for a facial cosmetic injection. Common injection-site reactions in more than 1% of subjects included injection-site erythema, bruising, swelling, pain, nodules, hemorrhage, papules, irritation, dermatitis, and pruritus. Adverse events occurring in less than 1% of subjects included flare of herpes labialis, hypersensitivity or decreased sensation of the injection site, hyperpigmentation, and post-procedural discomfort such as headache and dizziness. Ninety-eight percent of injection-site reactions were graded as mild or moderate (CTCAE). Ninety-five percent of local adverse events resolved within 30 days. Overall, the product-injection was well tolerated and without long-lasting sequelae within the period of clinical studies. The above local adverse events might be further decreased and managed by reinforcing training of the physicians and care providers who will perform the whole procedures from post-auricular biopsy to product injection. The appropriate training should include (1) screening subjects for appropriate population and indication, (2) biopsy techniques: sterility, identify tumor or abnormal appearance in the biopsy and injection sites, handling of the biopsied tissues; (3) handling of the product, (4) injection techniques, (5) identify and manage the adverse events, such as using prophylaxis.

Tumor Formation: The issue of tumorigenicity is a general concern for any novel gene and cellular product. Autologous fibroblasts may have risks of undergoing transformation in the cultured conditions during the manufacturing process, although no such case was identified by the existing screening standard in this BLA submission. There is also a risk of tumor growth generated from the biopsied tissue. One subject who received the product-injection in Study 005 developed basal cell cancer immediately adjacent to the injection site seven months after the initial treatment. Although this case may not represent a direct safety signal for the product, its conclusion whether the product promotes skin cancer awaits for a longer term observation with a larger population at risk. One-year observation of 508 subjects is not enough to provide a safety conclusion regarding the risk of tumor formation. Effective screening and surveillance measures for the suspicious skin lesion in the post-auricular/injection site and during manufacturing process might decrease the probability of tumor formation. For this product, it is necessary to warn the vulnerable population which includes the elderly, smokers, and patients with photo-damaged skin, or familial malignancy syndromes.

Concerns of potential adverse events in under-represented population: Dark-skinned individuals (Fitzpatrick skin type IV to VI) and subjects with certain ethnic background (African American and Asian) have an increased predisposition for keloid, hypertrophic scar formation and skin discolorations in reaction to even a minor skin injury. Keloids may form slowly in the year after the initial insult. Although there were no reported cases of such events in this BLA, the real risk whether this product may cause such events can not be explored in a small sample size of only 40 non-white subjects with a total of 9 African Americans. Post-treatment biopsy study on dark-skin population may shed light on the risks of scar formation in the dermis. For this product, it is necessary to warn individuals who have a history of keloid.

7.10 Review of Commercial Training Manual (To be used in the labeling)

Commercial Training Manual:

A draft of the training manual was included in the BLA for the training of practitioners (if BLA was approved). The objective of this training manual is to provide healthcare professionals with instructions in the clinical use of IT. The sponsor will provide the product only to trained practitioners who are specially certified in the IT program; therefore, only certified prescribers will be able to administer IT. The manual is designed for use in combination with practical demonstrations and training from Isolagen trainers. Training sessions with an experienced physician will be organized by Isolagen.

The training manual contains written instructions (and photos) for the following:

- Product description
- Patient selection criteria
- Proper biopsy collection and shipment
- Proper treatment preparation and injection scheduling and technique
- Proper logistics training from biopsy to injection
- Specification of the types and severity of expected AEs, appropriate treatment and follow-up, and AE reporting instructions.

Reviewer Comments:

1. *The commercial training manual did not provide sufficiently detailed instructions on the items outlined above.*
2. *All investigators certified by Isolagen in the clinical studies were physicians whereas commercial treatment is proposed to be given by “healthcare professionals” and “practitioners,” according to the commercial training manual submitted.*
3. *The sponsor should also provide videos/DVDs to supplement the training manual.*
4. *The quality of the photos in the manual submitted in this BLA was very poor.*

(See Pre-Approval Action for specific recommendation on the commercial training manual, Section 9.1)

8. ADVISORY COMMITTEE MEETING

An FDA Cellular, Tissue and Gene Therapies Advisory Committee meeting took place on October 9, 2009 in Bethesda, Maryland. The topics covered at the AC meeting were as follows (see full text of the questions in Appendix D):

- Tumorigenicity potential of the fibroblast cell suspension
- Potential risk for hypertrophic scarring and keloid formation, or abnormal pigmentation in the non-Caucasian population
- Potential safety risks in patients over 65 years of age and in males
- Post-market training program for practitioners proposed by the sponsor, specific recommendations for the training program, and any additional recommendations on how to minimize the adverse events presented in the trial safety data
- Do the data presented demonstrate safety for the proposed indication? (*Discussion then vote*)
 - If no, what additional studies should be performed?

- If yes, do you have any specific recommendations for the labeling?
- Do the data presented demonstrate effectiveness for the proposed indication?
(Discussion then vote)
 - If no, what additional studies should be performed?
 - If yes, do you have any specific recommendations for the labeling?

8.1 Summary and Discussion of Advisory Committee Meeting (bulleted texts summarizing the AC members' discussion)

8.1.1 Efficacy

- Efficacy voting: Yes:11; No:3
- Voting for YES: (1) data limited but majority of panel believed IT to be effective in improving nasolabial fold wrinkles (2) however, there was consensus that Isolagen has more work to do to understand how the drug works (3) little information on the elderly, non-Caucasian, smokers; no information on effectiveness of repetitive injections beyond three
- Voting for NO: (1) considered data presented to be preliminary; want more data; suggested comparing photographs (2) unconvinced of the safety therefore cannot vote yes; study too superficial; concerned about potential wide ramifications (for off-label use) if approved (3) concerned about the validity of the evaluators' assessment as a co-primary endpoint

Reviewer Comment: The majority of the AC panel believed IT is effective in improving nasolabial fold wrinkles. Although the data presented looked good, the panel felt the studies were too superficial, the study population limited and too many questions were left unanswered. The panel felt that answers about the fate of the cells (survival, proliferation, migration, transformation); what type of collagen, elastin at injection site; whether remodeling, repair or scar formation took place were very important and could be readily obtained from post-treatment biopsy to provide a minimal level of data that any transplantation study would require. The challenge is that the proposed indication is not a disease or life-threatening condition, therefore the bar is quite high, especially for safety.

8.1.2 Safety

- Safety voting: Yes: 6; No: 8
- Voting for YES: adequate clinical experience to demonstrate safety; autologous product is generally safe
- Voting for NO: (1) the bar for aesthetic and cosmetic product should be high for setting a precedent for cellular products, (2) the product does not meet the standard in terms of characterizing what happens underneath the skin surface after the treatment particularly with regard to scar formation, collagen, elastin, cell survival, migration, proliferation, regulation or transformation, viral contamination or serum growth factors (3) visible AEs are not bothersome, non-visible things bothersome.
- Local adverse events: expected, but not out of norm, manageable

- Unanswered questions: (1) what happening underneath the surface of the skin: scar or normal tissue, remodeling or repair process, what type and amount of collagen, what changes in elastin, (2) fate of cells after injection: cell survival, migration, proliferation, and regulation, (3) product characterization: cell transformation, viral contamination or serum growth factors, and phenotype,
- Suggested studies: (1) Stored tissues: do karyotyping, tumor markers P53/P16, PCR or kits, and standard assays for identifying tumors in culture, (2) tissue biopsy can be from forearm or retro-auricular areas, do series of biopsies; (3) place cells retroauricularly; sequential biopsies, to see if cells viable, proliferate, produce collagen type 1 or 3 or elastic tissues or hyaluronic acid. We have markers for all of these things.

Reviewer Comment: Overall, AC members considered the local adverse event profile expected and manageable, and had less concerns for them. However, they worried about the invisibles, such as underlying changes in the dermis, fate of the cells, tumor risks, and factors for cell transformation in the cell cultures. They considered setting the precedent for the future cell product with a high standard for approval. They considered that the sponsor did not meet the standard criteria for product safety in terms of product characterization and post-treatment biopsy. Not knowing the underlying mechanism of action will impede the physician's ability to prescribe, use the product, and decrease the adverse events.

8.1.3 Product Safety

- Residual bovine serum albumin in the final product: concerns over the source of the fetal bovine serum used in the culture and its residual quantity in the final product. Concerns regarding its potential to cause allergic reaction.
- Quantity of human collagen in the product: concern regarding endogenous collagen in the cell suspension and its potential to cause local ischemia and clotting after the product injection
- Viral contamination during manufacturing process in the cell culture: concern regarding the risk of contamination and lack of testing
- Fibroblast growth factors secreted *in vivo and in vitro*: concerns regarding their potential effects on fibroblast transformation
- Tumor cell identification at the manufacture level: concerns regarding the inadequacy of morphology screening by the standard method. Suggested testing: karyotyping, using tumor cell markers for actinic keratosis, squamous cell cancer, basal cell markers, such as P16 and P53

*Reviewer Comment: After -----
----- (b)(4) -----
----- therefore, there is
minimal chance of allergy and no need for skin testing for bovine serum albumin.
Collagen in the final cell suspension is also low; there is minimal chance of causing
clotting as in the case of bovine collagen derma filler. Please refer to CMC Section for
more detail.*

8.1.4 Injection-Site Adverse Events

- Local reactions are expected and manageable: common for any type of cosmetic facial dermal treatment; few concerns over the frequency and types of local AEs
- Prophylaxis for local AEs: examples: Vitamin C and retinoid used for post-inflammatory hyperpigmentation; antiviral medication for oral herpes.
- Immunological reactions: concerns over post-injection adverse reaction resembling the immunoreactions: such as oral herpes, parapsoriasis, alopecia.

Reviewer Comment: AC members had less concerns over common local AEs because these AEs are expected for any types of cosmetic product injection and mostly manageable. Some of these AEs can be prevented by taking prophylaxis medications. The local AEs may be mitigated by implementing mandatory training programs for the user and closely monitoring.

8.1.5 Tumor Formation

- Twelve-month data is not enough to determine long-term safety
- No major concern regarding autologous fibroblasts
- Biopsy site: careful selection of donor site to identify tumor such as melanoma; may check the morphology in part of biopsy tissue to screen for skin cancers or atypical cells
- Manufacture/cell culture: potential factors for cell transformation: prolonged doubling cycles, growth factors exogenous or endogenous in the culture media, viral contamination, any component of culture media, culture conditions: level of oxygen, temperature, and other unknown factors.
- Concerns regarding inadequacy of morphological criteria to identify tumor cells
- Vulnerable populations: elderly, photo-damaged skin, smokers, and family cancer syndrome
- Suggested studies: (1) analyze the stored tissues using tumor cell markers P16 and P53 to screen actinic keratosis/squamous cell cancer, (2) karyotyping, (3) fate of cells: short-lived fibroblasts may not pose long-term risk for tumor formation

Reviewer Comments: AC members had less concern regarding the potential transfer of cancerous cells from the biopsy site and less concerns regarding autologous fibroblast itself for mechanism of tumor formation. But AC members expressed concerns regarding the manufacturing process of the fibroblasts in the cell cultures and the many unknown factors for potential transformation of the cells. Strategies for cancer prevention, detection, and determination of causal relationship to the product should be implemented at several levels: (1) warning for vulnerable populations who have history of skin cancers, risk factor for cancer: such as smoking, precancerous skin lesions, and familial cancer syndrome: such as Lynch syndrome; (2) physician training for detection of skin cancers or suspicious skin lesions at biopsy and injection sites; (3) manufacture process: following GMP protocol. Proposed studies: karyotyping, tumor marker

screening, please refer to CMC Section for detail, (4) post-market surveillance: long-term follow-up and registry (PMC or PMR)

8.1.6 Race and Ethnicity

- Not enough data to assess increased risks for any population
- Small sample of African Americans, 1% in all studies, higher risk for keloid
- Long-term study needed: keloid is slow to form beyond one year
- Potential AEs in non-whites: hyperpigmentation, vitiligo, keloid scar, hypertrophic scar. Hyperpigmentation can be addressed by prophylaxis with Vitamin C and retinoid
- Unknown mechanism of action: scarring vs. collagen production; concern regarding possibility of scarring leading to keloid in dark-skin population
- Suggested studies: (1) characterize the cultured cells from different race and ethnicity backgrounds; (2) identify mast cells and types of growth factors such as transforming growth factor beta 1 and 2 in the cell culture (3) prospective and retrospective data collection for safety information,
- Exclusion criteria: previous history of keloid

Reviewer Comments: AC members agreed that the lack of safety information in non-white population is a concern. Potential adverse events in the subgroups are skin discoloration and keloid/hypertrophic scar formation. Potential solutions to decrease and detect those potential adverse events are: (1) precaution regarding potential keloid formation in subjects who have a history of keloid formation and who have Fitzpatrick Skin type IV to VI; (2) post-market surveillance for longer time and larger sample size for non-whites, (3) understanding mechanism of action: retrospective and prospective post-treatment biopsy study to determine whether scarring occurs in the dermis after the product treatment

8.1.7 Geriatric (> 65 years) and Male Population

- Male: no major concerns for safety and efficacy. Increased risk of skin cancers behind ears in males because of more sun exposure
- Concerns of efficacy for elderly: slowed rate of cell growth, less scar formation (if mechanism of action is by scarring), less receptive tissue for growth factor stimulation, and wrinkles that are difficult to treat
- Safety concerns for elderly: less immune response, more photo-damaged skin, and different levels of health status and co-morbidity
- Concerns regarding whether to exclude this group based on low efficacy
- Suggested studies: characterize the fibroblasts of elderly in the cell culture: such as rate of growth

Reviewer Comment: AC members had concerns regarding efficacy and safety of the product for the elderly population but not certain about restricting its use in the elderly because of limited data. AC members had less concerns regarding male population, except for increased sun-exposure over the post-auricular areas as a risk factor for

cancerous changes. Prospective post-market data collection in elderly population in post-market will allow further clarification regarding the safety and efficacy in a larger elderly population with a longer follow-up.

8.1.8 Physician Training

- Training is critical for decreasing AEs and increasing optimal outcomes
- Training should include (1) screening subjects for appropriate population and indication, (2) biopsy techniques: sterility, identify tumor or abnormal appearance in the biopsy and injection sites, handling of the biopsied tissues; (3) handling of the product, (4) injection techniques, (5) identify and manage the adverse events, such as using prophylaxis

Reviewer Comment: All AC members considered training to be crucial for decreasing adverse events and increasing optimal outcomes. They felt that training should be mandatory for all users, but it is difficult to regulate who will use the product and what areas are treated in the post-market setting. The commercial training manual should include (1) screening subjects for appropriate population and indication, (2) biopsy techniques: sterility, identify tumor or abnormal appearance in the biopsy and injection sites, handling of the biopsied tissues; (3) handling of the product, (4) injection techniques, (5) identify and manage the adverse events, such as using prophylaxis

8.1.9 Post-Treatment Biopsy

- Information derived from post-treatment biopsy is an essential factor for the safety and efficacy of the post-market use of the product.
- Post-treatment skin biopsy as a potential solution for the above concern
- Morphological and structural changes after the product injection: concerns over the abnormal structure formation such as scar, granuloma, persistent presence of inflammatory reactions such as mast cells
- Fate of the cells: migration, proliferation, longevity and transformation of the implanted autologous fibroblasts; whether they are quiescent, dividing, or die
- Worried about overgrowth of fibroblasts or over-secretion of collagen causing thickening of the wrinkled skin

Reviewer Comment: The issue of post-treatment biopsy is repeatedly mentioned in all discussions regarding the product safety. The post-treatment biopsy is considered to be feasible and productive to give desired information.

8.1.10 FDA Considerations for Elements of Post-Treatment Biopsy Study

Objectives:

- identify the abnormal structure and cells: such as significant scar formation, granuloma, prolonged inflammatory response, and atypical cells
- describe the structural and morphological changes in the dermis after the product injection

- measure the quantitative changes in the collagen, elastin, thickness of the dermis
- Design of the study:
- Option one: retrospective skin sampling
- recruiting volunteers from Studies IT-R-005 and 006 in both IT and vehicle-control groups
 - sample size: 20 to 30 subjects, 10 to 15 in each group
 - small punch-biopsy at bilateral post-treatment nasolabial fold areas
 - estimated length of study: depending on recruitment of subjects
- Option two: prospective
- treatment: two or three IT and vehicle treatments at 4 weeks apart
 - control: self-control, contra-lateral arm
 - biopsy time points: Months 3 and 6 after the last treatment, 10 to 15 subjects at each time point
 - Treatment and biopsy areas should be the same area area of the skin involved with motion, such as lateral antecubital crease or dorsal wrist crease, contra-lateral arm as control; other area suggested by AC member: retroauricular skin. two punch biopsies on each treatment area, four biopsy samples for each individual subject
 - sample size: 20 to 30 subjects, two groups, one group biopsy at Month 3 and one group at Month 6.
 - Estimated length of the study: 12 months
 - histological evaluation
 - a. histological evaluation: in comparison with the control skin, overall structure of the dermis, epidermis, distribution of the collagen fibers, types of collagen, density of the elastin, types of cells, density of the cells, any abnormal structure of the epidermis and dermis: scar, granuloma; measuring the thickness of the dermis and amount of collagen;
 - b. regular stain, special stain for elastin
 - c. evaluation by 2 independent dermatopathologist
- Interpretation of the results and approval standard
- completion of the study per protocol
 - summary of the histological changes of skin treated with the product as compared with the control
 - identification of abnormal structures and cells: may need more studies

9. CLINICAL RECOMMENDATIONS

9.1 Recommendations for Pre-Approval Actions

Based on the following clinical issues, we do not recommend the approval of this BLA:

1. Your application does not include sufficient data to determine whether azficel-T is safe for use under the conditions suggested in the proposed labeling draft (21 CFR §314.125(b)(4)). We note that there is essentially no information regarding the bioactivities of azficel-T and tissue responses to azficel-T, aside from that derived from visual inspection of the skin. The lack of such information limits our assessment of the safety of azficel-T. We are particularly concerned about the

- potential for scarring and inflammatory reactions following azficel-T injection. Additional data are needed to address these concerns. Such data should come from a histopathological study on biopsied tissue samples from patients following injection of azficel-T. We recommend that you discuss the study design with FDA prior to initiating the study.
2. Your application indicates that shipping errors during clinical development resulted in re-biopsy of several study subjects. We are concerned that such errors may adversely impact the safety and/or efficacy of your product. In order to ensure the quality of product, please submit the Clinical Support Center Policies and Procedures to specify your policies, procedures, and activities with regard to the commercial handling of biopsies and re-biopsies, product manufacturing and shipping, and product accountability for patient specificity.
 3. Your proposed manual for training health care providers in the administration of azficel-T does not include sufficient detail. This lack of detail may result in variations in administration that could lead to unacceptable variations in the efficacy and/or safety of your product. The training manual should include the following:
 - a. At a minimum, the level of detail that was provided in your manual for training clinical investigators in Studies IT-R-005 and IT-R-006.
 - b. The specific roles of the Centers of Excellence and Clinical Support Centers in training health care providers on biopsy collection, labeling and shipment, azficel-T injection technique, product accountability for patient specificity, and the reporting and management of adverse events or any product-related issues.
 - c. The details of common and less common adverse events reported in previous clinical trials and the management plans for those adverse events. This information will help health care providers to recognize, treat, and report adverse events.
 4. Your proposed prescribing information (PI) is in the general format set forth by the Physician's Labeling Rule. However, there are many inaccuracies in your proposal. We recommend that you consult 21 CFR §201.57 and revise your PI as described to be in compliance with that regulation. For additional assistance, you may consult the following guidances available on the FDA website (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065010.htm>):

Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format

Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products—Content and Format

Content and Format of the Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products

Labeling for Human Prescription Drug and Biological Products — Implementing the New Content and Format Requirements

In addition, we recommend that you amend your carton and container labels to be in compliance with 21 CFR §610.60, §610.61, and §610.62.

_____ We reserve further comment on the proposed labeling until the application is otherwise acceptable.

9.2 Recommendations for Labeling and Post-Approval Actions

We do not recommend the approval of this BLA. However, in the event of approval, we have following recommendations regarding the issues derived from our review.

1. Injection-site adverse events:

The most common adverse events associated with the product are injection-site adverse events. Most of these adverse events are mild, transient, and self-limiting. However, some cases of severe and long-lasting adverse events that may cause cosmetic concerns were reported in the seven IT clinical studies and prior commercial experience. To mitigate the injection-site adverse events and further identify and characterize the acute and long-term adverse events, we recommend the following:

- a. Reinforce a stringent physician training program. The commercial training program that was proposed in the BLA submission lacks the specific policy and procedure and details to address subject selection, biopsy, tissue handling, injection procedure, adverse events recognition, and the reporting and management of adverse events (labeling and Pharmacovigilance Planning [PvP])
- b. Inform patients regarding post-procedure instructions and potential risks (labeling, patient information)
- c. Design a prospective safety data collection and monitoring mechanism as a post marketing commitment (PMC), which includes the following: (1)

Scheduled visits with study personnel to collect data on the following adverse events: unplanned hospitalizations or ER visits; any facial surgery, scar or keloid formation near the biopsy or injection sites; infection or abscess formation requiring topical, oral or IV antibiotics; benign or malignant cancer on the face or elsewhere on the body; discoloration of the biopsy or injected areas; new lumps and bumps or worsening of facial appearance. (2)

Document subject demographic information, detailed description of adverse events, concomitant medication or procedures; onset and duration of AEs and outcomes; severity of AEs and action taken to treat the AEs (PMC or PMR, or REMS)

- d. Encourage adverse event reporting by patients and health care providers (labeling and passive surveillance)

2. Tumorigenicity

There is a potential risk for tumor formation either from transplantation of tumor cells from the biopsy site or transformation of fibroblasts through the manufacturing process in cell culture. One case of basal cell cancer adjacent to the IT injection site was reported from a population of 508 subjects who received at least one IT injection. There is uncertainty regarding the relationship of tumor formation with the product. To address the issue of tumorigenicity, we recommend the following:

- a. A prospective safety data collection system (registry): target adverse events of tumor formation; total of five years (PMC or PMR)
- b. Physician training for biopsy and injection site screening for suspicious lesions (REMS)
- c. Warning vulnerable population: elderly, subjects with a history of skin cancer or sun-damaged skin, smokers or familial cancer syndromes (labeling)
- d. Self or physician reporting of tumor (passive surveillance system, patient information)

3. Potential adverse events in under-represented population

Safety data collected from subgroups such as elderly (>65 years), males, and non-whites are inconclusive due to limited sampling in these subgroups. Concerns regarding specific adverse events such as keloid formation in African and Asian Americans were not sufficiently addressed in the BLA submission. To address this issue, we recommend the following:

- a. Design a prospective safety data collection system in an expanded subgroup population for up to 5 years of observation (registry, PMC or PMR)

- b. Appropriate warning for vulnerable population: subjects with a history of keloid, dark-skinned subjects (Fitzpatrick skin type IV to VI) (labeling)

4. Dosing regimen and product interaction

In the Studies IT-R- 005 and IT-R-006 that support the indication of the product in the BLA submission, subjects were treated with a maximum of three treatments in the nasolabial fold area at five-week intervals without other facial cosmetic product. However, multiple dosing, multiple facial region injections, various dosing intervals, and combination with other facial cosmetic product may not be avoidable in an open market after the product is approved. These activities of off-label use may pose safety concerns for the product.

- a. Multiple dosing: We recommend designing a prospective re-treatment study to assess the safety and efficacy of multiple dosing. The subjects may be accrued from Studies IT-R-005 and IT-R-006 (PMC)
- b. Multiple sites other than nasolabial region: multiple site injections, in up to 14 facial regions, were administered in Studies 001, 002, 003A&B, and 007. Some bothersome adverse events, such as injection-site ischemia and increased incidence of injection-site nodules, were reported in these trials. We recommend reinforcing physician training for the appropriate use of the product (labeling) and prospective data collection to identify and define the safety profile of the product (registry, PMC)
- c. Dosing interval and follow-up: A longer dosing-interval, such as 5 weeks in Studies IT-R-005 and IT-R-006, may play a role in reducing the frequencies of injection-site adverse events, as compared to the shorter interval of 2 weeks in other trials. Most injection-site adverse events occurred within two weeks after injection. We recommend avoiding any decrease from the recommended treatment intervals, close follow-up by the physician, and a patient diary through the first two weeks post-injection (physician training and labeling)
- d. Product interaction: there were no studies conducted in BLA submission to address the issue of product interaction, such as with dermal fillers and Botox. The use of multiple products in the post-marketing setting may make it difficult to attribute adverse events to a particular product. We recommend conducting in vitro and animal studies using fibroblasts in combination with other products to explore the safety profile of these combinations. We also recommend a biopsy study to evaluate the fate of the cells and morphological changes in the dermis (PMC).

10. APPENDICES

10.1 Appendix A: Abbreviations

AC	Advisory Committee
AEs	Adverse Events
BiMO	Bioresearch Monitoring
BLA	Biologic License Application
BSA	Bovine Serum Albumin
Bx	Biopsy
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CMC	Chemistry, Manufacturing, and Control
CMH	Cochran-Mantel-Haenszel
CRFs	Case Report Forms
CTCAE	Common Terminology Criteria for Adverse Events
CTGTAC	Cellular, Tissue, and Gene Therapies Advisory Committee
DCEPT	Division of Clinical Evaluation & Pharmacology/Toxicology (FDA)
DMEM	Dulbecco's Modified Eagle's Medium
DMSO	Dimethyl Sulfoxide
EE	Efficacy Evaluable
ER	Emergency Room
EWSA	Evaluator Wrinkle Severity Assessment
FBA	Fetal Bovine Albumin
FBS	Fetal Bovine Serum
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hx	History
IB	Investigator's Brochure
IND	Investigational New Drug
Isolagen	Isolagen Technologies Inc.
IT	Isolagen Therapy TM
ITT	Intent-To-Treat
mL	Milliliter
MITT	Modified Intent-To-Treat
MMR	Measels, Mumps and Rubella
MO	Medical Officer
NLF	Nasolabial Fold
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OBE	Office of Biostatistics and Epidemiology
OCTGT	Office of Cellular, Tissue, and Gene Therapy
PeRC	Pediatric Evaluation Regulation Committee
PMC	Post Marketing Commitment
PMR	Post Marketing Requirement
PvP	Pharmacovigilance Planning

REMS	Risk Evaluation and Mitigation Strategies
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SOC	System Organ Classes
SPA	Special Protocol Assessment
SWA	Subject Wrinkle Assessment
TEAEs	Treatment-Emergent Adverse Events
Tx	Treatment
US	United States
UK	United Kingdom
VAS	Visual Analog Scale

10.2 Appendix B: List of Documents Reviewed

BLA 125348, original submission

BLA supplements:

- Amendment 03 (8/10/2009): Response to Information Request by FDA - Sponsor responses to FDA questions/comments in BLA Review Letter dated May 19, 2009 addressing the following issues: CMC aseptic validation process; clinical information by sites for biopsy/rebiopsy; randomization lists; manufacture failures; IRB concerns; assessment of intra-rater and inter-rater variability; and status of the Proprietary Name Review
- Amendment 04 (8/14/2009): Response to Information Request by FDA - Reformatted Clinical Datasets
- Amendment 05 (8/18/2009): Response to Information Request by FDA - Information concerning biopsy-related AEs and the procedures for wrinkle assessments at Screening and Baseline/Biopsy
- Amendment 06 (9/10/2009): Response to Information Request by FDA - Draft of 12 Month Safety Data for Studies IT-R-005/006
- Amendment 10 (9/21/2009): Response to Information Request by FDA - Certain subject CRFs and data clarifications regarding information presented in the original BLA's Integrated Summary of Safety
- Amendment 12 (10/5/2009): Response to Information Requested by FDA - FDA provided Isolagen with 10 patient numbers: Photographs and Assessment Scores for Selected Patients from Studies 005 and 006. Per Agency request, the photos and data are considered fully redacted. Sponsor requested that the distribution be limited to FDA reviewers and AC members only.
- Amendment 13 (10/6/2009): Response to Information Requested by FDA - Tables of Rare Adverse Events and Associated CRFs.
- Amendment 14 (10/8/2009): Response to Information Requested by FDA - Data pertaining to AEs, long-term safety data, demographics, and disposition of subjects in the safety database
- Amendment 15 (10/15/2009): Sponsor's briefing package in support of the CTGTAC
- Amendment 18 (10/26/2009): Sponsor comments and responses regarding clinical questions raised during the CTGTAC, including data for post-injection biopsies

Clinical Review

BLA 125348

- by Dr. Boss and other researchers; and additional data to support the current identity and purity testing procedures for IT
- Amendment 21 (11/01/2009): Long-term clinical study reports for Studies IT-R-005, IT-R-006, and IT-R-007

FDA Internal Reviews of BLA 125348:

- CMC review
- Pharmacology/Toxicology review
- Statistical review
- OBE review
- BiMO review

FDA Consultations:

- CDRH (Charles Durfor, Ph.D.) 8/11/2009 review of BLA
- CDRH (Janette Alexander, M.D.) 8/1/2009 review of BLA
- CDER (Jane Liedtka, M.D.) 8/14/2009 review of BLA

Other Reviews:

- See References (Section 11.0)
- Medical Officer's Clinical Review BLA 103000 Botox Cosmetic
- Medical Officer's Clinical Review BLA 125274 Dysport
- CDRH, Summary of Safety and Effectiveness, Radiesse, Cosmetic tissue Augmentation
- CDRH, Summary of Safety and Effectiveness, Hydrelle, Cosmetic tissue Augmentation

10.3 Appendix C: Photoguide Used with the Evaluator Wrinkle Severity Assessment (Lemperle Scale)

The Evaluator Wrinkle Severity Assessment uses a 6-point ordinal scale with the following grading categories: 0= no wrinkle visible, 1= just perceptible, 2= shallow, 3= moderately deep, 4= deep and 5=very deep.



10.4 Appendix D: Advisory Committee Meeting Questions (October 9, 2009)

Safety

1. Tumorigenicity: If approved, IT™ will be the first cellular product for this indication, and the first fibroblast product that is an injectable cell suspension. Uncontrolled cell growth and/or tumor formation are risks posed by fibroblasts due to their proliferative nature. In addition, there is a possible risk of the post-auricular biopsy transferring abnormal or malignant cells that may not be detected in the quality controls of product manufacturing. Long term follow-up data are limited; one case of basal cell cancer occurred near the site of injection; however, the potential of IT™ to promote tumor formation cannot be assessed from this single case.

Based on the manufacturing and clinical data presented and your knowledge of the relevant literature, please discuss any safety concerns relevant to tumor formation for and the potential for longer term (beyond 12 months) risks with this product. If you believe there is potential risk, please discuss the basis for your opinion and your recommendations to address the risk(s). (Discussion)

2. Physician Training: The available safety data demonstrate a high incidence (up to 2/3 of subjects) of injection-site reactions. Those events tended to last longer in IT™-treated subjects than those in the vehicle-control group. About 6% of events in the IT™ treated group lasted beyond 30 days, and 6 of those events were still on-going by the end of the trials. It should be noted that such events may confer significant cosmetic complications for a healthy individual seeking

improvement of facial wrinkles. The applicant has suggested that proper injection technique can play a role in the frequency and severity of these reactions. The applicant is proposing a physician training program as a requirement for use of the product.

- Do you have specific recommendations for the content of a practitioner training program? (Discussion)
 - Do you have any other recommendations on how to minimize these adverse events? (Discussion)
3. Race and Ethnicity: An increase in safety events in non-Caucasian subjects in the trial was not observed; however, the sample size was small. Please discuss whether or not the data in the trial, and your knowledge of the literature, suggest that this product has the potential for causing risks such as hypertrophic scarring and keloid formation, or abnormal pigmentation in the non-Caucasian population. If you believe there is a potential increased risk, please provide your suggestions on how to minimize these adverse events. (Discussion)
 4. Age: The proportion of subjects over 65 years of age in the trial was small. Please discuss whether or not the data in the trial, and your knowledge of the literature, suggest any potential safety concerns with use of this product in this age range. (Discussion)
 5. Gender: the proportion of male subjects studied was small. Please discuss whether or not the data in the trial, and your knowledge of the literature, suggest any potential safety concerns with use of the product in this age range. (Discussion)
 6. Do the data presented demonstrate the safety of IT for moderate to severe nasolabial fold wrinkles in adults? (Discussion then vote)
 - If no, what other information is needed before approval of the product? After approval of the product? (Discussion)
 - If yes, is there specific safety information that you would recommend be included in the labeling for this product. (Discussion)

Efficacy

1. Do the data presented demonstrate the efficacy of IT for moderate to severe nasolabial fold wrinkles in adults? (Discussion then vote)
 - If no, what other information is needed. (Discussion)
 - If yes, is there specific efficacy information that you would recommend be included in the labeling for this product. (Discussion)

11. REFERENCES

- Berman B** et al. Keloids. *Journal of the American Academy of Dermatology*. 1995. Vol 33:1
- Boss WK**, et al. Autologous Cultured Fibroblasts as Cellular Therapy in Plastic Surgery. *Clinics in Plastic Surgery*. 2000. 27(4): 613-626
- Boss WK**, et al. Autologous cultured fibroblasts: A protein repair system. *Annals of Plastic Surgery* 2000. 44(5): 536-542
- Boyd CM**. Approaches to the aging face in African American patients. *Facial Plast. Surg. Clin. North Am.* 2002. 10:377
- Burgess CM**. Soft tissue augmentation in skin of color: market growth, available fillers, and successful techniques. *Journal of Drugs in Dermatology*. 2007. 6 (1) 51 -5
- Carruthers J** et al. Advances in facial rejuvenation: botulinum toxin type a, hyaluronic acid dermal fillers, and combination therapies--consensus recommendations. *Plastic and reconstructive surgery*. 2008.121 (5) Suppl 5-30
- Clark DP** Dermal Implants: Safety of Products Injected for Soft Tissue Augmentation. *Journal of the American Academy of Dermatology*. 1989. 21 (5), part 1: 992-998
- Cohen SR** et al. Artecoll: A Long-Lasting Injectable Wrinkle Filler Material: Report of a Controlled, Randomized, Multicenter Clinical Trial of 251 Subjects. *Plast. Reconstr. Surg.* 2004. 114: 964-976
- Dadzie OJ** et al. A pilot study to assess the efficacy of autologous fibroblasts treatment in acne scarring. *British Journal of Dermatology*. 2006. 155: 43-43
- De Boule K** Management of Complications after Implantation of Fillers. *Journal of Cosmetic Dermatology*. 2004. 3, 2-15.
- Downie JB** Esthetic considerations for ethnic skin. *Semin Cutan Med Surg.* 2006. 25(3):158-62.
- Gilchrest BA**. Skin aging and photoaging: an overview. *J Am Acad Dermatol*. 1989;21:6103
- Hata K** Current issues regarding skin substitutes using living cells as industrial materials. *Journal of Artificial Organs*. 2007. 10(3): 129-132
- Jackson, B. A.** Cosmetic considerations and nonlaser cosmetic procedures in ethnic skin. *Dermatol. Clin.* 2003. 21: 703
- Johnen CB**, Hartmann, et al. Skin cell isolation and expansion for cell transplantation is limited in patients using tobacco, alcohol, or are exhibiting diabetes mellitus. *Burns*. 2006. 32(2): 194-200
- Kadunce DP**, et al. Cigarette smoking: risk factors for premature facial wrinkling. *Ann Intern Med*. 1991;114:840-844
- Keller GJ**, et al. Safety of injectable autologous human fibroblasts. *Bull Exp Biol Med* 2000. 130(8): 786-9
- Lemperle, G** et al. A Classification of Facial Wrinkles. *Plast. Reconstr. Surg.* 2001. 108: 1735-1750
- Lemperle, G** et al. Avoiding and treating dermal filler complications. *Plast Reconstr Surg* 2006. 118(3 Suppl): 92S-107S.

McDaniel, DH, A phase III, double-blind, randomized, multicenter study evaluating the efficacy and safety of autologous human fibroblast therapy in contour deformities at 6 months. *Journal of the American Academy of Dermatology*. 2008. 58(2): AB136-AB136.

Odunze, M et al. Restylane and People of Color. *Plast. Reconstr. Surg.* 2007.120 (7), 2011-2016.

Smith, SR, Two phase III, multicenter, double-blind, randomized, placebo-controlled trials evaluating the efficacy and safety of autologous fibroblast therapy in the treatment of nasolabial fold wrinkles. *Journal of the American Academy of Dermatology*. 2008. 58(2): AB138-AB138.

Watson, D, et al Autologous Fibroblasts for Treatment of Facial Rhytids and Dermal Depressions. *Archives of Facial Plastic Surgery*. 1999. 1: 165-170.

Weiss RA, et al. Autologous cultured fibroblast injection for facial contour deformities: a prospective, placebo-controlled, Phase III clinical trial. *Dermatol Surg.* 2007 Mar. 33(3):263-S.

West, TB, et al, Autologous Human Collagen and dermal Fibroblasts for Soft Tissue Augmentation. *Dermatologic Surgery*. 1998. 24 (5): 510-512.

Zhao, Y, et al. Preliminary Survival Studies on Autologous Cultured Skin Fibroblasts Transplantation by Injection. *Cell Transplantation*. 2008. 17(7): 775-783.

Zheng, X, et al. Proteomic Analysis for the Assessment of Different Lots of Fetal Bovine Serum as a Raw Material for Cell Culture. Part IV. Application of Proteomics to the Manufacture of Biological Drugs. *Biotechnol. Prog.* 2006. 22, 1294-1300.
