

Teleconference with Dr. Lynn Drake, April 1, 2010 - Laviv

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Isolagen (Fibrocell) Teleconference with Dr. Lynn Drake
April 1, 2010 10am EST

FDA Participants:

- Yao Yao Zhou, Agnes Lim, Bruce Schneider, Wilson Bryan
- CDER (called-in): Jane Liedtka (dermatologist), Patricia Brown (dermatopathologist)

Re: Protocol IT-H-001 "A Vehicle Controlled Serial Skin Biopsy Study to Evaluate Tissue Histopathology Following Treatment with Azficel-T," submitted to the FDA in January 2010.

The Fibrocell BLA clinical reviewers forwarded the protocol along with following comments and questions for Protocol IT-H-001 to Dr. Drake and CDER reviewers. The purpose of today's teleconference was to mainly obtain Dr. Drake's response to the Agency's comments and questions, and any additional comments on the protocol.

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.***

Dr. Drake:

1. In order to better mimic the photo damage sustained by the nasolabial fold skin, evaluation of the outer upper arm instead of the inner upper arm would be preferred. However, this is not a major point.
2. In the Informed Consent, patients must be informed that a scar will result from each biopsy site.
3. The 4mm biopsy size proposed in the protocol is fine.

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.***

Dr. Drake:

1. This is a difficult question to answer. Usually, giving more drug results in greater side effects. While being mindful of the sponsor's financial limitations in designing their protocol, taking a shortcut would defeat the purpose of conducting the study. Giving one treatment dose is not the same as giving three treatment doses.

Dr. Liedtka:

1. The efficacy data (secondary endpoints) suggested clinical improvement after two treatments. Two doses might be acceptable if the sponsor could enroll enough patients, e.g. 5-6 patients, who have enough azficel-T available for two treatments.

Dr. Drake:

1. Dr. Drake agreed that 20 patients receiving two treatments would be fine.
- 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.**

Dr. Drake:

1. Regarding photo damaged skin versus sun protected skin, Dr. Drake commented that skin might heal better in a sun protected area. However, a control (the other arm) will be evaluated in this study.
2. The upper arm (inner under-surface area) is a friction area that might affect healing/scarring.

Dr. Liedtka commented that the sponsor might be concerned that it would be difficult to enroll patients if the biopsy was done in a sun damaged area (e.g. the face). One suggestion would be to conduct a new study offering free treatment as an incentive to do biopsy in a sun damaged area.

- 1. Please comment the use of -----(b)(4)----- staining in addition to standard -----(b)(4)----- 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.**

Dr. Drake:

1. The proposed tests are traditional tests for collagen and elastin. Assessments must be conducted by a board certified dermatopathologist, and Dr. Drake recommended using a dermatopathologist experienced in research.
2. Detail must be provided for what the dermatopathologist is looking at and how, and set up a grading scale. For example, the depth of the strata epidermis can be measured and graded on a 1-5 or a 10-point grading scale. A gross scale that can classify significant hypertrophy, granulation tissue, or anything abnormal would be fine. Evaluations should look at normal versus abnormal, and collagen or elastin should be graded, for example, 3+ or 4+ on a prespecified scale.
3. 20 patients would be sufficient to give a safety signal if something was going on.

Dr. Schneider commented that the control should make the comparisons better given the small number of patients in the study.

Dr. Brown suggested that planometric analysis might be useful.

4. Please comment on whether the primary endpoints meet the primary goal of the study. Please comment on whether any other endpoint(s) should be considered.

Dr. Drake:

What the dermatopathologist will measure is important in order to assess if anything “bad,” e.g. granulation tissue or edema, is going on.

Dr. Schneider: Descriptions of what is going on for both safety and efficacy do not necessarily need statistical analysis. Descriptions provided should be thorough and complete rather than just descriptions for collagen and elastin.

6. Please provide any additional comments or recommendations on the study design.

Dr. Drake:

1. The regional block anesthesia proposed in the protocol is unnecessary for a punch biopsy.
2. A punch biopsy needs to be performed by experienced clinicians. For example, improper technique in removing the tissue sample from the punch biopsy could mangle or destroy the tissue. The entire punch biopsy procedure must be defined and clearly spelled out in the protocol.
3. It is unclear whether there are one or more investigator(s) in the protocol. The sponsor needs to clarify.
4. Request the dermatopathologist’s CV for review.

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