

Teleconference, April 7, 2011 - Laviv

Time and Date: 10 to 11 AM, April 7, 2011

Consultant: Lynn Drake, MD (Special Government Employee), dermatologist/dermatopathologist

FDA attendees: Yao-Yao Zhu (clinical), Bruce Schneider (clinical, team leader), Agnes Lim (clinical), Craig Zinderman (OBE, post-market), Terrig Thomas (CMC), and Lori Tull (project manager)

Subject: BLA125348 Resubmission: Skin biopsy, serious adverse event (leukocytoclastic vasculitis), post-market plan, physician training manual, and labeling

Content of the Teleconference

Dr. Drake agreed on these Meeting Minutes as a way of documenting the discussion

Skin biopsy study (IT-H-001)

- Overall study findings: the overall results of the skin biopsy study are “not alarming” regarding the safety information and histological data.
- Histological findings: mild inflammatory infiltration was considered a reasonable tissue response to the injection; the minimal amount of fibrosis which is distributed in treated, placebo, and untreated samples is not worrisome.
- Safety profile: These findings in the histology study largely answered the questions that Dr. Drake had during the AC meeting regarding the safety of the product. However, some adverse events, such as nodule formation, may appear beyond seven months post-injection, as has been observed with some dermal filler products.
- Discrepancy between the two dermatopathologist: it is not unusual to have some different opinions as to the pathology finding among the dermatopathologists, depending on training, experience, judgment, etc. But the difference here is not significant.
- Impact of the skin biopsy study results on the labeling or post-marketing surveillance: objective description of these findings such as inflammatory infiltration, fibrosis, collagen/elastin structure, dermal thickness in the label may help prescribing physicians or patients to understand this product, but limitation in sample size and duration of the study (6 months) should be emphasized in the label.
- Mechanism of action: histology study provided no insight into any mechanism whereby the cellular product improved the appearance of nasolabial fold wrinkles in the two clinical trials.
- Qualification of histology slide reviewers: FDA asked Dr. Drake to review the overall qualifications of the two dermatopathologists who reviewed the histology data. Dr. Drake agreed.

Serious adverse event in skin biopsy study (leukocytoclastic vasculitis)

- Analysis of the case: the patient history is complex in regard to the possible etiology. Infection such as cellulitis of the wrist may relate to the onset of the small vessel vasculitis. However, the clinical data seem not sufficiently complete to make any further judgment regarding etiology. Information such as detailed history and laboratory work-up, if available, may be helpful. The main issue here is how we deal with this type of adverse event in labeling and marketing.
- Relationship to the product: If this is the only case out of 500 subjects who have been exposed to the product, Dr. Drake would consider the case as “probably not related” from the Investigator’s point of view. However, Dr. Drake acknowledged that the event was biologically plausible.
- Impact of SAE on labeling and post-marketing surveillance: Given the incomplete clinical information on the vasculitis, the main issue is to warn physicians and patients in the label regarding this case. Post-marketing monitoring for this type of SAE is necessary because of the serious nature of the case and the potential for this process to have more serious manifestations, such as internal organ involvement.

Post-Marketing Plan

- Basal cell cancer and leukocytoclastic vasculitis: one case of basal cell cancer is not a strong safety signal because basal cell cancer is very common in this population. Concern of basal cell cancer for the safety of this product was rated as 1 out 10 (10 being most worrisome). However, the occurrence of the cancer within, or close to, the injection tract increased concern. If a post-marketing study is conducted, there may be many confounding factors. Dr. Drake commented that FDA should not give the company unnecessary burdens by requiring a big study; she also suggested considering what type of studies have been required for dermal fillers in the past and if such a study would be an unequal burden compared to those requirements. If such a post-marketing study is required, she suggested FDA should include all types of skin cancers or any other types of cancers (e.g. metastatic cancer) in the vicinity of the product administration, instead of only non-melanoma skin cancers. Limitation of the scope of the study to cancers specifically occurring around the injection site would be a reasonable way to reduce the burden while still providing useful surveillance.
- Leukocytoclastic vasculitis: FDA should monitor for this type of adverse reaction post-marketing.
- Sponsor’s post-marketing protocol: Dr. Drake agreed to provide further consultation on the sponsor’s future post-marketing protocol.

Physician Training

- Who should administer the product: only physicians (as opposed to other health-care personnel) who have successfully completed Fibrocell’s product administration training program should administer the product. The physician training manual should be revised to consistently state that physicians “must” rather than “should” be trained.
- Injection procedures: “bend the needle upwards” (page 20 of Physician Training Manual) should be removed from the text because such practice is not safe and may cause needle breaks.
- Physician responsibility: training manual should not “micromanage” the practice of medicine by giving instructions that are too specific. For example, the instruction for handling adverse events such as allergic reactions is too specific and may give the erroneous impression that nothing else needs to be done. Physicians should have the leeway to do what is medically indicated and appropriate for the condition.