

# Fibrocell Histopathology Study Discussion Email, January 28, 2010 - Laviv

From: Dana Weinberger [dweinberger@cbrintl.com]  
Sent: Thursday, January 28, 2010 2:07 PM  
To: Schneider, Bruce  
Cc: Jeanne Novak; Dana Weinberger; Tull, Lori; Thomas, John  
Subject: Fibrocell histopathology study discussion

Attachments: IT-H-001 synopsis draft (28 Jan 2010).docx; emfalert.txt

Dear Dr. Schneider,

We'd like to thank you for agreeing to have a follow-up discussion today regarding Fibrocell's proposed histology study design, and for the guidance that you and the clinical team provided during the teleconference on Jan 12th. Attached, please find a revised synopsis for your consideration.

We have six points that we would like to discuss by phone today.

1. We plan to provide two injections of azficel-T to study subjects whenever possible, and anticipate that 5-10 of the 20 evaluable subjects will receive two injections of azficel-T, and the remainder will receive one injection. As previously discussed, the quantity of cryopreserved drug substance available for each patient will determine whether one or two injections will be administered. We would like to get your input on this plan to ?plan for two injections, but settle for one.?
2. As discussed during our call, standard --b(4)----- will be performed on sections of the biopsied dermal tissue to evaluate general histology. ---b(4)-  
-----) are proposed to be used to evaluate extra-cellular matrix structures (i.e., collagen and elastin). To accommodate the additional proposed staining, -b(4)- punch biopsies will be collected instead of 2 mm biopsies. We would like to discuss any additional comments or concerns about the additional proposed staining or size of biopsies.
3. As discussed during our previous call, Fibrocell intends to use existing inventory of azficel-T Drug Substance to prepare the injections that will be administered during this study. The Drug Substance has been stored in the vapor phase of liquid nitrogen since the time of its original manufacture. Our release testing includes viability and collagen content, and we are not concerned about the impact of storage time on product quality. We will provide a rationale in our cover letter to the protocol submission and also work with Dr. Thomas to determine if any additional data are needed to support this approach.
4. Please note that we have incorporated the Agency's recommendations to include saline as the control article instead of the originally proposed DMEM. We will also be taking an ?untreated? tissue biopsy from the same anatomical region as the azficel-T and placebo treatment sites at Month 3. The ?untreated? sample will be read blinded with the other two samples at Month 3.

Do you have any additional recommendations?

5. The proposed study (observational) endpoint is the histological analysis conducted on blinded, matched samples evaluated by a dermatopathologist. We are referring to this as the "Histology Endpoint," and it includes three qualitative comparisons. Do you think these will adequately collect the information desired?

6. In an effort to incorporate Agency recommendations that this study should evaluate patients six months after the initial injection, and also maintain as efficient a timeline as possible, Fibrocell plans to perform biopsies at both three and six months after the final injection. Fibrocell proposes to submit an interim CSR containing all data from the three month biopsy results as part of the Fibrocell "complete response" to the FDA's BLA review letter of December 18, 2009. This interim report would be submitted not later than August 2010, and it is Fibrocell's hope that the Agency will find this interim report sufficient to start the review clock for the complete response. A final report, including the six month biopsy results, would be submitted not later than November 2010, during the FDA review period. We would like to discuss the potential acceptability of the interim report as part of a "complete response." Can you advise us how we can get Agency concurrence?

We will call you at 2:30 pm EST today at 301-827-8343. Please let us know if a different time or number will be more convenient.

Kind regards,  
Dana

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