

Pharmacovigilance Review Memorandum
Office of Biostatistics and Epidemiology/Division of Epidemiology

BLA/Supplement Number: 125348/0

Submission Type: Original BLA (CR Response)

Product Name: **Azficel-T** (formerly Isolagen Therapy)

Ingredient: Autologous Human Fibroblasts

Sponsor: Fibrocell Technologies, Inc.

Indication(s): Cosmetic treatment of moderate to severe nasolabial (NL) fold wrinkles in adults 18 years old or older.

Date(s): CBER receipt of sponsor's response to CR: 12/21/2010
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Review Priority: Routine (CR Response: 6 months)

From: Craig Zinderman, MD, MPH
Medical Officer, Therapeutics and Blood Safety Branch (TBSB),
Division of Epidemiology (DE), Office of Biostatistics and
Epidemiology (OBE)

Through: Thomas Buttolph, MD
Chief, TBSB, DE, OBE

David Martin, MD, MPH
Acting Director, DE, OBE

Robert Ball, MD, MPH, ScM
Director, OBE

I. Introduction

OBE/DE has completed a review of STN 125348/0, an original BLA application for AzFicel-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 AzF BLA, Sections 2.7.3 (Summary of Clinical Efficacy) and 2.7.4 (Summary of Clinical Safety), the 12-month Safety Data Memorandum (submitted by Isolagen 9/4/2009), and the sponsor's response to CR Item #14 and Clinical Study Report IT-H-001, submitted 12/16/2010). Passages quoted directly from the sponsor's submissions appear in *italics*. Tables and diagrams presented in this document are copied from the applicant's submission as noted. Note: During the course of this BLA application 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 AzFicel-T and AzF-treated, respectively.

II. Product Background:

2.1 Product:

Autologous fibroblast cells are obtained through punch biopsy of the patient's post-auricular skin and then expanded in culture. (AzF BLA, Section 2.2, p.4) The final product, a fibroblast suspension, is administered via intradermal injection into the superficial dermis along the nasolabial (NL) folds. (AzF 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 (excluding the subsequent histopathology study IT-H-001 described below) occurred at 12 months after the last injection.

2.2 Regulatory History

The sponsor (then known as Isolagen therapy, Inc.) submitted an original BLA for approval on 3/6/2009. The product was presented to the FDA Cellular, Tissue and Gene Therapies Advisory Committee on 10/09/2009. In response to the question: "do the data presented demonstrate safety for the proposed indication", the committee voted no (6 to 8). The Committee commented on the lack of sufficient data related to the processing, characterization and collagen production of the injected cells. Some Committee members expressed concern that due to a lack of data on the mechanism of action, there was

insufficient information to assess the safety of the product and recommended collection of long-term follow-up data. Other Committee members commented that safety might be less of a concern as this is an autologous product and that the available clinical data did not suggest the product was unsafe. Regarding tumorigenicity, there was general consensus among the Committee that as the product is derived from autologous cells, the risk of tumorigenicity from these cells is low. However, the committee was concerned that insufficient data had been presented on the characterization of the implanted cells to adequately assess the safety of the product and commented that longer term follow-up studies may be needed.

CBER issued a complete Response (CR) to the sponsor on 12/18/2009 citing 20 CMC, Clinical, and labeling items, including #14 which noted insufficient data to determine whether azficel-T safety, particularly the lack of information regarding the bioactivities of azficel-T and tissue responses to azficel-T. The letter requested a histopathological study involving biopsies of treated patients.

2.3 Cosmetic Benefit and Similar Products

See PV Final Review Memorandum (12/8/2009) for this information.

III. Non-Clinical Studies:

No formal animal studies were conducted with AzF for the treatment of NL folds due to previous commercial experience in humans (AzFBLA, 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 (AzF 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 (AzF BLA, Section 2.5, p 3).

IV. Clinical Studies:

See PV Final Review Memorandum (12/8/2009) for this information.

V. Safety Database:

5.1 Safety Population

The total safety database consists of 821 subjects among 7 clinical trials, including 508 subjects that received Azficel-T (AzF) (including 41 control patients in IT-R-001 that were subsequently treated with AzF) and 467 who received control (injection with vehicle only). Twenty-nine of the 508 AzF treated subjects received additional doses of AzF as part of a histopathology study (IT-H-001, described below).

The subjects were >90% female and >90% Caucasian. Their ages ranged from 20 to 82 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).

5.2 Adverse Events

The most frequently observed treatment-related AEs were mild to moderate, local injection site reactions (68% of AzF-treated and 40% of placebo patients). More subjects in the AzF 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.

-At the end of the 6 month follow-up period in the 2 large, pivotal studies (IT-R-005 and IT-R-006 which included 100 and 110 AzF treated patients, respectively), there were six AzF-related events (injection site swelling, erythema, reaction, alopecia, hypoaesthesia, and eyelid edema) and two vehicle control-related events (injection site anesthesia and urticaria) that were ongoing.

-A basal cell carcinoma (BCC) was diagnosed in a 76 year-old Caucasian female who received three AzF injections in the pivotal trial IT-R-005. ~5 months after the last injection, a BCC was discovered in the right upper lip near the right NL 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%)

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).

5.3 Long term study phase

A total of 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.

Continuing Adverse Events

In Study IT-R-005, the majority of AEs that had been ongoing at the end of the acute phase 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 ongoing AEs 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, 74% of ongoing AEs in the AzF -treated group and 37% of ongoing AEs in the control group had resolved. In study IT-R-006, one ongoing AE (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 in either study.

New Adverse Events

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

5.4. Other Safety Results:

See PV Final Review Memorandum, 12/8/2009 (Section IV. "Safety Database"), for full information.

5.5 Histopath Study

The Histopathology study (IT-H-001) was an intra-patient controlled study. AzF and placebo were injected in separate sites (AzF-treated site, the placebo site, and a non-treated site) in each subject's upper arms. Twenty-nine subjects received 1 to 3 injections each. All 3 sites were biopsied after 3 months and 6 months.

In general, the histology across all treatment groups represented normal healthy skin. There were no reports of abnormal fibroblast morphology, structural changes to the subcutis, dermis or epidermis, scarring, increased cellularity, overt thickening of dermal layers or evidence of underlying pathology. Tissue treated with AzF was more likely to contain a mild degree of inflammatory cellular infiltrate than placebo-treated or untreated tissue. The sponsor concluded that this finding reflects a localized, resolving inflammatory reaction consistent with implantation of bioactive autologous cells. The sponsor concluded that there is no adverse affect on cellular morphology or organization of the extracellular matrix after AzF treatment and no evidence of clinical or sub-clinical scarring of dermal tissue. The infiltrate associated with azficel-T injection represents an indication of product activity and not a product safety risk according to the sponsor.

Adverse Events:

-Overall, 13 of the 29 subjects (45%) experienced 40 TEAEs; all were expected injection site reactions that were mild in severity and generally resolved within seven days. No treatment area AEs were ongoing at 6 months.

-There was one SAE: **Leukocytoclastic Vasculitis**. A 67 years old white male with PMH of HTN, hypercholesterolemia, prostate hypertrophy, fibromyalgia, osteoarthritis, and tobacco use received his first treatment on June 25, 2010, with 0.2 mL azficel-T to his right arm and 0.2 mL saline control to his left arm. Eight days post study treatment, he presented to emergency room with symptoms of weakness, rapid pulse, and a skin rash

on his arms and lower legs with the lower legs predominating. The rash was described as 10 to 15 small necrotic, erythematous lesions on his legs with impression of small-vessel vasculitis. The biopsy of the lesion showed leukocytoclastic vasculitis. The subject was also diagnosed with left arm cellulitis (the following day) in a non-treatment area. He received vancomycin, ceftriaxone, methylprednisolone in the hospital and was discharged after 1 day with vibromycin and diflucan. The Investigator and Sponsor considered this SAE (**Leukocytoclastic Vasculitis**) to be unrelated to study treatment.

-This subject had previously participated in the AzF clinical trial and received 3 AzF injections to his bilateral nasolabial fold wrinkles from July 2007 to October 2007. He experienced one AE--acute bronchitis which occurred a month after the second treatment and resolved 47 days later with antibiotics, cough syrup, and inhaler.

-This leukocytoclastic vasculitis case may represent a delayed allergic reaction to previous repeated exposure to the study treatment in 2007, which may sensitize the subject with preformed circulating immune complexes. Relation to the study product cannot be ruled out based on the timing of the adverse event and the absence of other co-existing clinical findings at presentation. However, the patient was diagnosed with cellulitis on the following day (although the timing of onset of this condition is unclear) and was taking several concomitant medications (anti-hypertensive medications) which could be alternative etiologies for the vasculitis.

5.5 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 injections 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. (AzF BLA, Section 2.4, p.3 and Section 5.3.5.4)

5.6 Adverse Events Reported for Dermal Filler Devices

See PV Final Review Memorandum, 12/8/2009, for this information.

VI. Pharmacovigilance Planning

6. 1 Proposed PV Plan (PVP):

The sponsor proposes to conduct long-term safety follow-up by monitoring 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. (AzF BLA Section 1.12.2)

The sponsor has not proposed any additions or changes to the PVP since the original submission. Please see PV Final Review Memorandum, 12/8/2009 (Section V. “PV Planning”) for further details.

6.2 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. Uncontrolled cell growth and/or tumor formation could be potential risks of cultured fibroblasts due to their proliferative nature. However, because the product is derived from autologous cells, the risk of tumorigenicity of these cells is likely to be low. Safety follow-up in the clinical trials (12-15 months) was not sufficient to evaluate the long-term risk of tumor formation by culture-expanded autologous fibroblasts.
- One subject developed BCC near the injection site. This subject had other risk factors for BCC (age, sun-exposure). The role of the fibroblast treatment in the development of BCC in this subject, if any, is unknown.
- There is a possibility of expanding cells from the biopsy that are already dysplastic or malignant and then implanting them with the injection. (The sponsor includes this potential risk in the proposed labeling).
- Previous commercial experience: no complaints of tumors in Isolagen-treated patients in US (1995 to 1999) and UK (2002 to 2007). (No established surveillance program during this period).

2. Risk of delayed immune mediated hypersensitivity reactions such as hypersensitivity vasculitis

- Hypersensitivity vasculitis (leukocytoclastic vasculitis) denotes small vessel vasculitis, with an incidence of 10-30 cases per million people per year as reported from studies in Spain. There are multiple etiologies: antibiotics, infections, foods, collagen-vascular diseases, inflammatory bowel disease, and malignancy but a cause is usually not found in half of patients. Circulating immune complexes play a role in the pathogenesis. The role of the fibroblast treatment in the development of leukocytoclastic vasculitis in this subject, if any, is unknown.
- There was no such adverse event occurring in the safety population of the previous trials. There were no vasculitis cases reported in the US or UK in the pre-IND period. Nevertheless, the existing safety database is not large enough to exclude a possible association with such a rare event.

3. Risk of Injection Site reactions

- High incidence (up to 2/3 of subjects) of treatment-related injection site reactions.

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

- More common in individuals with darker pigmented skin; only 1% of trial subjects were African-American and 1% were Asian (AzF BLA, Section 2.5.4.1 p 17, and 2.5.4.7 p 32). Please see PV Final Review Memorandum, 12/8/2009 (Section V. “PV Planning, Safety Concerns”) for further details.

VII. PV Assessment and Recommendations:

1. The BCC case represents a signal of a serious risk (for non-melanoma cancer) as defined in FDAAA and, thus, meets the FDAAA criteria for a Post-market Requirement (PMR). (Note: Please see the OBE/DE PV Final Review Memorandum for a complete rationale of why the BCC represents a signal of a serious risk. The SAE of leukocytoclastic vasculitis also represents a signal of a serious safety risk meeting criteria for inclusion in the PMR. Because of the rarity of this event, the incidence in AzF treated patients cannot be assessed by the relatively small clinical trials and histopathology study. Although only one case was observed, this case was temporally associated with administration of the product and is a biologically plausible reaction to Azficel-T. 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. Thus, systemic hypersensitivity reactions such as leukocytoclastic vasculitis or other immune mediated reactions represent a signal of a serious risk as defined under FDAAA and meets criteria for a PMR.
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 months. The two safety signals identified above does not preclude the sponsor from collecting other AEs as part of the same or a different post-market study or surveillance.
3. We recommend a post-licensure registry study to further evaluate the risk of non-melanoma cancer and systemic hypersensitivity reactions such as leukocytoclastic vasculitis or other immune mediated reactions in AzF-treated patients through follow-up of all enrolled patients. The sponsor should develop a detailed protocol, including planned enrollment size, data to be collected, follow-up schedule, and follow-up methods. The study should be of sufficient size to detect an excess of cancer or tumor formation AEs in AzF-treated patients when compared to the background incidence of cancer in a similarly aged population.

The sponsor will determine the methodology that they will use to satisfy the PMR, but a preliminary design and study size should be agreed upon during the BLA review. Below are some suggested points for discussion with the sponsor:

Study format:	A registry study is a particularly feasible pharmacovigilance method for this autologous product since information is already collected on each patient and provider.
Study population:	Enroll patients 40 years old and over who receive at least one injection of AzF. Enrollment should continue until the target size is reached.

Study size:	<p>2700 subjects (based on 80% power to detect a tripling of the background incidence of BCC and published estimates of BCC incidence of 114-200/100,000 (see sample size calculation below).</p> <p>The size should be sufficient to detect a clinically meaningful difference (3 fold increase) in the incidence of non-melanoma skin cancer between AzF treated patients and the background risk of non-melanoma skin cancer in the U.S.</p>
Baseline Data Collection:	<p>Collect baseline information at time of first injection: information on age, gender, Fitzpatrick skin type, history of skin cancer, other co-morbidities, smoking status, and use of concomitant medications and non Azf facial treatments (e.g., dermal fillers) in the preceding 12 months. The anatomic location of the non Azf facial treatments (e.g. NL folds, glabellar wrinkles) should also be recorded. Collect information on use of non-AzF facial treatments and their anatomic location at each follow-up contact.</p>
Outcome Assessment	<ul style="list-style-type: none"> -The PMR will require collection of the following outcomes: -Any non-melanoma cancers on the face or near other treated areas, with identification of the specific type of cancer. The sponsor will record the anatomic site with reference to distance from the treatment site for all cancers near treated areas. Cancers occurring on the head or neck must be specifically located anatomically with reference to distance from the treatment site and distance from anatomic landmarks on the head or neck. -All systemic hypersensitivity reactions
Follow-up	<p>The sponsor will actively contact the physician of each enrolled patient 60 days after the last injection, one year after the last injection, and annually thereafter for 2 years. The sponsor should attempt to contact the patient in cases where the physician is no longer able to provide follow-up information. Patients should be asked to update their contact information with the sponsor directly for the duration of the registry.</p>
Statistical Analysis	<p>No formal hypothesis testing will be specified in the approval letter. The study should assess the frequency of non-melanoma skin cancer events in AzF treated patients relative to the expected incidence of skin cancer in adults over 40 years old. The frequency of systemic hypersensitivity reactions, if any, will be assessed, along with potential alternative etiologies in these patients.</p>

Interim reports	The sponsor will submit semi-annual interim reports as specified in draft approval letter statement below. The interim reports should include the total number of patients treated thus far; the number of patients enrolled in the registry categorized by age, gender, and skin type; the proportion of subjects for which the sponsor successfully obtained follow-up information; and the proportion of subjects with non-melanoma cancers and systemic hypersensitivity reaction events categorized by age, skin type, and length of time since injection.
Timeline	The sponsor should propose to FDA a due date for submission of the final protocol after product approval (if approved). However, this due date should not exceed 6 months post approval. The sponsor should also propose a date for completion of the study and for submission of a final study report to FDA.

Sample Size Estimate:

Background Rate: range from 114 to 200 new cases/100,000 = range between 0.114% and 0.2%

Objective: To determine the size of a registry study required to detect a tripling of the background risk.

Size of the registry study depends on the expected BCC rate (here tripling the background rate), % of power, and significance level (usually 5%). The following table summarizes the sample sizes:

Significance level 0.05 (or 5%)	Expected BCC rate = 0.6% Background rate=0.2%	Expected BCC rate = 0.342% Background rate=0.114%
Power		
80%	1511	2652
75%	1236	2169
70%	981	1721
65%	924	1622
Calculations are based on the exact method in StatXact.		

Letter Ready Comments:

Pending further internal review team discussion