

Draft registry outline for PMR Email, June 15 2011

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From: Tull, Lori
Sent: Wednesday, June 15, 2011 3:13 PM
To: 'Jeanne Novak'
Cc: 'Dana Weinberger'; 'Kevin Hennegan'
Subject: Draft registry outline for PMR

Hi Jeanne,

Below is a list of requests and comments for consideration in preparing your final registry protocol. After you have a chance to review these items, if you wish to have a teleconference for further discussion, we can arrange it. The final protocol is not due until September, so these items don't need to be resolved this week.

Also, Dr. Zinderman asked me to let you know that your proposed timeline for submission is acceptable.

Information Requests and Recommendations:

1. Will the first follow-up contact be 60 days after the last injection or first injection? Please consider conducting the initial follow-up contact sooner than 60 days after treatment (e.g., 10 days or 30 days), to allow for better ascertainment of acute hypersensitivity events.
2. Please clarify if the enrolled population participating in IND studies will be receiving the product according to the labeled indication (i.e., improvement of the appearance of moderate to severe nasolabial (NL) fold wrinkles). Because the population receiving the product in the post-market setting may differ from a population enrolled in a clinical trial, please limit the proportion of the registry patients who are also participating in IND studies to no more than 20% of the total registry study population.
3. Please specify the baseline information that will be collected on each subject at enrollment. Age, gender, race, Fitzpatrick skin type, history of skin cancer, and any history of AzF use should be collected for all enrolled patients. Other important information could include any co-morbidities, smoking status, use of concomitant medications, and use of non-AzF facial treatments (e.g., dermal fillers) in the preceding 12 months and the location in which they were used (e.g. NL folds, glabellar wrinkles). Do you plan to develop an enrollment form that specifies the information to be collected?
4. Information collected and analyzed for events of skin cancer in the area of an AzF injection should include any skin cancers in facial areas and specific description of the location of the growth and distance from the injected area (e.g., in centimeters or millimeters). The term skin cancer should be considered to include carcinomas (basal cell cancer, squamous cell cancer, and carcinomas of adnexal origin), melanomas, tumors of intermediate malignancy (e.g., dermatofibrosarcoma tuberans), and sarcomas. Immune hypersensitivity reactions should include (but not be limited to) anaphylaxis, vasculitis, systemic skin eruptions, and angioedema.

5. Please clarify if Fibrocell will analyze and summarize all AEs identified through the registry or only certain ones.
6. Will there be assessment for adverse events during the second and third injections as part of the study?
7. Consider adding a secondary contact method if unable to reach the patient via phone (e.g., certified letter or possibly contact from the physician's office).
8. If a patient experiences a serious adverse event (AE) and is hospitalized, how will Fibrocell learn of the event? Will patients be instructed at enrollment to contact the treating physician if hospitalized, so that the physician can notify Fibrocell of the AE?
9. Please consider collecting information at each treatment visit and follow-up contact on the use of non-AzF facial treatments and the location in which they were used.
10. Please describe Fibrocell's methods for investigation of AEs reported as part of the study. For instance, for skin cancer events, will Fibrocell follow-up with physicians to ascertain additional information about the event (e.g., onset of the event in relation to the AzF injection, concomitant treatment, type and exact location of the lesion, facial photographs, biopsy/pathology report, physician progress note, summary of diagnosis and clinical outcome)? Please revise the protocol to specify reporting requirements for submission of adverse events to FDA (e.g., serious adverse events as per 21CFR600.80).
11. Please revise the protocol to include submission of interim reports semi-annually instead of annually. The interim reports should include the total number of patients treated thus far; the number of patients enrolled in the registry categorized by age, gender, and skin type; the proportion of subjects for whom the sponsor successfully obtained follow-up information; and the proportion of subjects with reports of skin cancer and systemic hypersensitivity reaction events categorized by age, skin type, and length of time since injection.

Comments on telephone script:

1. The telephone script indicates that the first call will be at 3 months, while the protocol indicates 60 days; please clarify.
2. Question 2c should specify side of the face (left, right, both sides).
3. Question 4 should also ask about diagnoses of anaphylaxis and angioedema. Question 4b should specify approximate distance from Azficel injection site.
4. Question 6: list of possible skin cancers should include sarcomas or other spindle cell tumors.
5. Question 7: please consider revising to specify conditions that are possibly related to AzF (e.g., "...medical conditions that began after your Azficel-T treatment" or "adverse events or side effects from your AzFicel-T treatment").
6. Please consider collecting information on the seriousness of each adverse event (e.g., life-threatening, hospitalization? ER visit required? etc.).

7. Please ensure that Fibrocell records the number of injections received and the dates for each injection, if not on the script form, then elsewhere in your records for each enrolled patient.

Best Regards,

Lori

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