

CLINICAL REVIEW OF BLA RESUBMISSION

Division of Clinical Evaluation and Pharmacology/Toxicology, Office of Cellular,
Tissue, and Gene Therapies, Center for Biologics Evaluation and Research

TITLE AND GENERAL INFORMATION

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

BLA #: 125348, Resubmission, Amendments 31, 32, 37, 39, and 41

Related IND #: IND (b)(4)

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Submission Received by FDA: December 22, 2010

Review Due Date: June 22, 2011

Review Completed: June 20, 2011

Recommended Action: Approval

Product

Proper Name or Established Name: Autologous human fibroblast cells

Established Trade Name: azficel-T, formerly known as Isologen Therapy™

Established Proprietary Name: LAVIV®

Product Formulation(s): A sterile suspension of each patient's own cultured living fibroblasts in Dulbecco's Modified Eagles Medium without phenol red at a concentration of $1.0 - 2.0 \times 10^7$ cells/mL.

Applicant

Fibrocell Technologies, Inc., formerly known as Isologen Technologies, Inc.

Pharmacologic Class or Category

Cell Therapy

Indication

LAVIV[®] (azficel-T) is an autologous cellular product indicated for improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults.

The safety and efficacy of LAVIV for areas other than the nasolabial folds have not been established.

The efficacy of LAVIV beyond six months has not been established.

Indicated Population

Adults

Dosage Form and Route of Administration

Inject LAVIV at 0.1 milliliter per linear centimeter intradermally into the nasolabial fold wrinkles. The recommended treatment regimen is three treatment sessions at 3-6 week intervals.

Documents Reviewed:

- Amendment 31 (Fibrocell Response to FDA Complete Response (CR) Items 14 to 20; revised Clinical Support Center Policies and Procedures Manual for Item 15 “shipping errors”; revised Physician Training Manual, and revised Prescribing Information, submitted on December 15, 2010
- Amendment 32 (Study Report IT-H-001, 3-month biopsy), submitted on December 16, 2010
- Amendment 37 (Study Report IT-H-001, 6-month biopsy), submitted on March 15, 2011
- Amendment 39 (combined safety data of six studies under (b)(4) INDs), submitted on April 8, 2011
- Amendment 41 (serious adverse event (SAE), subject -(b)(6)- in IT-H-001), submitted on May 5, 2011
- Dermatologist Consultation: Jane Liedtka, M.D., Division of Dermatology Drug Products (DDDP), CDER, April 7, 2011: Consult# 1360 (IT-H-001); May 10, 2011: Consult # 1342 (Physician Training Manual)
- Dermatopathologist Consultation: Lynn Drake, M.D., Special Government Employee, April 7, 2011: Teleconference regarding Study IT-H-001, post-market plan, and Physician Training Manual

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY.....	4
2. REGULATORY BACKGROUND.....	6
3. HISTOLOGICAL STUDY: IT-H-001 (CR ITEM# 14).....	7
3.1 Clinical Study Protocol	
3.2 Study results	
3.2.1 Study subjects	
3.2.2 Histology results	
3.2.3 Exploratory assessments of appearance improvement	
3.2.4 Safety results	
3.3 Summary of Study IT-H-001	
4. COMBINED SAFETY ANALYSIS FROM SIX COMPLETED CLINICAL STUDIES UNDER –(b)(4) INDS.....	20
5. CLINICAL REVIEW OF POLICIES AND PROCEDURES FOR SHIPPING ERRORS (CR ITEM # 15).....	23
6. CLINICAL REVIEW OF PHYSICIAN TRAINING MANUAL (CR ITEM # 16).....	24
7. CLINICAL REVIEW OF PRESCRIBING INFORMATION (CR ITEM # 17 TO # 18).....	24
8. POST-MARKETING PLAN FOR SAFETY MONITORING.....	25
9. CONSULTATIONS.....	26
10. CONCLUSIONS AND RECOMMENDATIONS.....	26

1. Executive Summary:

Azficel-T is a cellular product consisting of autologous fibroblasts derived from patients' post-auricular biopsies and expanded in cell culture. The applicant submitted the original Biologics License Application (BLA) on March 6, 2009 for the indication of moderate to severe nasolabial fold wrinkles, based on seven clinical trials. The efficacy of the product was supported by two Phase 3 studies, each of which demonstrated statistically superior clinical outcomes, compared to vehicle-control. The safety data analysis showed that most adverse events consisted of transient and tolerable injection-site reactions. One case of basal cell cancer was diagnosed near the product injection site six months after the first treatment.

A Cellular, Tissue and Gene Therapies Advisory Committee (AC) meeting was held in October 2009 to discuss six questions regarding tumorigenicity, subgroup representation, physician training, and the safety and efficacy of azficel-T. The committee members voted 11 Yes vs. 3 No to the question whether the product had demonstrated efficacy and 6 Yes vs. 7 No to the question whether there was sufficient safety information. AC members also noted that the company had provided no information regarding the mechanism of action and the biological activity of the product at the histological level and that gaining such knowledge would provide additional understanding of the possible risks associated with use of the product.

FDA issued a Complete Response (CR) letter to the applicant in December 2009. The CR letter includes 20 CMC, clinical, and labeling items. On December 22, 2010, the applicant resubmitted the BLA with complete response to all FDA's information requests in the CR letter.

During the clinical review of the BLA resubmission, FDA requested that the applicant submit a combined safety data analysis on active INDs using azficel-T. The submitted data included studies of the product for (b)(4) indications, including wrinkles (clinical safety data from the skin biopsy study is included with this indication), -----(b)(4)-----
----- (b)(4)----- These data are reviewed here as well.

This memorandum contains clinical reviews of: (1) study reports of the skin biopsy study IT-H-001 (CR Item#14), (2) standard operating procedures (SOPs) for shipping errors (CR Item#15), and (3) Prescribing Information (CR Item#17 and 18). The Physician Training Manual (CR Item#16) has been reviewed separately by Bruce Schneider, M.D., with a consult from Jane Liedtka, M.D. (Center for Drug Evaluation and Research). A clinical review of the additional requested safety information (described above) is also included in this memorandum.

Study IT-H-001 (CR Item #14) was a double-blind (subject and dermatopathologist-blinded), intra-subject-controlled examination of the histology of cutaneous tissue of the upper arms following treatment with azficel-T, compared to the histology of tissue

treated with saline and that of untreated tissue. The primary objective of the study was to gain qualitative information regarding local histological reactions to injections of azficel-T. There was no formal hypothesis testing. In all 29 subjects enrolled in the study, mild inflammatory cellular infiltrate was found in superficial dermis, with more inflammation in azficel-T treated tissue than in controls. The inflammation decreased by six months. There was no histological evidence of abnormal fibroblasts, significant scar formation, or abnormal organization of the extracellular matrix. One case of leukocytoclastic vasculitis was reported nine days after azficel-T administration.

A standard operating procedure for preventing and managing shipping errors (CR Item #15) was submitted and reviewed. Our concern is that shipping errors, which occurred with a frequency of 1.5% during the clinical trials, resulted in a need for repeat post-auricular biopsy in several cases, which is an unnecessary burden for patients. In response, the applicant submitted revised policies and procedures. Both clinical and CMC teams have reviewed the submitted policies and procedures for shipping errors and concluded that the applicant has demonstrated adequate compliance with 21 CFR 1271.290.

The Physician Training Manual (CR Item # 16) was reviewed separately by Bruce Schneider, MD, with consultation from Jane Liedtka, MD, CDER.

The applicant's proposed Prescribing Information (PI, CR Items #17 and 18) was revised. The indication was modified to reflect the results of the seven clinical trials for facial wrinkles. The revised labeled indication is stated above. Common injection-site reactions and rarely-occurring adverse events (such as basal cell cancer and leukocytoclastic vasculitis), as well as potential risks (such as keloid scar), are written into the label. The applicant has accepted all FDA's revision in the PI.

Additionally, as noted above, in response to a request by FDA on March 29, 2011, the applicant submitted a combined safety data analysis for six completed studies under – (b)(4)---- INDs. This combined safety data includes a total of 158 subjects who were exposed to up to three treatments with azficel-T: 29 in the histopathology study described above and 129 in studies of azficel-T for other indications, including ---(b)(4)-----
----- (b)(4)----- . Aside from one case of leukocytoclastic vasculitis that occurred during the skin biopsy study as mentioned above, the safety data analysis showed local adverse reactions, such as injection-site erythema, swelling, bruising, induration, acne, rash, nodules, pain, and discoloration – an adverse event profile similar to that in the seven trials for the treatment of facial wrinkles.

In conclusion, the applicant has addressed all the clinical issues raised in the FDA Complete Response (CR) letter, by providing skin biopsy study results, revised policies and procedures for shipping error, a revised physician training manual, and a revised label. Based on review of the safety data from 508 subjects in seven previous trials of azficel-T for facial wrinkles, histology and clinical safety data from 29 subjects in the skin biopsy study, and the combined safety data from another 129 subjects in five studies under --- (b) (4) --- INDs for other (i.e., non-wrinkle) indications, the safety and tolerability

of azficel-T are acceptable for the proposed indication. Based on review of the efficacy data from 421 subjects in the two pivotal trials, azficel-T is effective for the indication of improvement of the appearance of nasolabial fold wrinkles.

Based on the above conclusions, I recommend that azficel-T be approved for market licensure. The Prescribing Information accurately and clearly describes the safety and efficacy of the product, based on data from the seven clinical trials for facial wrinkles. For adequate post-market safety monitoring of this novel cellular product, a registry study is required to evaluate both the occurrence of facial skin cancer at or near the site of azficel-T administration, as well as immune hypersensitivity reactions to the product.

2. Regulatory Background:

The applicant submitted the original BLA on March 6, 2009 for the indication of moderate to severe nasolabial fold wrinkles, based on seven clinical trials. The efficacy and safety were summarized in Clinical Review for BLA125348/0 completed by clinical team on December 9, 2009.

A Cellular, Tissue and Gene Therapies Advisory Committee (AC) meeting was held in October 2009 to discuss six questions regarding tumorigenicity, subgroup representation, physician training, and the safety and efficacy of azficel-T. The committee members voted 11 Yes vs. 3 No to the question whether the product had demonstrated efficacy and 6 Yes vs. 7 No to the question whether there was sufficient safety information. AC members also noted that the company had provided no information regarding the mechanism of the action or biological activity of the product at the histological level and that gaining such knowledge would provide additional understanding of the possible risks associated with use of the product.

FDA issued a CR letter in December 2009 based on results of both FDA reviews and recommendations of the AC. There were 20 CMC, clinical, and labeling questions. Items 14 to 18 are clinical issues. In Item 14, a histological study was requested; in Item 15, revised policies and procedures regarding the shipping errors were requested. In Item 16, a revised Physician Training Manual with improved detail was requested. In Items 17 to 18, a revised label was requested to comply with 21CFR201.57 and FDA guidance. The review of the above items is included in the memorandum. On December 22, 2010, the applicant resubmitted the BLA with complete response to all FDA's information requests in the CR letter.

During the clinical review of the BLA resubmission, FDA requested that the applicant submit a combined safety data analysis on all active INDs for azficel-T. The data were derived from the applicant's study of the product for (b)(4) indications (IND (b)(4) for wrinkles [skin biopsy study IT-H-001 is included under IND (b)(4)], IND ----(b)(4)-----, IND -----(b)(4)-----, and IND -----(b)(4)-----). These safety data are covered in this review.

3. Histological Study: IT-001-H (CR Item#14)

Title of Study: “A Placebo-Controlled Serial Skin Biopsy Study to Evaluate Tissue Histology Following Treatment with Azficel-T”

Protocol Number: IT-H-001

Date of First Enrollment: June 3, 2010

Date of last phone call contact: February 28, 2011

Study centers: Six U.S. sites in Texas, California, North Carolina, and Georgia.

3.1 Study Protocol

Objectives: To qualitatively evaluate human cutaneous tissue by histology three and six months following up to three azficel-T treatments, and to compare the histology of the azficel-T-treated tissue to that of untreated tissue and sterile saline-treated tissue.

Study endpoints

Histology

- Qualitative comparison for clinically meaningful differences in the cellular morphology of the dermis, subcutis and epidermis among azficel-T treatment, sterile saline treatment, and untreated control sites at each biopsy time point (i.e., three months and six months).
- Qualitative comparison of differences in inflammatory cell infiltrates among azficel-T treatment, sterile saline treatment, and untreated control sites at each biopsy time point.
- Qualitative comparison of differences in the structure and organization of collagen and elastin fibers among azficel-T treatment, sterile saline treatment, and untreated control sites at each biopsy time point.

Histology Criteria for Evaluation:

- The -----(b)(4)----- stained sample was used for evaluation of the morphology of the dermis, subcutis and epidermis, and for determining the presence of inflammatory cells.
- -----(b)(4)-----, was used for detection of collagen fibers in dermis.
- -----(b)(4)----- and was used for evaluation of the structure and organization of elastin fibers and as a secondary evaluation of collagen.

Safety: Incidence of treatment-emergent adverse events throughout the study.

Exploratory objective: to evaluate the durability of the wrinkle improvement

- Subject and Investigator assessments of nasolabial fold wrinkle severity following previous azficel-T treatment for facial wrinkles or creases for subjects previously enrolled in Studies IT-R-005 and IT-R-006.
- Subject Skin Quality Assessment

Study design

- Double-blind (subjects and two dermatopathologists), intra-patient-controlled study to evaluate the histology of cutaneous tissue treated with azficel-T, compared to untreated tissue and tissue treated with sterile saline.
- Location of administration: cutaneous tissue of the lateral upper arm.
- Subjects were randomized to receive azficel-T on either their right or left arm; the other arm received sterile saline, which served as a control.
- Test or saline control was injected intradermally in two locations on each arm at each treatment visit. Second and third treatment visits took place at five-week intervals.
- The second and third treatments were injected at positions on the limb identical to those of the first treatment.
- Cutaneous punch biopsies (4 mm) were collected from azficel-T- and saline-injected sites at three and six months following the last treatment. As an additional control, a 4-mm cutaneous punch biopsy of an untreated area of the arm was also collected three months following last administration of azficel-T.
- Fixed and stained tissue sections from the biopsies were evaluated by two independent dermatopathologists in a blinded fashion. The 3-month and 6-month tissue sections were evaluated independently.
- The untreated 3-month tissue sections were used as a control for both the 3-month and 6-month evaluations.
- The two dermatopathologists were board-certified, and each has more than ten years of clinical and research experience.

Number of subjects

- 24 subjects were planned, with a target of 20 being evaluable
- 29 subjects were enrolled in the study to receive azficel-T treatment, with the number of subjects limited by the availability of cryopreserved cells. One subject received only one of three planned administration sessions (two additional planned sessions were stopped due to an SAE of leukocytoclastic vasculitis); 21 subjects received two administration sessions; and seven subjects received three administration sessions.
- Safety population: All subjects (29) who received at least one injection with azficel-T
- Histology Evaluable Population : All subjects (29) who received at least one injection with azficel-T and had cutaneous punch biopsies collected at three and six months after last treatment
- Participation in previous studies: 13 subjects had participated in the IT-R-005 and IT-R-006 studies for the treatment of nasolabial fold wrinkles; 16 subjects had

Test Product, Dose and Mode of Administration

- 0.2 milliliter (mL) azficel-T ($1.0\text{--}2.0 \times 10^7$ cells/mL) was administered intradermally to the lateral aspect of the upper arm at 0.1 mL per linear centimeter (cm) in two 1-cm lines at least two cm apart, per each treatment, the same dose regimen as in the previous studies.

Inclusion Criteria

- Participated in Study IT-R-005, IT-R-006, IT-R-007, or IT-A-008 and had available azficel-T in cryopreservation.
- In general good health.

Exclusion Criteria

- Participating, or had participated within 30 days prior to enrollment, in another clinical trial evaluating an investigational drug or device.
- Scarring, tissue damage (e.g., sunburn, wound), or other tissue abnormality at the treatment and biopsy sites that would preclude intradermal injection.
- Any disorder that, in the Investigator's opinion, may have interfered with study compliance, such as history of chronic alcohol or drug abuse, significant untreated mental or nervous disorder, or other illness.
- Pregnant or lactating women or women trying to become pregnant during the study
- Use of systemic agents that may increase bleeding or clotting and that could not be interrupted for seven days before each study treatment. This included chronic use of non-steroidal anti-inflammatory drugs (NSAIDs), aspirin at more than 81 mg per day, Vitamin E in excess of 1000 IU, and the use of oral herbal supplements that inhibit clotting, such as feverfew, ginger, ginseng, garlic, ginko biloba, and/or St. John's wort.
- Use of systemic or local (at the site of treatments) corticosteroids, or other similar immunosuppressive, antineoplastic, or antimetabolic agents with a significant impact on immune function. Subjects using prescribed intranasal or inhaled corticosteroids at doses consistent with their labeling (e.g., for control of seasonal rhinitis or asthma symptoms) could be included.

Criteria for Evaluation:

Histology:

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

- Qualitative evaluation: two independent dermatopathologists in a blinded fashion.
- The -----(b)(4)---- sections: morphology of the dermis, subcutis and epidermis, and for detection of the presence of inflammatory cells.
- -----(b)(4)-----: collagen fibers in dermis.
- -----(b)(4)-----: the structure and organization of elastin fibers and for secondary evaluation of collagen.

Safety:

- Incidence and severity of adverse events.

Exploratory: Wrinkle Appearance: This was an exploratory study to evaluate the durability of azficel-T for the treatment of nasolabial fold wrinkles at two to three years after the main efficacy clinical studies by using the following endpoints:

- Wrinkle Assessments for participants in IT-R-005 and 006: Investigator and Subject 5-point assessment of nasolabial fold wrinkles prior to first treatment in IT-001-H. Wrinkle appearance was compared to photographs taken at baseline.
- Skin quality assessment: a multiparameter binary scale prior to first treatment.

Data analysis/Statistical Methods:

- Histology: a qualitative histological comparison, descriptive statistics, and no formal statistical hypothesis testing.
- Safety: No formal hypothesis testing

Table 1. Schedule of Procedures and Assessments

Procedure	Screening	Treatment #1	Treatment #2	Treatment #3	Biopsy #1	Bx #1 f/u visit	Bx #1 f/u call	Biopsy #2	End of study	Bx#2 f/u call
Informed Consent	X									
Eligibility	X									
Medical History	X									
Urine Pregnancy Test	X									
Fitzpatrick Skin Type	X									
Concomitant Medication	X	X	X	X	X	X	X	X	X	
*Tattoo	X	X	X	X	X					
Study Agent Administration		X	X	X						
Biopsy					X			X		
Adverse Events		X	X	X	X	X	X	X	X	X
Biopsy and injection site exam	X	X	X		X	X		X	X	

*Tattoo is used to mark the injection/biopsy sites in the upper arms

Reviewer Comments: The skin biopsy study was well designed and attempted to match the Phase 3 clinical trial in the number of treatments (up to three treatment sessions), cell dose, and duration of observation (three and six months after the last treatment session). Both the patients and pathologists were blinded with regard to the azficel-T and saline control samples. The lateral side of the upper arm was chosen because the area receives

more sun exposure than the inner side of the arm and therefore may mimic the facial skin aging process. The study is limited by its sample size, biopsy site on arms rather than facial wrinkles, and qualitative nature of the analysis.

3.2 Study Results

3.2.1. Study Subjects

Demographic Characteristics (Table 2): a total of 29 subjects with average age of 50 years, ranging from 26 to 75 years, were enrolled and completed the skin biopsy study. Thirteen subjects had participated in studies IT-R-005 and 006 for the indication of nasolabial fold wrinkles. Sixteen subjects had participated in IT-A-008 for the treatment of acne. White females represented 79% of the total population. Fitzpatrick skin types 1 to 3 represented 71% of the total population.

Table 2. Demographics, Study IT-H-001

Categories	Description	One or Two Treatments (N=22) n (%)	Three Treatments (N=7) n (%)	All subjects (N=29) n (%)
Age and Groups	Age Mean (range)	54 (26, 75)	39 (27, 54)	50 (26, 75)
	≤ 50	8 (36%)	6 (86%)	14 (48%)
	> 50 and ≤ 65	9 (41%)	1 (14%)	10 (34%)
	> 65	5 (23%)	0	5 (17%)
Gender	Male	5 (23%)	1 (14%)	6 (21%)
	Female	17 (77%)	6 (86%)	23 (79%)
Ethnicity	Hispanic or Latino	2 (9%)	2 (29%)	4 (14%)
	Not Hispanic or Latino	20 (91%)	5 (71%)	25 (86%)
Race	White	18 (82%)	5 (71%)	23 (79%)
	Asian	0	1 (14%)	1 (3%)
	Black or African-American	1 (5%)	0	1 (3%)
	Other	3 (14%)	1 (14%)	4 (14%)
Fitzpatrick skin type	Type 1	1 (5%)	0	1 (3%)
	Type 2	8 (36%)	2 (29%)	10 (34%)
	Type 3	9 (41%)	1 (14%)	10 (34%)
	Type 4	3 (14%)	3 (43%)	6 (21%)
	Type 5	1 (5%)	1 (14%)	2 (7%)
	Type 6	0	0	0

Disposition of subjects (Table 3): All 29 randomized subjects received at least one treatment session and completed the 3- and 6-Month Biopsy and Follow-up Visits. No subjects discontinued from the study prior to study completion. All subjects enrolled in the study were assigned to receive either two (21/29 subjects) or three (8/29 subjects) treatment sessions with azficel-T and placebo, based on the availability of cellular product. All but one subject received the assigned number (either two or three) of azficel-T and placebo treatments. Subject –(b)(6)- discontinued study treatment following Treatment Visit 1 as a result of an SAE (leukocytoclastic vasculitis). This case is discussed in further detail under Safety Results. Due to an adverse event of

leukocytoclastic vasculitis, one subject discontinued study agent administrations. However, all subjects continued to be followed for their scheduled biopsies. Therefore, no subject discontinued the study prematurely

Table 3. Exposure and Disposition

Patient Population	One Treatment Session	Two Treatment Sessions	Three Treatment Sessions	Month 3 Biopsy	Month 6 biopsy	Total
Subjects enrolled and treated	1	21	7	29	29	29
Participated in IT-R-005 & 006	1	11	1			13
Participated in IT-A-008		10	6			16
Safety population	1	21	7	29	29	29
Histology Evaluable Population	1	21	7	29	29	29
*Wrinkle Assessment Population	1	11	1	13	13	13

*subjects in wrinkle assessment population participated in exploratory assessments of appearance improvement (see Section 3.2.3)

***Reviewer Comment:** Because insufficient numbers of cryopreserved cells were available, not all 29 subjects received three treatments: 21/29 subjects received two treatments; 7/29 received three treatments; and one subject received one treatment. Although number of treatments does not strictly match the Phase 3 protocol, two treatments of azficel-T are sufficient to provide information about the tissue response to the product. All subjects received skin biopsy at 3 and 6 months. All biopsy specimens were judged adequate for histological examination.*

Protocol Deviations (Table 4):

Table 4. Protocol Deviations in Study IT-H-001

Description	3-Month Report (n=29)	6-Month Report (n=29)
Major Deviation	0	0
Minor Deviation	19	3
Received excluded concomitant medication	1	1
Received additional biopsy on untreated skin	0	2
Received incorrect dose	5	0
Received treatment to alternate location (inner vs. outer arm)	8	0
Biopsy visit out of window	5	0

Protocol deviations in 3-Month Report:

- Eight subjects (28%) received treatment to the inner rather than outer arm.
- Five subjects (17%) received 0.4 mL of azficel-T and placebo at each treatment visit instead of the protocol-specified 0.2 mL.
- Five subjects (17%) were biopsied out of the protocol-specified window: Four subjects were biopsied three or six days earlier than specified; one subject was biopsied 14 days earlier.

- Subject –(b)(6)-- was administered a brief course of oral prednisone for the treatment of poison ivy dermatitis approximately seven weeks following her final treatment visit.

Protocol deviations in 6-Month Report

- Subject –(b)(6)- received a brief course of oral prednisone for the treatment of an upper respiratory infection five months following the subject’s final treatment visit.
- Subjects –(b)(6)- and –(b)(6)- had an additional biopsy sample taken from an untreated area of the upper arm at the Biopsy 2 visit, because the initial biopsy taken from an untreated area at Biopsy 1 was unacceptable for assessment of dermal thickness.

***Reviewer Comment:** The protocol deviations should not have significant effect on histological evaluation or safety observations.*

3.2.2. Histology Evaluation: Methods and Results

Methods: The Histology Report Forms directed the two independent dermatopathologists to evaluate the biopsy tissue samples in two different ways:

- Non-comparative assessment: observations for each individual sample (azficel-T, saline, and untreated) based on the following parameters:
 - inflammatory cell infiltration
 - abnormal fibroblast morphology
 - fibrosis or other evidence of scar tissue
 - abnormal collagen and elastin organization or appearance by -----
------(b)(4)-----
- Comparative Assessments: intra-subject comparison of azficel-T to saline, azficel-T to untreated, and saline to untreated for each of the --(b)(4)--- based on the following parameters:
 - Differences in tissue architecture
 - Differences in inflammatory cell infiltrates
 - Differences in cellular morphology
 - Differences in epidermal thickness
 - Differences in dermal thickness
 - Differences in collagen quantity
 - Difference in elastin density

Results of Non-comparative assessment (Table 5): Both dermatopathologists (Reviewers 1 and 2) documented increased numbers of subjects with inflammatory cell infiltration in biopsies of azficel-T-treated sites (58% of subjects, Reviewer 1; 41% of subjects, Reviewer 2) at 3 months. Corresponding proportions were 3% and 10% of subject biopsies of saline-treated sites, and 14% and 0% of subject biopsies of untreated sites. The numbers of subjects with biopsies showing inflammatory cell infiltration decreased at the 6-month biopsy of the azficel-T sites (21% of subjects, Reviewer 1; 35% of

subjects, Reviewer 2). Corresponding numbers for the saline-treated sites were 14% and 10% of subjects, and 3% and 0% of subjects for the untreated sites. No abnormal fibroblasts were described in tissue samples at three or six months.

Nature and degree of the inflammatory cell infiltrate:

- Location: perivascular, in the superficial dermis
- Degree of infiltrate: mostly very mild or mild; one observation of moderate infiltration and three observations of mild to moderate infiltration
- Cell types: lymphocytic or mononuclear, occasionally histiocytic
- Time course: fewer azficel-T site biopsies were positive for inflammatory infiltrates at 6 months (6 and 10 for Reviewer 1 and Reviewer 2, respectively) than at 3-months (17 and 12 for Reviewer 1 and Reviewer 2, respectively)

Table 5. Assessment of Cellular Morphology, Inflammatory Infiltrate, and Fibrosis with --(b)(4)--- at 3- and 6-Month Biopsies, Study IT-H-001

Qualitative Analysis#		Azficel-T (*N=29) **n (%)				Saline (*N=29) **n (%)				Untreated (*N=29) **n (%)			
		Reviewer #1		Reviewer #2		Reviewer #1		Reviewer #2		Reviewer #1		Reviewer #2	
		3-M	6-M	3-M	6-M	3-M	6-M	3-M	6-M	3-M	6-M	3-M	6-M
Inflammatory Cell Infiltration	Y e s	17 (59)	6 (21)	12 (41)	10 (35)	1 (3)	4 (14)	3 (10)	3 (10.)	4 (13.)	1 (3.4)	0	0
Fibrosis	Y e s	0	1 (3.4)	8 (28)	7 (24)	0	0	5 (17)	3 (10)	0	0	4 (14)	***6 (21)

* Number of subjects

** Numbers and percentages of subjects with positive findings at the specific site.

***Biopsy tissue slides at 3 months were used for controls at 6 months.

Non-comparative evaluation of extracellular structures

- Collagen structure: Neither dermatopathologist Reviewer identified any abnormalities in collagen, based on a review of the -----(b)(4)----- stained slides, except one case (in placebo-treated site biopsy) by Reviewer 2 at 3-month biopsy.
- Elastin structure: Reviewer 1 scored a total of 7 samples at 3-Months and 2 samples at 6-Month biopsy in -----(b)(4)----- stained samples as positive for “abnormal elastin organization”; 4 azficel-T samples, 4 placebo samples and one untreated sample. Reviewer 2 did not score any sample as abnormal for elastin organization.

Reviewer Comment: *The most prominent finding from the above histological results is mild inflammatory cell infiltration in the dermis, seen mostly in azficel-T-treated samples. The cell infiltration subsided with time. These findings do not represent a safety concern. The dermatopathologists described no other abnormalities, such as scar formation, extracellular matrix structure changes, or abnormal cells.*

Results of Comparative Assessments among azficel-T, saline, and untreated samples:
Two independent dermatopathologists reported differences in the amount of inflammatory cell infiltrates between azficel-T-treated samples and saline-treated or untreated samples taken from the same subject. No notable differences in tissue architecture, cellular morphology, epidermal/dermal thickness, and dermal cellularity between azficel-T and saline samples were described.

Table 6 shows results of histological assessments of differences in tissue architecture and inflammatory infiltrates when the azficel-T-treated samples were compared to saline-treated and untreated skin areas in the same subject.

Table 6. Comparative Histological Evaluations of Dermis and Epidermis by Treatment with ----(b)(4)----- Study IT-H-001

Qualitative Analysis*		Azficel-T to Saline (N=29) *n (%)				Azficel-T to Untreated (N=29) n (%)				Saline to Untreated (n=29) n (%)			
		Reviewer #1		Reviewer #2		Reviewer #1		Reviewer #2		Reviewer #1		Reviewer #2	
		3 M	6 M	3 M	6 M	3 M	6 M	3 M	6 M	3 m	6 M	3 M	6 M
Difference in tissue architecture	Yes	0	1 (3)	12 (41)	1 (3.4)	0	1 (3.4)	10 (35)	1 (3)	0	0	8 (28)	2 (7)
Difference in inflammatory cell infiltrates	Yes	17 (59)	10 (35)	13 (45)	10 (35)	15 (52)	7 (24)	12 (41)	10 (35)	6 (21)	4 (14)	1 (3)	3 (10)

* Numbers and percentages of subjects with differences in tissue architecture or in inflammatory cell infiltrates compared to their own control samples.

Table 7 shows results of histological assessments of differences in dermal thickness and cellularity when the azficel-treated samples were compared to saline-treated and untreated skin areas in the same subject. As shown in this table, there were no differences in dermal thickness and dermal cellularity among azficel-treated, saline-treated, and untreated groups.

Table 7. Dermal and Epidermal Thickness Comparisons with ----(b)(4)----, IT-H-001

Qualitative Analysis		Azficel-T to Saline (N=29) *n (%)				Azficel-T to Untreated (N=29) n (%)				Saline to Untreated (N=29) n (%)			
		Reviewer #1		Reviewer #2		Reviewer #1		Reviewer #2		Reviewer #1		Reviewer #2	
			6 M	3 M	6 M	3 M	6 M	3 M	6 M	3 M	6 M	3 M	6 M
Dermal Thickness	Thicker	0	1 (3.4)	2 (6.9)	2 (6.9)	0	1 (3.4)	3 M	4 (15)	0	0	3 (11)	5 (17)
	Thinner	0	0	0	3 (10)	0	0	1 (3.7)	1 (3.4)	0	0	1 (3.7)	1 (3.4)
	No Difference	29 (100)	28 (97)	27 (93)	24 (83)	29 (100)	28 (97)	22 (82)	24 (83)	29 (100)	29 (100)	23 (85)	23 (85)
Dermal Cellularity	Thicker	0	1 (3.4)	5 (17)	3 (10)	0	1 (3.4)	5 (17)	4 (14)	0	0	2 (6.9)	1 (3.4)
	Thinner	0	0	1 (3.4)	0	0	0	0	0	0	0	0	0
	No Difference	29 (100)	28 (97)	23 (79)	26 (90)	29 (100)	28 (97)	24 (83)	25 (86)	29 (100)	29 (100)	27 (93)	28 (97)

* Numbers and percent of subjects with differences in dermal thickness or dermal cellularity, compared to their own control samples

Table 8. Comparative Histological Evaluation of Extracellular Matrices by Treatment by ----(b)(4)----, IT-H-001

Qualitative Analysis		Azficel-T to Saline (N=29) *n (%)				Azficel-T to Untreated (N=29) n (%)				Saline to Untreated (N=29) n (%)			
		Reviewer #1		Reviewer #2		Reviewer #1		Reviewer #2		Reviewer #1		Reviewer #2	
		3 M	6 M	3 M	6 M	3 M	6 M	3 M	6 M	3 M	6 M	3 M	6 M
Collagen Quantity (b)(4)	Increased	0	0	0	1 (3.4)	0	0	3 (10)	2 (6.9)	0	0	3 (10)	3 (10)
	Decreased	0	0	0	2 (6.9)	0	0	0	1 (3.4)	0	0	0	1 (3.4)
	No difference	29 (100)	26 (89)	29 (100)	26 (89)	26 (89)	26 (89)	26 (89)	26 (89)	29 (100)	26 (90)	26 (89)	25 (86)
Elastin Density (b)(4)	Increased	1 (3.4)	0	3 (10)	1 (3.4)	4 (14)	0	4 (15)	0	5 (17)	0	1 (3.4)	0
	Decreased	2 (7)	1 (3.4)	1 (3.4)	0	2 (6.9)	1 (3.4)	1 (3.7)	0	3 (10)	0	1 (3.7)	1 (3.4)
	No difference	26 (89)	28 (97)	25 (86)	28 (97)	23 (79)	28 (96)	24 (83)	0	21 (72)	0	27 (93)	28 (97)

* Numbers and percentages of subjects with differences in Collagen Quantity or Elastin Density, compared to their own control samples.

Table 8 shows the results of differences in collagen quantity and elastin density when the azficel-treated samples were compared to saline-treated and untreated skins in the same subject. As shown in Table 8, there were no differences in collagen quantity and elastin density among treatment sites.

Reviewer Comment: The results of comparative assessments parallel the findings from the non-comparative assessments. The only positive finding was an increase in inflammatory cell infiltrates in the dermis, mainly in response to azficel-T.

3.2.3 Exploratory Assessments of Appearance Improvement: The subjects and investigators were asked to evaluate the severity of nasolabial fold wrinkles using

baseline photographs from the previous Phase 3 trials as a control. The objective was to evaluate the long-term durability of the cosmetic effects of azficel-T. The subjects were also asked eight questions regarding their skin quality after treatment with azficel-T.

***Reviewer's Comments:** Any conclusion is limited because this was an open-label study. It is also not clear whether the assessment tool for skin quality has been validated.*

3.2.4. Safety Results

Table 9 displays the most common treatment-emergent adverse events during Study IT-001-H. The most common local treatment-emergent adverse events (TEAEs) were injection-site erythema (45% of azficel-T treated sites and 10% of saline-treated sites), induration (10% azficel), pain (7% azficel), and discoloration (3% azficel). There was one case of dehiscence of the saline-treated biopsy site. Other systemic adverse events occurring at low rates (such as traffic accident, upper respiratory infection) are unlikely related to azficel-T. These events are not shown in this table. One serious adverse event (SAE), leukocytoclastic vasculitis, is discussed in the SAE section.

Table 9. Injection-Site Adverse Events, IT-H-001

Injection-Site Adverse Events	Azficel-T (N=29) n (%)		Saline (N=29) n (%)	
	Subjects	Events	Subjects	Events
Injection-Site Erythema	13 (45)	25	3 (10)	5
Injection-Site Induration	3 (10)	3	0	0
Injection-Site Pain	2 (7)	2	0	0
Injection-Site Discoloration	1 (3)	1	0	0
Contusion	2 (7)	3	1 (3)	2
Wound dehiscence	0	0	1 (3)	1

Table 10 shows the severity of injection-site adverse events in azficel- and saline-treated sites. Most of the injection-site reactions were graded mild. There was no severe injection-site reaction.

Table 10. Incidence of Injection-site Reactions by Severity, IT-H-001

Severity	Azficel-T (N=29) n (%)	Saline (N=29) n (%)
Any TEAE	13 (45)	4 (14)
Mild	12 (41)	3 (10)
Moderate	1 (3)	1 (3)
Severe	0	0 (0)

Table 11 shows the relationship of injection-site adverse events to study treatment, as judged by the investigators. The majority of the injection-site adverse events were related to the azficel treatment by the investigators.

Table 11. Relationship of adverse events to study agent, IT-H-001

Relationship	Azficel-T (N=29) n (%)	Saline (N=29) n (%)
Any treatment-emergent adverse event (TEAE)	13 (45)	4 (14)
Unrelated	0	0
Unlikely	0	0
Possible	2 (7)	0
Probable	0	0
Definite	11 (38)	4 (14)

Duration of adverse events: Most of the TEAEs at the injection site resolved within a week. Six events resolved in more than one week: Subject –(b)(6)--: induration and erythema at the azficel-T-treated site resolved in 11 days; Subject –(b)(6)--: contusion below the azficel-T biopsy site resolved in 14 days; Subject –(b)(6)--: contusion at both the azficel-T and placebo-treated sites resolved in 26 days; Subject –(b)(6)--: erythema at the azficel-T-treated area resolved in 28 days; dehiscence of the saline-site biopsy wound resolved in 51 days; Subject –(b)(6)--: discoloration at the azficel-T injection site resolved in 61 days; and Subject (b)(6) leukocytoclastic vasculitis, resolved 35 days after onset.

Ongoing adverse events: Mild erythema and induration at the injected sites was noted at the time of 3-month biopsy in three subjects: Subject –(b)(6)--, Subject –(b)(6)--, and Subject –(b)(6)--. No ongoing TEAEs at the saline-treated biopsy site were noted. There was no action taken for these adverse events, which resolved by the time of the 6-month biopsy.

Serious Adverse Event (SAE): leukocytoclastic vasculitis

Subject –(b)(6)-- was a 67 year-old white male with a past medical history of hypertension, hypercholesterolemia, prostate hypertrophy, fibromyalgia, osteoarthritis, and tobacco use. He participated in Study IT-R-006 and received three administrations of azficel-T injected into his bilateral nasolabial fold wrinkles, per protocol, from July 2007 to October 2007. He completed the study with only one reported adverse event, acute bronchitis, which occurred a month after the second administration and resolved 47 days later after treatment with antibiotic, cough syrup, and inhaler. Although the subject reported a three-point improvement in his wrinkle score, the physician evaluator reported no change.

The subject was enrolled in Study IT-H-001 with planned three treatments to his arms. He 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. On July 3, 2010, eight days after study treatment, the subject presented to the emergency room with symptoms of weakness, rapid pulse, and a skin rash on his arms and lower legs, with lower legs predominating. He was discharged the same day but returned to the emergency room on July 4, 2010 with similar symptoms. The rash was described as 10 to 15 small necrotic, erythematous lesions on his legs. The clinical impression was small-vessel vasculitis. The patient was

admitted to the hospital. Biopsy of the lesion showed leukocytoclastic vasculitis. The subject was also diagnosed with left arm cellulitis in a non-treatment area. He received vancomycin, ceftriaxone, methylprednisolone, and Percocet in the hospital and was discharged on vibromycin (doxycycline) and diflucan. This serious adverse event was considered to be unlikely related to study treatment by the Investigator and Sponsor.

Reviewer's comments: Hypersensitivity vasculitis (leukocytoclastic vasculitis) is a histopathologic term commonly used to denote a small vessel vasculitis, with an incidence of 10-30 cases per million people per year. Leukocytoclastic vasculitis is commonly caused by antibiotics, various infections, foods or food additives, collagen-vascular diseases, inflammatory bowel disease, malignancy, or a larger-vessel vasculitis, but a cause is not found in approximately 50% of patients. Circulating immune complexes play a role in the pathogenesis of hypersensitivity vasculitis. Other autoantibodies, such as antineutrophil cytoplasmic antibody (ANCA), and other inflammatory mediators, adhesion molecules, and local factors may be associated with disease manifestations.

Cellulitis of the left wrist may have been a cause for the vasculitis. However, the time of onset of the cellulitis is not clear, making it difficult to assess the temporal relationship of the two events. Additional laboratory and clinical details are not known. IV infiltration of the left wrist during the admission was reported. The possible relationship of this SAE to the product is biologically plausible because of the temporal relationship to product administration, past exposure (with possible sensitization) to the same product 2 to 3 years previously, and no clear alternative cause. Although there was no such adverse event occurring in the safety population of seven trials, there were cases of anaphylaxis in UK in the pre-IND period. The relationship of the UK product and its adverse events to LAVIV is unclear because the components of the marketed product in UK differed from those of azficel-T. Furthermore, a definitive conclusion of the relationship of the UK product to the anaphylaxis could not be drawn because only a brief case description of the anaphylaxis was submitted during the original BLA submission due to the limited medical documentation.

Because of the serious nature of this adverse event, and the potential for this type of reaction to have even more severe clinical consequences than in this subject, this case should be described in the Warnings and Precautions Section of the Prescribing Information. To monitor for similar occurrences, active post-marketing surveillance of hypersensitivity reactions in a registry study is necessary.

3.3. Summary of Study IT-H-001:

- 29 subjects received biopsy at Month 3 and Month 6 post-treatment with azficel-T. One subject received one treatment; 21 subjects received two treatments; and 7 subjects received three treatments.
- No drop-outs and no major protocol deviation.
- Subgroups: geriatric: 5 (17%), male: 6 (21%), African American or Asian: 1 (3%) of each; dark-skin population (Fitzpatrick >4): 8 (28%).
- Biopsy results
 - Abnormal fibroblasts were not observed in skin biopsy samples.

- Mild inflammatory infiltrate was found at three months (50% of azficel-T sites; 6.5% of saline-treated sites; 7% of untreated sites). This mild inflammatory infiltration decreased at the 6-month biopsy.
- Fibrosis: There is discrepancy between the two dermatopathologist reviewers in the estimated occurrence of fibrosis at either three or six months. Only Reviewer 2 described positive findings fibrosis: in 28% of biopsies of azficel-T-treated sites; 17% of biopsies of saline-treated sites; and 14% of biopsies of untreated sites.
- No abnormal collagen organization was described by either of the two reviewers.
- Only Reviewer 1 described abnormality in elastin organization: in 10% of biopsies of azficel-T-treated sites; 14% of biopsies of saline-treated sites; 7% of biopsies of untreated sites. The reason for this discrepancy is unclear, but this degree of variability may not be clinically important.
- Epidermal and dermal thickness: no differences were described among the three treatment sites.
- Injection-site reactions: erythema, (38% of azficel-T injection sites; 10% of saline injection sites), pain (7%; 0), discoloration (3%; 0), induration (3%; 0), and contusion (3%; 0). Most AEs disappeared by 11 days; discoloration lasted for 61 days.
- Serious AE: leukocytoclastic vasculitis in subject --(b)(6)--. The vasculitis appeared in both legs and both arms nine days after product administration in the right arm.

4. Combined Safety Analysis from Six Completed Clinical Studies under --(b)(4)- INDs

BLA#125348/Amendment 39

Date of Amendment Submission: April 7, 2011

Background: On March 29, 2011, a teleconference was initiated by FDA to discuss efficacy and safety labeling issues with the applicant. During the discussion, FDA requested a summary of safety data from clinical studies conducted with azficel-T under different INDs (Table 12).

Summary of additional completed clinical studies under -----(b)(4)----- INDs: Table 12 summarizes six completed studies with azficel-T for --(b)(4)- indications (under (b)(4) INDs). These six studies include the skin biopsy histology study. A total of 158 subjects participated in these six studies, ranging in development from Phase 1 to 3, from 2004 to 2011. Azficel-T was used to treat skin of the arms (for the skin biopsy study), --(b)(4)----- (b)(4)----- IT-G-003 was a follow-on study, which enrolled 12 of the 20 subjects who previously participated in IT-G-002. Also, IT-H-001 enrolled 16 subjects who previously participated in IT-A-008. All the studies were conducted with an intra-patient vehicle control.

Table 12. Summary of Studies with Azficel-T under Four INDs

Study	IND #	Indication	Year Completed	Phase	Subject #	Study Design
IT-H-001	(b)(4)	Facial wrinkles and creases	2011	1	29	Randomized, single-blind, inpatient saline-controlled; 3 treatment administrations in arms; Skin biopsy at 3 & 6 months; 2 to 4 weeks apart
IT-V-001	(b)(4)	----- (b)(4) -- -----	2007	1	5	Open-label; up to 3 treatment administrations in --- (b)(4) ---
IT-G-001	(b)(4)	---- (b)(4) ---- ----- ----- -----	2004	1	21	Randomized, double-blind, inpatient vehicle-controlled; up to 3 treatment administrations in -- (b)(4) ---; 2 to 4 weeks apart
IT-G-002	(b)(4)	---- (b)(4) ---- -----	2005	2	20	Same design as IT-G-001 up to 3 treatments, one week apart
IT-G-003	(b)(4)	---- (b)(4) ---- -----	2008	2	12	Open-label; up to 5 treatment sessions; Day 0, Wk 1, 2, Months 2, 4
IT-A-008	(b)(4)	-- (b)(4) --	2008	2-3	99	Randomized, double-blind, inpatient vehicle-controlled; up to 3 treatment administrations in face, 2 weeks apart
Total	(b)(4) INDs		2004 to 2011		158*	

*Note: 12 subjects participated in both IT-G-002 and IT-G-003, and 16 subjects participated in both IT-A-008 and IT-H-001.

Study subjects: Table 13 provides the demographic characteristics and the disposition of 158 subjects who participated in six studies with azficel-T. Twenty-eight subjects participated in more than one trial. The average age of the subjects is 46 years, with 67% females and 78% white. Nine subjects (6%) withdrew from the six studies; most (6 out of 9) were lost to follow-up in the acne study. No subject withdrew due to an AE. An AE led to the discontinuation of the study treatment in one subject in IT-H-001 due to leukocytoclastic vasculitis, as described in the section above (see Section 3.2.3).

Adverse Events: Table 14 shows the frequencies of the injection-site adverse reactions in a total of 158 subjects in all six studies. The most common adverse events are injection-site erythema, swelling, bruising, induration, acne, rash, nodules, pain, and discoloration. These adverse reactions were observed in both azficel-T and vehicle-treated sites and at similar rates, except erythema, induration and acne, which occurred more frequently at azficel-T sites than at saline or vehicle sites. One case of leukocytoclastic vasculitis occurred in the skin biopsy study (not shown in Table 14; see detail in Section 3.2.4). Other systemic adverse events, such as traffic accident and upper respiratory infection, occurred in <1% of all subjects. These systemic treatment-emergent adverse events are unlikely related to azficel-T. These systemic events are not shown in Table 14.

Table 13. Demographics and Disposition in Six Studies under (b)(4) INDs with Azficel-T

Categories	IT-H-001 (N=29)	IT-V-001 (N=5)	IT-G-001 (N=21)	IT-G-002 (N=20)	IT-G-003 (N=12)	IT-A-008 (N=99)	All (%) (N=158)*
Age							
Mean	50	55.6	54.5	51.4	51.2	41.6	46.4
(Range)	(26, 75)	(35, 68)	(41, 67)	(35, 68)	(38, 59)	(19, 64)	(19, 75)
Gender							
Female	23	2	18	17	9	56	105 (66%)
Male	6	3	3	3	3	43	53 (34%)
Race							
White	23	5	19	17	12	69	122 (77%)
Hispanic	1	0	1	0	0	0	1 (<1%)
Black or African American	0	0	1	2	0	7	10 (6%)
Asian	1	0	0	1	0	5	6 (4%)
American Indian or Alaska Native	0	0	0	0	0	1	1 (<1%)
Other	4	0	0	0	0	17	18 (11%)
Disposition:							
Withdrawal	0	0	0	1 (subject withdrawal)	1 (sponsor request)	1 (subject withdrawal); 6 (lost to follow-up)	9 (6%)
Completed	29	5	21	19	11	92	177 (94%)

*Note: 12 subjects participated in both IT-G-002 and IT-G-003, and 16 subjects participated in both IT-A-008 and IT-H-001.

Table 14. Adverse Events at the Injection Sites in Six Studies under (b)(4) INDs

Injection-Site Reactions	All AEs (N=158) n (%)
Injection-site erythema	20 (13)
Injection-site swelling	10 (6)
Injection-site bruising	4 (3)
Injection-site induration	4 (3)
Injection-site rash	3 (2)
Injection-site nodule	2 (1)
Injection-site pain	2 (1)
Injection-site discoloration	1 (<1)
Injection-site dryness	1 (<1)
Injection-site irritation	1 (<1)
Acne	4 (3)

Summary of the combined safety data from six studies under (b)(4) INDs

- Safety database: a total of 158 subjects in six studies (Phase 1, 2, 3) under ----(b)(4)----- INDs, using azficel-T for ---(b)(4)-----, skin biopsy (under IND for facial wrinkles), ----(b)(4)-----

- Demographics: The average age of the subjects was 46 years with 67% females and 78% white.
- Most common adverse events were injection-site reactions including injection site erythema, swelling, bruising, induration, acne, rash, nodules, pain, and discoloration. These adverse reactions were observed in both azficel-T and vehicle-treated sites at similar rates, except that erythema, induration, and acne occurred more frequently in azficel-T sites.
- Severity of AEs: all of the adverse events were graded as mild to moderate in severity.
- Relationship to product injection: sponsor lists the following AEs as related to product injection: Injection-site erythema, bruising, induration, rash, nodules, pain, discoloration, irritation, contusion, procedural pain, wound dehiscence, acne, headache, and dysphonia

Conclusion: The adverse events in the combined safety data in this BLA resubmission show a safety profile for azficel-T that is similar to the safety profile seen in the seven trials of azficel-T in wrinkles that were submitted with the original BLA. With the exception of the single case of leukocytoclastic vasculitis, no new safety issues were raised in the review of this resubmission.

5. Clinical Review of Clinical support Center Policies and Procedures for Shipping Errors (CR Item#15)

Background: During Studies IT-R-005 and 006, a total of six documented shipping errors (6/421= 1.5%) occurred, resulting in repeat biopsy of the subjects. Three of the shipping errors were due to transportation of biopsies by ground shipment instead of air shipment. The other three errors were due to delays in the delivery by the courier. In FDA CR letter Item#15, the applicant was requested to submit revised Clinical Support Center Policies and Procedures for preventing the shipping errors.

Clinical review of SOPs (Standard Operating Procedures): In response to CR Item# 15, the applicant provided three draft documents regarding the shipping errors: (1) scheduling Biopsy Collection Dates (CSC SOP 001), (2) Management of Biopsy and LAVIV Shipping Errors (CSC SOP 004), and (3) Physician Training manual including step-by-step instructions for shipment. In the SOPs and Physician Training Manual, the applicant has adequately identified the potential errors that may occur during the shipments of biopsy kits, biopsied tissue samples, and LAVIV product between the clinics and Fibrocell. These potential errors include incorrect customer information, missing contents of the biopsy kit, mishandling by the shipper, shipping delays, packaging damage, improper identification by the clinic, mechanical failure, weather delays, loss of package by courier, missed delivery, and incorrect or inadequate customer information on the label. To avoid these errors, the applicant has revised the related SOPs and Physician Training manual to clearly describe responsibilities of the medical clinic and the Clinical Support Center in the shipment process. A total of four forms regarding biopsy inventory, product ordering, injection, and manufacturing scheduling have been created to document and archive the entire biopsy and product handling

process for easy trouble-shooting of the shipping errors. The follow-up action plan is clearly outlined for the incidence of shipping errors.

Recommendation: The submitted SOPs and relevant sections of the Physician Training Manual were reviewed by a joint effort from CMC and clinical teams. The Policies and Procedures are considered adequate for the prevention of the shipping errors. In addition, the potential risk of the need of repeat biopsy as a result of shipping errors has been written into the PI along with the risk of manufacturing failure. The applicant is required to document and report the occurrence of the shipping errors to FDA in their post-market annual report.

6. Clinical Review of Physician Training Manual (CR tem#16)

The Physician Training Manual has been reviewed by the clinical team in consultation with dermatologists. (Refer to Clinical Review by Bruce Schneider, MD; CDER consultation by Jane Liedtka, MD; and SGE consultation by Dr. Lynn Drake).

7. Clinical Review of Prescribing Information (PI) (CR Item#17 –18)

The applicant submitted a revised PI based on FDA CR Letter Items 17 and 18. This proposed PI was revised by a joint effort of CMC, clinical, and the Advertising and Promotional labeling Branch (APLB) review teams together with the applicant. The main changes are summarized below:

Indication: the indication was modified to “LAVIV[®] (azficel-T) is an autologous cellular product indicated for improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults. The safety and efficacy of LAVIV for areas other than the nasolabial folds have not been established. The efficacy of LAVIV beyond six months has not been established.”

Contraindications: allergy to antibiotics used in the manufacture process, allogenic use, and facial infection are included in this section of the label.

Warnings and Precautions: adverse reactions (bleeding/bruising, herpes labialis, vasculitis, basal cell cancer) and potential risks (such as keloid) are included in this section of the label.

Adverse reactions: common adverse events in >1% of trial population and rare events in <1% clinical trial population are included in this section of the label.

Histology Study: information on skin biopsy study is now included in the label.

Geriatric population: data limitation of the geriatric population is now described in the label.

Mechanism of action: a statement regarding mechanism of action has been deleted from the label because there are insufficient data to support the proposed mechanism.

Clinical outcomes: tables and graphs showing other than pre-specified endpoints consistent with the Data Analysis Plan are deleted.

Discrepancy of the age ranges in the safety analysis and efficacy analysis: the age range in the safety population is 20 to 79 years. However, the age range in the efficacy trials is 23 to 81 years. The safety database includes subjects in some studies which did not contribute to the efficacy database. These subjects account for the lower age limit of 20 years in the safety database, compared to the lower age limit of 23 years for the efficacy database. In addition, some subjects in the pivotal efficacy studies were randomized but did not receive an administration of either azficel-T or control (e.g., due to manufacturing failure). Such subjects were included in the efficacy database but not in the safety database. These subjects who did not receive either azficel-T or control account for the upper age limit of 81 years in the efficacy database although the upper age limit for the safety database is only 79 years.

Manufacture failure and shipping error: risk of repeat biopsy as a result of manufacture failure or shipping errors is now described in the label.

Patient labeling: the patient labeling was revised to ensure the consistency with the PI, using non-technical language.

8. Post-Marketing Plan for Safety Monitoring

In a joint effort by the Pharmacovigilance and clinical teams, FDA has proposed a post-marketing registry study as a Post-Marketing Requirement (PMR) to the applicant. The purpose of this registry study is to evaluate the incidence of rare pre-specified adverse events over a two-year follow-up period after the treatment with the product. The targeted adverse events include facial skin cancers near the product injection site and immune hypersensitivity reactions (such as anaphylaxis, vasculitis, systemic skin eruptions and angioedema). The study is designed to include 2700 patients who receive at least one injection of the product. These subjects will be followed up at 1 to 2 weeks, 60 days, 1 year and 2 years by the applicant through telephone contact using an interview script that queries the subject about the onset and location of the pre-specified AEs, actions taken, concomitant medications and procedures, and other medical problems.

The applicant has accepted the FDA's proposal for a registry study as a PMR. The applicant's proposed study protocol meets the minimum requests by FDA (registry design with 2700 patients and an active follow-up contact for two years). The applicant has proposed the following dates for implementing the registry study: final Protocol Submission September 2011, Registry Completion Date September 2016, and Final report Submission December 2016.

9. Consultations

During the review of the resubmission documents, dermatologists and dermatopathologists from the Center for Drug Evaluation and Research (CDER) and a Special Government Employee (SGE) were consulted regarding the Clinical Study Report of IT-H-001 (skin biopsy study), the case of leukocytoclastic vasculitis, Physician Training Manual, labeling, and post-marketing surveillance plan. Most of their suggestions were addressed. Although there was some variability among the consultants regarding the need for post-marketing surveillance, each consultant thought that a post-marketing study was reasonable to assess at least one of the safety concerns (i.e., local skin cancer or hypersensitivity reactions).

10. Conclusions and Recommendations

Conclusion: The skin biopsy study was adequately designed and executed. The predominant finding of the study is mild inflammatory infiltration in the superficial dermis in response to primarily the product administration, a reaction that gradually decreased with time. This finding does not represent a safety concern. One SAE of leukocytoclastic vasculitis may be a safety signal for an allergic reaction in response to the product, but has not been observed in previous clinical trials of this product.

The safety data from additional studies (combined safety data) in other indications (i.e., indications other than wrinkles) did not provide any concerning safety signal. The overall adverse event profile is similar to that of the seven trials of azficel-T for treatment of wrinkles.

The Prescribing Information has been revised to ensure that the efficacy and safety claims in the PI are consistent with the efficacy data derived from the two Phase 3 trials and to be consistent with the safety data derived from all seven trials in wrinkles.

The SOPs for preventing shipping error has been reviewed and accepted by both CMC and clinical teams. The risk of requiring repeat post-auricular biopsy was written into the PI.

For post-marketing safety monitoring, active surveillance for pre-specified adverse events is necessary for this novel autologous cellular product. The two pre-specified serious safety events include facial skin cancer near the injection site and immune hypersensitivity reactions.

Recommendations: Based on the review of safety data from 508 subjects in seven previous trials in wrinkles, safety data from 29 subjects in the skin biopsy study, and the combined safety data from trials in non-wrinkle indications, the overall safety profile of azficel-T is acceptable. Based on review of the efficacy data from 421 subjects in the two Phase 3 trials in wrinkles, azficel-T is effective for the indication of improvement of nasolabial fold wrinkles. Therefore, I recommend approving azficel-T for market

licensure. For the safe use of this product, a revision of the Prescribing Information was done to reflect safety and efficacy of the product as demonstrated in the seven facial wrinkle trials. For safety monitoring of this novel cellular product, a registry study is required to evaluate the occurrence of facial skin cancer in the vicinity of product administration and immune hypersensitivity reactions.

