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M E M O R A N D U M

Date: April 8, 2011

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To: Yao-Yao Zhu, M.D, Medical Officer, OCTGT/DCEPT/CEB

Cc: Julie Beitz, M.D., Office Director, ODE 3, CDER

Re: DDDP Consult # 1343 STN125348

Autologous Fibroblasts Expanded Ex-Vivo, Administered Intradermally

Material Reviewed:

STN125348:

Revised Protocol IT-H-001, "A Placebo-Controlled Serial Skin Biopsy Study to
Evaluate Tissue Histology Following Treatment with Azficel-T"
Clinical Report for Study IT-H-001
Amendment to a pending application: Clinical response to FDA's Complete
Response Letter dated 18 December 2009

Background

On March 6, 2009 CBER received a BLA from sponsor Isolagen Technologies Inc (now known as Fibrocell Technologies Inc) for use of IsolagenTherapyTM (now known as

azficel-T), an injectable autologous cellular product composed of fibroblasts, indicated for the treatment of moderate to severe nasolabial fold wrinkles in adults.

In June of 2009 CBER consulted DDDP regarding multiple clinical issues pertaining to this BLA submission including adverse events, population, labeling language, post-marketing surveillance, endpoints, photographic assessment and safety. The DDDP consultation report was finalized and sent to CBER in August of 2009.

An advisory committee was held on Oct 9, 2010. At the Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC), committee members raised serious concerns about the lack of any *in vivo* information on the following issues

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

A Complete Response letter was sent to the sponsor on Dec 18, 2009. This letter outlined numerous deficiencies including item #14 detailed below:

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

On Jan 8, 2010 the sponsor submitted a draft clinical trial outline for the recommended histologic study. Teleconferences were held on Jan 12, 2010 and Jan 28, 2010 between the sponsor and CBER and the draft protocol was amended to include the Agency's recommendations. The sponsor submitted this revised protocol for study IT-H-001, "A Placebo-Controlled Serial Skin Biopsy Study to Evaluate Tissue Histology Following Treatment with Azficel-T" on Jan 30, 2010 and was the subject of another consultation with DDDP. The questions for this second consult are below:

1. The sponsor proposed to inject study agent and perform post-injection biopsies at the medial aspect of the upper right arm. Please comment on whether the proposed site would adequately mimic the characteristics of the nasolabial fold skin that was studied in the pivotal studies, IT-R-005 and IT-R-006.
2. Please comment on whether the 1-2 treatments proposed in this study would adequately mimic the 3 treatments that were administered in the pivotal studies in order to evaluate the product's safety profile and provide some information on the product's mechanism of action, histologically.
3. Please comment on whether the study procedures (including number and time-points of treatment, skin biopsy procedure, and preparation of the tissues, tissue stains, etc) will adequately evaluate the histology of azficel-T-treated tissue compared to saline-treated and untreated dermal tissues.
4. Please comment the use of Verhoeff-VaGieson and Masson's trichrome staining in addition to standard H & E staining for detecting skin changes at the molecular, cellular and structure levels. Please comment specifically on the adequacy of these stains to evaluate dermal collagen and elastin at post-treatment sites, and whether you would recommend any additional histological studies
5. Please comment on whether the primary endpoints meet the primary goal of the study.
6. Please comment on whether any other endpoint(s) should be considered.
7. Please provide any additional comments or recommendations on the study design.

The second consult was completed on April 21, 2010. On Oct 21, 2010 a third consult was requested regarding the histology study for Fibrocell (IND (b)(4)). The following questions were posed:

The objective of Study IT-H-001 is to qualitatively evaluate human dermal 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.

The goal is to obtain a descriptive analysis for the blinded histological assessments by two independent board-certified dermatopathologists for all specimens.

Questions for the consultants:

1. Are the histological read procedure outlined in the Histology Report Guidelines acceptable and would you recommend any revisions?
2. Would answers/descriptions to the questions in the Histology Report Form (See attachment) for each of the stains (H&E, Masson's Trichrome, and

Verhoeff-Van Gieson) be adequate to achieve the objective for Study IT-H-001?

3. Do you have any additional comments, recommendations or questions for the sponsor's general histology evaluation plan?
4. Do you have any additional comments, recommendations or questions for the Histotechnologist Laboratory Instruction, Histology Report Guidelines, or the Histology Report Form?

The third consult was completed on Nov 19, 2010. On Feb 14, 2011 a fourth consult was requested regarding the histology study preliminary report (3 month biopsy results) for Fibrocell (IND (b)(4)). The following questions were posed:

1. The two blinded dermatopathologists reported "mild perivascular inflammatory cell infiltrate" in up to 58% of subjects and mild fibrosis in 27% (only by reviewer #2) of subjects who received fibroblast product at Month 3 biopsy. The similar findings were also observed in tissue slides of placebo and untreated skins, but to a lesser degree, especially for cell infiltration. Please provide your comment on the significance of these finding in terms of potential safety issues and any suggestions regarding whether additional information is needed (e.g. slide reviewing) and whether Month 6 biopsy data are important. (CDER and SGE)
2. Discrepancy of reading was present between two blinded dermatopathologists in determining the existence of "fibrosis". Please comment on whether the discrepancy between the two reviewers is critical and whether it requires third party adjudication. (CDER and SGE)
3. One case of Leukocytoclastic Vasculitis was described in the Safety report of Serious Adverse Event for subject -(b)(6)- in IT-H-001 (tissue biopsy study) eight days after the product administration. This event was considered as unrelated to the product by the investigator. Please provide your thought on the relationship of this case with the product and your comment on the necessity of monitoring this type of reactions on post-marketing registry study. (CDER and SGE)

Review

Overview of protocol and study results

The objective of Study IT-H-001 was to qualitatively evaluate 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. This was a single blind (subject blinded), intra-patient, controlled study. Although the investigator was unblinded to treatment, the central laboratory dermatopathologist remained blinded to treatment. 29 subjects from Studies IT -R-005, IT -R-06, IT -R-007, and IT-A-008 that had available azficel- T inventory for one to three additional treatments were enrolled in this study; one

received one treatment injection, 21 received two treatment injections, and seven received three treatment injections. Efficacy response in the previous studies was not considered when determining eligibility for this study.

Subjects were randomized to receive azficel-T on either their right or left arm with the opposite arm receiving sterile saline. Throughout the course of the study, 29 subjects received between one to three treatments separated by 5 weeks \pm 10 days. Cutaneous tissue punch biopsies (4 mm) were collected from the two treatment areas three months (Biopsy 1) following the last treatment with azficel- T and sterile saline. A single biopsy from an untreated control area was collected at the three month visit. Additional biopsies are planned for 6 months (Biopsy 2) following the last treatment with azficel- T and sterile saline. The untreated skin will be biopsied only once, the same slides of untreated skin will serve as a control for both evaluation periods.

The biopsies were processed and sent out for interpretation by a central histology laboratory. Each biopsy was stained with three stains: Hematoxylin & Eosin, Masson's Trichrome, and Verhoeff-van Gieson. The H & E stained sample was used for evaluation of the morphology of the dermis, subcutis and epidermis, as well for determining the presence of inflammatory cells. Masson's trichrome stain, which stains collagen fibers blue, cell nuclei black, and the background red, was used for detection of collagen fibers in dermis. Verhoeff-Van Gieson stains elastin black and collagen red, and was used for evaluation of the structure and organization of elastin fibers, and as a secondary evaluation of collagen. The tissue samples were interpreted in a blinded fashion at 3 months (Biopsy 1). Similar processing and interpretation is planned for 6 months (Biopsy 2). Safety was monitored through the biopsy follow-up visit 10 \pm 3 days after the biopsy.

A written report for each subject's samples was prepared independently by the two dermatopathologists for each subject for Biopsy 1. At each evaluation a box of slides was prepared for each subject containing 9 slides (three tissue samples, three stains per slide). Each tissue sample was identified by a unique numerical blinding code. The slide box was labeled with the subject identifier. The pathologists were blinded to treatment but were unblinded with respect to the subject (i.e. they knew that samples were from a single subject).

The histology endpoints for study IT -H- 001 were as follows:

1. Qualitative comparison for clinically meaningful differences in the cellular morphology of the dermis, subcutis and epidermis between azficel-T, sterile saline treatment, and untreated control sites at each biopsy timepoint.
2. Qualitative comparison of differences in inflammatory cell infiltrates between azficel- T treatment, sterile saline treatment, and untreated control sites at each biopsy timepoint.
3. Qualitative comparison of differences in the structure and organization of collagen and elastin fibers between azficel- T treatment, sterile saline treatment, and untreated control sites at each biopsy timepoint.

With regard to endpoint 1, no clinically meaningful differences were observed in the cellular morphology of the dermis, subcutis or epidermis when biopsies from tissue treated with azficel-T were compared to either placebo-treated or untreated tissue in the IT-H-001 study.

With regard to Endpoint 2, tissue treated with azficel-T was more likely to contain mild degree of cellular infiltrate than placebo-treated or untreated tissue. In general, both Reviewers made similar comments regarding the nature and degree of the inflammatory cell infiltrate. Both noted that the infiltrates were perivascular, often in the superficial dermis, and when a Reviewer commented on degree of infiltrates they were predominately graded as mild or sparse, with no grades greater than moderate. When cell types were identified, cellular infiltrate was noted to be lymphocytic or mononuclear (occasionally histiocytic) in these samples. These observations were similar for azficel-T as well as placebo and untreated samples.

Table 12: Assessment of Cellular Morphology and Inflammatory Infiltrate with Hematoxylin & Eosin Staining (Histology Evaluable Population)

	Slides Analyzed (N=29)					
	Azficel-T		Placebo		Untreated	
	Reviewer 1	Reviewer 2	Reviewer 1	Reviewer 2	Reviewer 1	Reviewer 2
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Presence of Inflammatory Cell Infiltration						
Yes ¹	17 (58.6)	12 (41.4)	1 (3.4)	3 (10.3)	4 (13.8)	0 (0)
No	12 (41.4)	17 (58.6)	28 (96.6)	26 (89.7)	25 (86.2)	29 (100)
Abnormal Fibroblast Morphology						
Yes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
No	29 (100)	29 (100)	29 (100)	29 (100)	29 (100)	29 (100)

Source: Statistical Table 14.2.1

¹ In the majority of samples scored as “Yes,” the inflammation was noted as “mild” or “sparse.”

Source: Clinical Study Report Fibrocell Technologies, Inc. Protocol Number IT-H-001 pg 41

Table 13: Distribution of Subjects with Samples Scored as Positive for Inflammatory Cell Infiltrate by Each Independent Reviewer with Hematoxylin & Eosin Staining (Histology Evaluable Population)

	Reviewer 1 (N=29)	Reviewer 2 (N=29)
	n (%)	n (%)
Subject Biopsy Samples		
Total Number of Subjects with Azficel-T Samples Scored as Positive	17 (59)	12 (41)
Only Azficel-T Sample	12 (41)	12 (41)
Both Azficel-T and Placebo Sample	1 (3)	0 (0)
Both Azficel-T and Untreated Sample	3 (10)	0 (0)
All Three Samples (Azficel-T, Placebo and Untreated)	1 (3)	0 (0)

Source: Listing 16.2.10.

Source: Clinical Study Report Fibrocell Technologies, Inc. Protocol Number IT-H-001 pg 42

With regard to Endpoint 3, no abnormalities or consistent differences were found in the structure and organization of either collagen or elastin fibers. Only a single slide from a placebo treated sample was scored as positive for abnormal collagen organization by either Reviewer. Reviewer 2 reported that collagen bundles in the mid-dermis appeared “thickened” when viewed at 100X magnification in a single placebo-treated, Masson’s trichrome-stained slide. Reviewer 1 did not

score any Masson's-stained samples as positive for abnormal collagen organization. Neither Reviewer 1 nor Reviewer 2 scored any samples positive for the same parameter when evaluating slides stained with the Verhoeff-Van Gieson stain. Reviewer 1 scored a total of nine Verhoeff-Van Gieson stained samples as positive for "abnormal elastin organization;" three azficel-T samples, four placebo samples and two untreated samples. Nearly all of these observations (eight of the nine total samples) were described by Reviewer 1 as increases in the number, thickness and/or density of elastic fibers in the dermis. The only apparent abnormal elastin organization finding was one of "fragmentation of elastic fibers, especially in the papillary dermis" for a single placebo-treated sample. Reviewer 2 did not score any sample as abnormal for elastin organization.

Table 16: Direct Histological Assessment of Extracellular Matrix Structures by Masson's Trichrome and Verhoeff-Van Gieson Staining (Histology Evaluable Population)

	Slides Analyzed (N=29)					
	Azficel-T		Placebo		Untreated	
	Reviewer 1	Reviewer 2	Reviewer 1	Reviewer 2	Reviewer 1	Reviewer 2
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Abnormal collagen organization or appearance (M)						
Yes	0 (0)	0 (0)	0 (0)	1 (3.4)	0 (0)	0 (0)
No	29 (100)	29 (100)	29 (100)	28 (96.6)	29 (100)	29 (100)
Abnormal collagen organization (V)						
Yes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
No	29 (100)	29 (100)	29 (100)	29 (100)	29 (100)	29 (100)
Abnormal elastin organization (V)						
Yes	3 (10.3)	0 (0)	4 (13.8)	0 (0)	2 (6.9)	0 (0)
No	26 (89.7)	29 (100)	25 (86.2)	29 (100)	27 (93.1)	29 (100)

Source: Statistical Table 14.2.1

(M): Masson's Trichrome-stained tissue section; (V): Verhoeff-Van Gieson-stained tissue section.

Source: Clinical Study Report Fibrocell Technologies, Inc. Protocol Number IT-H-001 pg 45

Each biopsy sample stained with H & E was also evaluated for "presence of fibrosis or other evidence of scar tissue" (Table 14). The Reviewers differed in this assessment. The presence of fibrosis was only noted by Reviewer 2. There were no positive scores for fibrosis for any sample evaluated by Reviewer 1. Reviewer 2 scored "yes" for this parameter in 27.6% of azficel-T-treated samples, 17.2% of placebo-treated samples, and 13.8% of untreated samples. The description of fibrosis provided by Reviewer 2 for all samples, across all treatment groups was similar and described as "mild dermal fibrosis" or "very mild fibrosis."

Table 14: Assessment of Fibrosis or Other Evidence of Scar Tissue with Hematoxylin & Eosin Staining (Histology Evaluable Population)

	Slides Analyzed (N=29)					
	Azficel-T		Placebo		Untreated	
	Reviewer 1	Reviewer 2	Reviewer 1	Reviewer 2	Reviewer 1	Reviewer 2
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Fibrosis						
Yes	0 (0)	8 (27.6)	0 (0)	5 (17.2)	0 (0)	4 (13.8)
No	29 (100)	21 (72.4)	29 (100)	24 (82.8)	29 (100)	25 (86.2)

Source: Statistical Table 14.2.1

Source: Clinical Study Report Fibrocell Technologies, Inc. Protocol Number IT-H-001 pg 43

Of the eight azficel-T samples scored by Reviewer 2 as positive for fibrosis, six were positive for fibrosis in azficel-T samples only. The additional two (of the eight) subjects who had positive azficel-T samples also had either placebo or untreated samples that were scored positive for fibrosis. One subject had both the azficel-T sample and the placebo sample scored as positive for fibrosis (Table 15).

Table 15: Distribution of Subjects with Samples Scored as Positive for Fibrosis (or Other Evidence of Scar Tissue) by Each Independent Reviewer with Hematoxylin & Eosin Staining (Histology Evaluable Population)

	Reviewer 1 (N=29)	Reviewer 2 (N=29)
	n (%)	n (%)
Subject Biopsy Samples		
Total Number of Subjects with Azficel-T Samples Scored as Positive	0 (0)	8 (28)
Only Azficel-T Sample	0 (0)	6 (21)
Both Azficel-T and Placebo Sample	0 (0)	1 (3)
Both Azficel-T and Untreated Sample	0 (0)	1 (3)
All Three Samples (Azficel-T, Placebo and Untreated)	0 (0)	0 (0)

Source: Listing 16.2.10

Source: Clinical Study Report Fibrocell Technologies, Inc. Protocol Number IT-H-001 pg 44

Summaries of the results of the dermal and epidermal thickness comparisons collected 3 months following azficel-T and saline treatment are shown in Table 18 for both dermatopathologists (Reviewer 1 and Reviewer 2). The Reviewers compared epidermal thickness, dermal thickness, and dermal cellularity for each sample against the others for each subject in a blinded fashion. Neither Reviewer noted a difference in epidermal thickness among the comparisons. While Reviewer 1 noted no difference in dermal thickness among the comparisons, Reviewer 2 noted a few cases where differences in dermal thickness were noted among all three comparisons (azficel T to placebo, azficel-T to untreated, and placebo to untreated).

Table 18: Dermal and Epidermal Thickness Comparisons with Hematoxylin and Eosin Staining (Histology Evaluable Population)

	Slides Compared (N=29)					
	Azficel-T to Placebo		Azficel-T to Untreated		Placebo to Untreated	
	Reviewer 1	Reviewer 2	Reviewer 1	Reviewer 2	Reviewer 1	Reviewer 2
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Epidermal Thickness						
Thicker	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Thinner	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
No Difference	29 (100)	29 (100)	29 (100)	29 (100)	29 (100)	29 (100)
Dermal Thickness						
Thicker	0 (0)	2 (6.9)	0 (0)	4 (14.8)¹	0 (0)	3 (11.1)¹
Thinner	0 (0)	0 (0)	0 (0)	1 (3.7)¹	0 (0)	1 (3.7)¹
No Difference	29 (100)	27 (93.1)	29 (100)	22 (81.5) ¹	29 (100)	23 (85.2) ¹
Dermal Cellularity						
Increased	0 (0)	5 (17.2)	0 (0)	5 (17.2)	0 (0)	2 (6.9)
Decreased	0 (0)	1 (3.4)	0 (0)	0 (0)	0 (0)	0 (0)
No Difference	29 (100)	23 (79.3)	29 (100)	24 (82.8)	29 (100)	27 (93.1)

¹ This parameter scored for only 27 of the 29 subject slides by Reviewer 2.

Source: Statistical Table 14.2.2

Source: Clinical Study Report Fibrocell Technologies, Inc. Protocol Number IT-H-001 pg 49

Overall, 13 of the 29 treated subjects (45%) experienced a total of 40 treatment- emergent adverse events (TEAEs) during the IT-H-001 study. The TEAEs experienced at the azficel-T treatment area were erythema (21 events in 11 subjects), pain (two events in two subjects), discoloration (one event in one subject), and induration (one event in one subject). The only injection site reaction reported more than twice during the IT-H-001 study was erythema. All events were mild and most resolved within 24 to 48 hours.

At the time of biopsy, there were no ongoing adverse events. There were no reports of abnormal skin appearance or reactions at the site of treatment just prior to biopsy. There was no correlation between local adverse events that occurred shortly after the time of injection such as inflammation, induration or erythema in some (11 of 29) subjects and the microscopic and histological observations of “inflammatory infiltrate.” Of the 19 subjects for whom inflammatory cell infiltrates were observed by Reviewer 1 and Reviewer 2 (in any sample), only 11 of those had an injection site reaction. Conversely, of the 11 subjects who had any injection site reaction at any site at any visit, only seven of those were scored as having a cell infiltrate.

All TEAEs that occurred at body sites other than the treatment area were experienced by one subject each. These events were road traffic accident, cellulitis, contact dermatitis, leukocytoclastic vasculitis, hypoesthesia, positional vertigo, and vaginal infection. The one SAE that was reported, leukocytoclastic vasculitis, was considered unlikely to be related to study treatment by the investigator and resulted in discontinuation of study treatment in that subject.

Subject -(b)(6)-, a 67-year-old white male, experienced a Serious Adverse Event of moderate severity, leukocytoclastic vasculitis. On 25 June 2010 the subject received 0.2 mL azficel-T to his right arm and 0.2 mL placebo (saline) to his left arm. On -(b)(6)-, 2010 -(b)(6)- post study treatment) the subject presented to the emergency room (ER) with complaints of weakness, rapid pulse, and a skin rash on his arms and lower legs, with the lower legs predominating. Subject was discharged on the same day but re-presented to the ER on (b)(6)- 2010 with the same complaints and was admitted on -(b)(6)- 2010 for treatment of suspected vasculitis. Medical evaluation disclosed 10 to 15 small necrotic, erythematous lesions on his legs. The impression was small-vessel vasculitis. He underwent skin biopsy. The subject also reported a tender left wrist and right elbow on 04 July 2010, and was diagnosed with cellulitis of the left arm treated with Percocet, vancomycin, ceftriaxone, methyl prednisolone. The cellulitis occurred at a non-treatment area and was considered moderate in severity and unrelated to study treatment. He was discharged on -(b)(4)- 2010, apparently stable on vibramycin and diflucan. The event resolved as of 06 August 2010.

No life threatening or severe TEAEs or deaths were reported and no TEAEs led to discontinuation of study participation.

Discussion

The main findings of likely significance that were agreed upon by both dermatopathology reviewers was the increased number of “positive” scores for “inflammatory cell infiltrate” in approximately 40-50% of azficel-T treated tissue samples.

Fibrosis was noted in 27% of samples but only by Reviewer 2. The fact that mild fibrosis was also noted by this reviewer in both the untreated (13.8%) and placebo (17.2%) samples make it less likely that this finding is significant. In a similar fashion only Reviewer #1 noted occasional abnormal elastin organization in 10% of azficel-T samples. Again, the fact that changes in elastin were also noted by this reviewer in both the untreated (6.9%) and placebo (13.8%) samples makes it less likely that this finding is significant.

Pertinent negative findings included the lack of abnormalities or consistent differences in the structure and organization of the collagen fibers and the lack of changes in cellular morphology.

- 1. The two blinded dermatopathologists reported “mild perivascular inflammatory cell infiltrate” in up to 58% of subjects and mild fibrosis in 27% (only by reviewer #2) of subjects who received fibroblast product at Month 3 biopsy. The similar findings were also observed in tissue slides of placebo and untreated skins, but to a lesser degree, especially for cell infiltration. Please provide your comment on the significance of these finding in terms of potential safety issues and any suggestions regarding whether additional information is needed (e.g. slide reviewing) and whether Month 6 biopsy data are important. (CDER and SGE)**

DDDP Response

Mild inflammation is not an unexpected finding in tissue that has undergone a procedure involving placement of organic material into the dermis. The mild degree of the inflammatory changes is reassuring. This degree of inflammation is unlikely to result in long term clinically significant changes. Obviously with such a small sample size it is not possible to rule out a more vigorous reaction in some recipients but overall the findings are reassuring.

The 6 month findings will be helpful in determining whether these “mild reactions” are short-lived. The 6 month findings will also help to clarify whether the inconsistent findings of fibrosis and elastin changes are of significance.

- 2. Discrepancy of reading was present between two blinded dermatopathologists in determining the existence of “fibrosis”. Please comment on whether the discrepancy between the two reviewers is critical and whether it requires third party adjudication. (CDER and SGE)**

DDDP Response

The discrepancy of readings noted between the two blinded dermatopathologists in determining the existence of “fibrosis” and elastin changes is not unexpected. The number of involved specimens was small and as previously stated; the presence of similar findings in the controls suggests this is not likely to be of clinical significance. A difference in “threshold” for readings between pathologists is well-documented in the literature¹. An additional reading by a third dermatopathologist is more likely to provide a third opinion rather than a tie-breaker and is not recommended.

¹ Shoo BA, Sagebiel RW, Kashani-Sabet M Discordance in the histopathologic diagnosis of melanoma at a melanoma referral center. *J Am Acad Dermatol*. 2010 May; 62(5):751-6.

- 3. One case of Leukocytoclastic Vasculitis was described in the Safety report of Serious Adverse Event for subject –(b)(6)- in IT-H-001 (tissue biopsy study) eight days after the product administration. This event was considered as unrelated to the product by the investigator. Please provide your thought on the relationship of this case with the product and your comment on the necessity of monitoring this type of reactions on post-marketing registry study. (CDER and SGE)**

DDDP Response

The case of leukocytoclastic vasculitis (lckv) seen in the histopathologic study may represent a chance finding. The patient was noted to have a cellulitis of the wrist at the time of presentation with this adverse event and since infection can be a trigger for lckv this is a confounding factor. This single case does not seem to justify screening of this adverse event at the registry level. Should a signal for lckv arise in postmarketing surveillance then further investigation may be warranted. For now, routine surveillance measures should be adequate.