

**Final Review Memorandum
OBE/DE Review for Pharmacovigilance Planning**

BLA: 125348/0
AzFibrocel-T, Autologous Human Fibroblasts
Fibrocell Technologies, Inc.

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I. Introduction

OBE/DE/TBSB has completed a review of STN 125348/0, an original BLA application for AzFibrocel-T (AzF), autologous human fibroblasts. The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety monitoring, studies, or other pharmacovigilance activities, should the product be licensed. Information on the clinical studies and safety data in this review is derived from the clinical summaries presented in the Isolagen BLA, Sections 2.7.3 (Summary of Clinical Efficacy) and 2.7.4 (Summary of Clinical Safety), and the 12-month Safety Data Memorandum (submitted by Isolagen 9/4/2009). Tables and diagrams presented in this document are copied from the applicant's submission. Note: During the course of this BLA review the sponsor changed the product name from Isolagen Therapy to AzFibrocel-T. For the purpose of this review memorandum, the terms Isolagen Therapy (IT) and IT-treated are synonymous with AzFibrocel-T and AzF-treated, respectively.

II. Product Background

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

AzF is the first cellular product for this cosmetic indication and the first autologous fibroblast product. The co-primary efficacy endpoints (patients' and evaluators' assessments using validated rating scales) were successfully met in studies of 421 randomized patients (210 AzF and 211 vehicle controls). The final assessment for safety occurred at 12 months after the last injection.

Cosmetic Benefit and Similar Products

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

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

Non-Clinical Studies

No formal animal studies were conducted with AzF for the treatment of NL folds due to previous commercial experience in humans (Isolagen BLA, Section 2.4, p 3). The sponsor does, however, reference animal studies of autologous fibroblasts (mice, rabbits) in literature that did not demonstrate any oncogenic potential (Isolagen BLA Section 2.5.3.1, p 14).

Market Experience

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

III. Clinical Studies

AzF was evaluated in three Phase II studies and four Phase III studies. IT-R-005 and IT-R-006, Phase III trials performed under SPA, were the pivotal studies. Additional supportive Phase III trials include IT-R-003A and IT-R-003B. One other Phase III trial (IT-R-002) and two Phase II trials (IT-R-001 and IT-R-007) were also conducted.

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

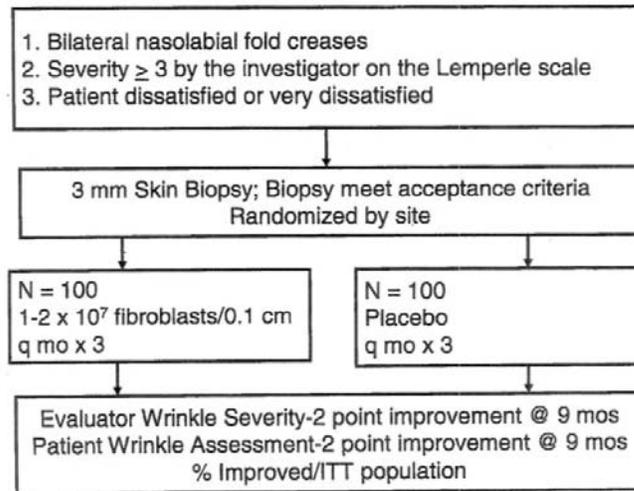
IT-R-005 and IT-R-006 (Pivotal Studies):

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

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

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

Each subject received three treatments at intervals of 4-6 weeks. The primary evaluation occurred through visit 6, six months after the final treatment and each subject had, on average a total of five visits. Each subject was contacted by telephone 12 months after the final study treatment to follow-up on unresolved adverse events, identify any new adverse events, record any changes in cosmetic or medical procedures, and document changes in medication. The studies had two primary endpoints for efficacy, the Subject Wrinkle Assessment and the Evaluator Wrinkle Severity Assessment; they demonstrated efficacy on both endpoints. See diagram below for the flow of the study.



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

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

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

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

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

Other Studies:

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

IT-R-001

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

IT-R-002

IT-R-002 was a Phase III, double-blind, randomized, placebo-controlled study of AzF for the treatment of facial contour deformities and scars. Out of the 158 subjects randomized, 111 subjects were treated with 3 injections of AzF (2.0×10^7 cells/mL) and 40 received placebo. Additionally, after the acute phase of the study was completed (four months after the first injection), 31 of the placebo group subjects chose to receive open-label re-treatment with AzF. In this longer term phase of the study all subjects were to be followed for 12 months after their initial treatment. Of the 142 subjects in the long-term phase of the study, 122 completed the study.

IT-R-007

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

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

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

IV. Safety Database

The total safety database includes 508 subjects who received AzF across all trials (including 41 placebo patients in IT-R-001 that were subsequently treated with AzF) and 354 who received placebo (i.e., injection with the vehicle only). The subjects were >90% female and >90% Caucasian. Their ages ranged from 20 to 77 years old with fewer than 12% age 65 or older. The only statistically significant demographic difference between the AzF and control groups was the mean age, which was 52 years in the AzF group and 54.2 years in the control group (p-value = 0.0009).

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

Adverse Events

The most frequently observed treatment-related AEs were mild to moderate, local injection site reactions (68% of IT-treated and 40% of placebo patients). More subjects in the Isolagen group (3) reported severe treatment-related adverse events than in the control group (1). The severe adverse events were injection site ischemia, pain, swelling, erythema and bruising, lasting one to 10 days.

All but 14% of IT-treatment reported events and 9% of placebo-treatment reported events resolved within seven days of onset. Six percent of treatment-related events lasted beyond 30 days. At the end of the study, there were six Isolagen-related events (injection site swelling, erythema, reaction, alopecia, hypoesthesia, and eyelid edema) and two vehicle control-related events (injection site anaesthesia and urticaria) that were ongoing.

A basal cell carcinoma (BCC) was diagnosed in a 76 year-old Caucasian female who received three Isolagen injections in the pivotal trial IT-R-005. About five months after the last injection, a BCC was discovered in the right upper lip near the right nasolabial injection site. The relationship between the fibroblast treatment and the development of BCC in this patient is unknown.

The sponsor conducted its primary analysis for safety using treatment-emergent adverse events (TEAE), which they defined as “any adverse medical occurrence that begins or worsens on the first day of treatment administration or any day thereafter during the study period” (2.5.5.4, p 38). The most frequently reported TEAEs (i.e., reported in >1% of subjects) by PT in the AzF - treated group versus the placebo treated group (respectively) were:

- Injection Site Erythema (16% vs. 9%)
- Injection Site Bruising (11% vs. 14%)

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

Severity of TEAEs

The majority of all TEAEs were classified by the sponsor as mild to moderate in both treatment groups (Isolagen BLA, Section 2.7.4).

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

Severe AEs were also reported in other SOC classes:

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

Overall, AzF-treated subjects more often reported moderate injection site-related TEAEs, while vehicle control-treated subjects more often reported mild TEAEs. More AzF-treated subjects reported at least one severe AE than vehicle control-treated subjects and more of the severe AEs reported by AzF-treated patients were considered to be possibly, probably or definitely related to the study treatment.

Relationship of TEAEs to the Study Treatment

Overall, the majority of the TEAEs in the GDASC class, mainly localized injection site reactions, were considered possibly, probably or definitely related to the study treatment:

- Possibly (9% AzF-treated vs. 1% vehicle control-treated)
- Probably (11% AzF-treated vs. 4% vehicle control-treated)
- Definitely (33% AzF-treated vs. 29% vehicle control-treated)

The sponsor concluded that TEAEs reported in other SOC classes were mainly considered unlikely or unrelated to study treatment with 1% or fewer of these events being considered possibly, probably, or definitely related to the study treatment. Additionally, they felt that AzF-

treatment showed a similar safety profile to vehicle control-treatment and that most events related to study treatment were those that would be expected from injection of any type of material.

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

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

Other Safety Results:

Nodules:

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

Ischemia:

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

Deaths:

Two deaths in study subjects occurred and were considered by investigators to be unrelated to study treatment. A 57-year-old female subject died from a myocardial infarction after three treatments with vehicle control, and a 77-year-old female subject died from heart failure after biopsy, but prior to study treatment

Study Terminations:

Three subjects who received AzF-treatment were terminated from the study for AEs. Two of these had moderate injection site pain that resolved without sequelae and one had severe injection site bruising that resolved in 10 days. One subject discontinued treatment for an AE

(severe injection site erythema, swelling, and pain, which resolved in three to four days), but remained in follow-up.

Clinical Laboratory Investigations:

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

Long-term Safety Follow-up for Clinical Studies IT-R-005 AND IT-R-006

A total of 359 subjects (168 subjects in IT-R-005, 191 subjects in IT-R-006) completed the acute phase, and 350 subjects (167 subjects in IT-R-005 and 183 subjects in IT-R-006) completed the 12 month long-term phase of the study, which collected data on AEs continuing since the last study visit (6 months after final treatment) and on new AEs.

Continuing Adverse Events

In Study IT-R-005, 24% of AzF-treated subjects and 18% of control subjects had continuing AEs as of Visit 6. The majority of these continuing AEs remained unresolved at the long-term follow-up (only 26% of events in the AzF -treated group and 35% of events in the control group had resolved). However, only three subjects (two AzF -treated subjects and one control subject) reported ongoing AEs at Visit 6 that were considered possibly or probably related to the study treatment. Two of these (numbness at NL fold (control subject) and puffiness at NL fold (AzF patient)) were resolved at the long term follow-up. A third (mild ridge at the injection site above the right nasolabial fold (AzF patient)), was still unresolved at long term follow-up.

For Study IT-R-006, 16% of AzF -treated subjects and 13% of control subjects had continuing AEs as of Visit 6. Of these continuing AEs, 74% of events in the AzF -treated group and 37% of events in the control group had resolved. In study IT-R-006, one ongoing AE at visit 6 (mild swelling on the upper left and right eye lid in an AzF treated subject) was considered possibly or probably related to the study treatment and was still unresolved at long-term follow-up. There were no ongoing SAEs from Visit 6 in either study.

New Adverse Events

In Study IT-R-005, Eleven (14%) AzF -treated subjects reported 27 new AEs and 17 (19%) control subjects reported 36 new AEs. No new AEs reported in Study IT-R-005 were local to the injection site and none were considered possibly, probably or definitely related to study treatment. Two AzF -treated subjects and three control subjects in Study IT-R-005 reported experiencing new Serious Adverse Events (SAEs).

For Study IT-R-006, Eight (9%) AzF -treated subjects reported eight new AEs and nine (9%) control subjects reported 12 new AEs. None were documented as being related to study treatment. Two control subjects in Study IT-R-006 reported experiencing new Serious Adverse

Events (SAEs). In both studies, all SAEs reported after Visit 6 were considered unrelated to study treatment. These SAEs included atrial fibrillation, adenocarcinoma of the colon, herniated disks (2), CVA, COPD, and elective foot surgery.

Market Experience:

Between 1995 and 1999, approximately 1,100 patients were treated with AzF in the U.S. by about 200 physicians in 110 clinics. AzF was used to treat facial rhytids, scars, hypoplastic lips, burns and other problems. In the U.K., between 2002 and 2007, there were approximately 6,000 patients treated with IT. In non-regulated spontaneous reporting, there were no documented significant adverse events. As in the clinical trials, most complaint reports to the manufacturer during this time were mild to moderate injection site reactions. All resolved in seven days to five months. There was one case of herpes outbreak after injection. Three severe AEs were reported: angioedema, severe allergic reaction, and a lump requiring surgical removal. In a U.S. retrospective study report from 2003, no serious AEs were observed in the 354 patients reviewed (Isolagen BLA, Section 2.4, p 3 and Section 5.3.5.4).

Adverse Events Reported for Dermal Filler Devices:

Information on Dermal Fillers in this review is derived from the Executive Summary on Dermal Filler Devices prepared by the Center for Device and Radiological Health (CDRH) for the November 18, 2008 General and Plastic surgery Devices Panel Advisory Committee Meeting available at <http://www.fda.gov/ohrms/dockets/ac/cdrh08.html#Generalplastic>.

Dermal fillers (DF) are absorbable or nonabsorbable synthetic or biologic materials injected into the mid to deep dermis of the face and other areas for correction of moderate to severe wrinkles and folds. Because DFs have a similar indication and administration method to AzF, analysis of the adverse event profile for DFs may add insight to possible safety issues with AzF.

CDRH received 930 unique medical device reports for DFs from 1/1/2003 through 9/20/2008. Of the 804 reports indicating gender, 763 were in females. Nasolabial fold was identified as the site of injection in 191 reports; 345 reports identified another site. No deaths were reported. The reported events were categorized by CDRH reviewers as follows:

Frequency of Adverse Event Occurrence by Category of Event

Category	No. of events
Swelling	334
Inflammation	292
Erythema	275
Allergy	230
Vascular events*	163
Infection	150
Pain	140
Lumps/bumps	44
Blister/cyst	39
Numbness	15
Migration	13
Bleeding	13
Others**	22

Notes: the number of events (1730) does not equal the number of reports (930) because a single report could contain multiple events (e.g., redness, swelling, and a rash in a single patient),

*Vascular events included: bruising, bleeding, hematoma, necrosis and scars, blanching and discoloration, and ischemia.

**“Other” included all other adverse events that occurred in fewer than 10 reports. Some AEs in this category included blurred vision, disfigurement, overcorrection, retained foreign body, fainting, tear duct obstruction and soreness, and heart attack.

Surgical Intervention, emergency room visits, and hospitalizations were tabulated to assess severity of the reported AEs. Ninety-four of 823 reports indicated surgical intervention. Surgical procedures ranged from opening an abscess for drainage of pus to excision of nodules and biopsy of lesions. Nineteen reports indicated emergency room visits due to severe hypersensitivity reactions such as swollen tongue, difficulty breathing, and anaphylactic shock. Twelve patients required hospitalization for extended IV antibiotic therapy and monitoring.

Conclusions for DF AEs Reported to FDA and Relevance to AzF

1. Similar to AzF, the majority of reported adverse events involve local injection site reactions such as minor swelling and erythema. These are expected problems with DFs and are specified in the labeling.
2. Of the reports that include information on site of injection, the majority involve sites other than the nasolabial folds, the approved indication for use of most of them. Based on this experience, such off-label use could occur with AzF. The adverse event profile in other anatomic sites has not been fully studied. Post-market pharmacovigilance monitoring will be important for assessing possible new safety risks when used off-label. PV planning should include documentation of indication and anatomic site.
3. Although rare, several life-threatening allergic events were reported with DFs and required emergency intervention. AzF, an autologous cellular product, is not likely to have the same risk of allergic response.
4. Several serious and unexpected events such as facial, lip, and eye palsy, disfigurement, and retina vascular occlusion were reported. These events appeared to be rare relative to the overall volume of DFs likely in use, although these data are from passive surveillance and may underestimate the true incidence rates for such complications. No clear relationship between these events and DFs has been established.

5. A relatively large number (150) of infection events were observed. Some of these reports involved hospitalization for antibiotic treatment and/or abscesses requiring surgical drainage or removal. As with any product introduced via injection, AzF treatment has a risk of local contamination and infection.

V. Pharmacovigilance Planning

Proposed Pharmacovigilance Plan (PVP)

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

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

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

The sponsor plans to require physicians who will be receiving the product to attend training at a “Center of Excellence” established by the sponsor. Centers consist of trained staff specializing in facial aesthetic treatments and will include training on proper biopsy collection and shipment, proper treatment preparation and injection technique, and the types and severity of AEs expected, and appropriate treatment and follow-up. Certification of completed training will be required to receive the AzF product. A copy of the training manual is included with the BLA submission (Isolagen BLA, Section 1.12).

Safety Concerns

1. Risk of Tumor Formation

The risk of tumor formation by culture-expanded autologous fibroblasts has not been definitively ruled out in the available safety database. Safety follow-up in the clinical trials (12-15 months) was not sufficient to evaluate the long-term risk of tumor formation. The subject in IT-R-005

who developed BCC near the injection site has other reasonable risk factors for BCC (age, sun-exposure), however, the role of the fibroblast treatment in the development of BCC in this subject, if any, is unknown. Additionally, there exists the possibility of expanding cells from the biopsy that are already dysplastic or malignant and then implanting them with the AzF injection. The sponsor includes these potential risks in the proposed labeling. The post-auricular region recommended for the biopsies is vulnerable to BCC, although nasal lesions are more common.

2. Risk of Injection Site reactions

The available safety data demonstrate a high incidence (up to 2/3 of subjects) of treatment-related injection site reactions. Although about 90% of local adverse events resolved within two weeks, about 6% of events lasted beyond 30 days. Eight of those events (six in the IT group and two in the control group) were still on-going by the end of the trials.

3. Risk of keloids, hypertrophic scars, and/or pigmentation changes in non-Caucasians

Individuals with darker pigmented skin, who were underrepresented in clinical trials, may experience these AEs in response to skin/tissue trauma. Only 1% were African-American and 1% were Asian (Isolagen BLA, Section 2.5.4.1 p 17, and 2.5.4.7 p 32). Epidemiologic data on hypertrophic and keloidal scars are limited but suggest higher rates of keloids in African-Americans, Hispanics, and Asians. Overall, the risk of developing keloids is approximately 15 times higher in dark-skinned individuals compared with whites.¹ The incidence of keloids in blacks and Hispanics varies from 4.5% to 16%, with higher incidences during puberty and pregnancy.² Pigmentary changes are also of concern in this subgroup and can include temporary and permanent hypo and hyperpigmentation. A previous history of either pigmentary change or keloid formation is a risk factor for development of these adverse events.

Questions for Post-licensure Pharmacovigilance:

- What is the risk of cancer from malignant transformation in implanted cells or from transplanted dysplastic or malignant cells from the biopsy location?
- What is the risk of keloid formation and pigmentation changes after AzF treatment, particularly in non-Caucasian, dark-skinned individuals?
- How long do the transplanted cells survive? Does their survival or death provoke inflammatory or other specific risks?
- How can injection site reactions be minimized and serious procedure-related adverse events, such as embolization, be avoided?

¹ A.E. Brissett and D.A. Sherris, Scar contractures, hypertrophic scars, and keloids, *Facial Plast Surg* 17 (2001), pp. 263–272.

² T. Akoz, K. Gideroglu and M. Akan, Combination of different techniques for the treatment of earlobe keloids, *Aesthetic Plast Surg* 26 (2002), pp. 184–188.

VI. Assessment and Recommendations

1. The subjects participating in the pivotal trials IT-R-005 and IT-R-006 were followed for adverse event occurrence for 15-18 months after Azficel-T injection. This length of follow-up is limited in ability to detect events of potential long latency such as tumorigenicity. To increase the length of follow-up, the sponsor could attempt to re-contact subjects from these trials and collect data on adverse events since completion of the trial. The current review cycle is expected to end in a complete response (CR) to the sponsor based on inadequate data to assure safety. Although this information would be helpful in assessing safety and would add to the available safety database, the data already submitted to FDA as well as that requested in the CR is expected to be sufficient for evaluating the product for licensure, and addition of this activity the CR would not necessarily be required. Review and discussion of post-market safety studies, including consideration of this activity, can be completed once the sponsor responds to the CR and additional safety data is reviewed.

If the sponsor does conduct this activity, important safety data to be collected includes: the number of subjects successfully contacted for extended follow-up; patient demographics (age, gender, smoking status); adverse events with onset dates, treatments and outcomes; and use of any concomitant facial treatments or injections since the trial ended. Confounding by use of concomitant facial aesthetic treatments or procedures is an important limitation and should be recognized. The proportion of subjects successfully re-contacted for additional follow-up might also be limited. Further, the advantages and disadvantages of collecting retrospective data in this activity should be compared to the possibility of collecting prospective data from patients using the product after licensure.

2. The PVP lacked detail on the surveillance plans (periodicity of follow-up, content of questionnaires, methods for contacting patients/physicians, etc.). The proposed 100-subject size of the “Long-Term Safety Follow-Up” would not be sufficient to detect uncommon adverse events and a longer follow-up period would be necessary to assess safety of AzF beyond 12-18 months.

3. The primary safety concerns for post-market planning include:

- Risk of tumor formation
- Risk of keloids, hyperpigmentation/hypopigmentation in non-Caucasian subjects
- High incidence of injection site reactions

4. The adverse events observed with dermal filler (DF) devices were predominantly local injection site reactions and are consistent with the safety profile expected for any product injected into dermis. Most reported adverse events for DFs involved off label use (for unlabeled indications or unlabeled anatomic sites) and this would likely also occur with AzF once marketed. Safety monitoring post-approval should document the intended use and anatomic location. The observation that many reported AEs for DFs may have involved inadequately trained personnel supports the sponsor’s plan to require training.

5. Pharmacovigilance Study Planning

Because the current review cycle is expected to end in a complete response (CR) to the sponsor based on inadequate data to assure safety, final assessment and recommendations for post-market safety studies cannot be completed at this time. Further review and discussion of post-market safety studies can be completed once the sponsor responds to the CR and additional safety data is reviewed. However, based on the evaluation of safety data presented to date, we recommend a post-licensure registry study to:

- Further define the risk of tumor formation in IT-treated patients through follow-up of all consenting patients.
- Address the limited safety information available for non-Caucasians.

A registry study is a particularly feasible pharmacovigilance method for this autologous product since information is already collected on each patient and provider. A detailed protocol should be developed, including planned enrollment size, follow-up schedule, data to be collected, and follow-up methodology. The sponsor should develop a protocol for the registry that includes a sufficient sample size to detect an excess of cancer or tumor formation adverse events in AzF-treated patients when compared to the background incidence of cancer in a similarly aged population. Enrollment should include at least a specified minimum proportion of non-Caucasian patients.

The registry study would also assess the risk of keloid formation and other dermatologic adverse events in non-Caucasian subjects. Based on peer-reviewed medical literature, as presented above, these adverse events occur more frequently in non-Caucasians. Information on age and smoking status of registry patients could also be collected with subsequent documentation of adverse event trends in elderly patients and smokers.

6. Adverse event of BCC is a weak signal of a serious risk

Based on the safety data presented to date, the adverse event of BCC in an AzF-treated clinical trial subject represents a signal of a serious risk as defined under FDAAA. Final Assessment of the risk of tumor formation in AzF-treated patients will depend on review of any additional safety data collected and presented by the sponsor in response to the CR. Culture-expanded fibroblasts probably present a low risk of tumorigenicity given their autologous nature. However, tumor formation, either from cellular transformation or from transplantation of abnormal cells from the biopsy site, remains a potential safety concern with AzF.

In the guidance document on *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, the FDA defines a safety signal to be a “concern about an excess of adverse events compared to what would be expected to be associated with a product’s use”. This definition of “signal” is broad and allows for a range of levels of concern based on: strength of the association (e.g., relative risk in a controlled study), temporal relationship of product and event, consistency of findings across available data, evidence of dose response effect, biologic plausibility, and the susceptibility of the methods used to confounding, bias, and chance. Levels of concern can range from low (an unexpected serious AE in the setting of substantial methodological limitations in data or study design); to high (an unexpected serious AE with statistically significant increased relative risk and few limitations in data or study design). Identifying the levels of concern helps to establish what actions are required, with lower levels of concern typically handled by postmarketing surveillance and studies. In contrast, higher levels of

concern might require additional studies before a product can be marketed.

Using this framework, the patient with BCC represents a weak signal (low level of concern). Only one BCC was observed, but it was temporally and spatially (anatomically) associated. There is biologic plausibility for tumor formation from culture-expanded fibroblasts, but this probably represents a low risk, given the product's autologous nature.

The guidance notes that a single well-documented case can be viewed as a signal. The relatively small size of the clinical trial population limits our ability to conclude that this case does not represent an excess over the expected background rate. Additionally, the follow-up time in the trials may not have been sufficient to detect additional cases. There are several features of this case that are consistent with a signal as defined in the guidance:

- Anatomic proximity of the lesion to the injection site and onset within an appropriate timeframe after treatment to reasonably be associated with AzF.
- The patient did not have cancerous or pre-cancerous lesions prior to treatment. Subjects with a prior history of skin cancer were excluded from the trial.
- The pharmacological/toxicological effects of AzF, including the risk of malignancy, have not been fully established. There is also the possibility of expanding cells from the biopsy that are already dysplastic or malignant and then implanting them with the treatment. The pharmacological/toxicological effects of products in this class are unknown since this is the first expanded fibroblast product.

7. Ensure safe application of the product

Based on the safety data presented to date, we concur with the sponsor's proposal to require training prior to product administration. Training would include administration methods to minimize the frequency and severity of injection site reactions and the importance of avoiding pigmented lesions or abnormal skin in the biopsy site. Although most injection site reactions are not intrinsically serious, they represent important complications for healthy patients seeking cosmetic benefit. As noted above, injection site reactions were more frequent in AzF-treated subjects than controls, occurring in up to 2/3 of AzF-treated subjects, and they tended to last longer.

Based on experience with supportive clinical trials and the later pivotal trials, the sponsor suggests that proper injection technique can reduce the frequency and severity of injection site reactions. All physicians in the pivotal clinical trials received training, so there is no comparison group for evaluating the risk of injection site reactions after use by trained versus untrained providers. However, the rate of injection site reactions in AzF treated subjects in the 2 pivotal studies, in which training was provided, was 37% (in IT-R-005) and 32% (in IT-R-006). These rates were lower than the rate of injection site reactions in AzF-treated subjects in all 7 studies combined (67%). While there may be other factors contributing to this decrease (wider interval between follow-up visits, change in dosing schedule), the addition of training for the pivotal trials may have had substantial impact. The sponsor also noted that one possible reason for failure of an efficacy endpoint in an earlier supportive study (IT-R-003A) was "insufficient investigator training..."(2.5.1.4, p 10). After this trial, the sponsor observed the investigators' injection technique and, noting large variability, instituted training for all investigators as part of the more recent, pivotal studies.

We did not find published data for other injectables demonstrating lower rates of injection site reactions when used by trained personnel. However, several articles on injectable dermal fillers conclude that proper technique can help avoid adverse events. Improper injection (e.g., too superficial injection) of dermal fillers caused adverse events at injection sites that were severe and lasted longer than controls.³ Injections that are too superficial can produce nodules and sausage-like deformities on the skin surface with indurations that may last for weeks.⁴

VII. Letter Ready Comments

None at this time.

³ Gauthier-Hazan N et al. Avoiding and treating dermal filler complications. . Plast Reconstr Surg. 2006 Sep; 118(3 Suppl): 92S-107S

⁴ Coleman KM et al. Hyaluronic acid fillers. Dermatologic Therapy. Vol 19, 2006. 141-150