



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Date: May 11, 2011

To: H.S. Nielsen, Jr., Ph.D.
President
Allermed Laboratories, Inc
7203 Convoy Court
San Diego, CA 92111

Our review of your Biologics License Application (BLA) for Spherusol Skin Test Antigen, STN 125354/0, is ongoing. You have not sufficiently analyzed the data submitted with your application, including the subsequent amendments. Please note that the data obtained from each study need to be analyzed and presented in a form that describes in either text or tabular form the results for each study. Tabular listings of study outcomes for individual subjects are not adequate to finalize the review of the product. In this regard, we have the following comments:

Study S101-A:

1. Please provide a summary and analysis of adverse events and safety outcomes for the subjects enrolled in the clinical study S101A. You indicate that all adverse reactions were unsolicited in this study. We request that the events be assessed using the toxicity grading scale submitted to the protocol (See question 3 below for an example of presentation of the data). Please provide narrative summaries of all adverse events which were followed after the 48 hour. Please provide a copy of the subject diary card that was used by subjects to record adverse events and the case report forms that were used to capture adverse event data.

Studies S104-1, S104-2 and S104-3:

2. Please provide the following information for Study S104-1:
 - a. Number of subjects with evaluable responses (defined as no induration responses ≥ 5 mm to saline placebo and/or thimerosal control) who never received any antifungal therapy for the treatment of coccidioimycosis and the mean induration response at 48 hours for this group. Please include the range of induration responses for Spherusol within the table for each cohort.

- b. Number of subjects with evaluable responses (defined as no induration responses $\geq 5\text{mm}$ to saline placebo and/or thimerosal control) that previously received any antifungal treatment at any time for treatment of coccidioimycosis and the mean induration response at 48 hours for this group. Please include the range of induration responses for Spherusol within the table for each cohort.
- c. Number of subjects with evaluable responses (defined as no induration responses $\geq 5\text{mm}$ to saline placebo and/or thimerosal control) that were receiving antifungal medications for the treatment of coccidioimycosis at the time of the study and the mean induration response at 48 hours for this group. Please include the range of induration responses for Spherusol within the table for each cohort.

Please present the above results for the combined study, not for the individual study sites (Tucson and Bakersfield).

3. We note that the number of subjects reporting adverse events associated with the administration of Spherusol, Candin and Trichophyton and the two controls is not consistent between the responses contained in your September 15, 2010 submission (response to FDA letter dated August 26, 2010) and information in the original BLA submission of May 14, 2009. For example, in section 11.2 of the final study report for S104-1 (dated 17 November 2008) the number of subjects reporting any intensity of itching is 45. However, in Table 1, page 3/13 of your September 15, 2010 submission, the number of subjects reporting itching is given as 44. We also note discrepancies between the number of subjects reporting swelling, pain and ulceration. For systemic adverse events, we note a discrepancy between the two reports in the number of subjects reporting dizziness. Please complete the following table with the safety data collected in Study S104-1. All subjects should be included in the safety analysis.

Table X. Study S104-1: Subjects with solicited local and systemic adverse events within 7 days of following administration of Spherusol, Candin, Trichophyton, Thimerosal control, Saline placebo (N=53)

| Symptom | Intensity of adverse event n (%) | | | |
|----------------------|-------------------------------------|------|----------|--------|
| | Any | Mild | Moderate | Severe |
| Itching* | | | | |
| Swelling* | | | | |
| Pain* | | | | |
| Necrosis/ulceration* | | | | |
| Increased heart rate | | | | |
| Weakness | | | | |
| Faintness | | | | |
| Dizziness | | | | |
| Nausea /Cramps | | | | |
| Flu-like symptoms | | | | |

| | | | | |
|--|--|--|--|--|
| Difficulty breathing/shortness of breath | | | | |
|--|--|--|--|--|

Mild=

Moderate =

Severe=

Any = subjects experiencing adverse event of any intensity

Thimerosal control contains.....

N= number of subjects experiencing intensity of adverse event

%= percentage of all subjects experiencing adverse event

*Number and percentages include local reactions occurring at any injection site

Please provide a similar table(s) for studies S104-2 and S104-3.

4. For all studies, please provide a narrative for all “severe” reactions, defined as needing medical attention, to include identification of test agent producing the severe reaction, any medical intervention which occurred, sequelae due to the reaction and identification and duration of the adverse event.
5. For all studies, please provide a summary of any unsolicited reactions by study cohort that occurred following the placement of the skin test antigens and the timing of the occurrence of these reactions.
6. In the response to the CR letter of 26 August 2010 you provided three tables (page 3/13) describing the frequency of adverse events in studies S104-1, S104-2 and S104-3. Please indicate the time period over which these events were collected.
7. For each study please provide a narrative to describe the general frequencies, intensities and timing of adverse events which occurred. For example, in Study S104-1: “Of the 53 subjects evaluated following administration of the five reagents, 48 (91%) reported solicited adverse events during the 7 days following injection. Of the local reactions reported X percent resolved within Y days following administration. Severe reactions occurred in 2 subjects (describe to include treatment and medical follow-up and timing of resolution, see comment above).
8. For each study we note that you have provided line listings of demographic data for subjects enrolled in the clinical study. Please provide an analysis of the data. For examples in Study S101A a summary presentation of the data might read: “The demographics of the study cohort subjects were 28% women; 70% Caucasian, 11% Hispanic, 11% African-American, 0.02% Asian, 0.02% Native American and 0.04% who did not specify ethnicity.” This may be accompanied by a summary table if you wish. Please provide a mean age and age range of enrolled subjects.

Study S104-2:

9. You report the occurrence of ulceration at the “skin test site” for three subjects in Study S104-2. Please indicate which skin test reagent or control was administered at the site of the ulceration. Please provide the following information on these subjects:
 - a. The timing of the occurrence of the ulceration following administration of the skin test reagent or control;
 - b. The duration of the ulceration;
 - c. The length of treatment for the two subjects treated with topical steroid cream; and
 - d. The time to resolution of the ulceration and whether there were sequelae (e.g., scarring) following resolution of the acute event.
10. In study S104-2 you state that none of the adverse events were due to Spherusol (section 11.2.3, Study S104-2). However, it does not appear that individual adverse event data was collected for each reagent placement. Therefore, all adverse events shall be described as due to the combination of test agents. If safety data was collected for individual local reactions following the placement of each test product, please submit them to the BLA. Documentation supporting the claim that no adverse events occurred during the study due to Spherusol is needed to support the claim in the license application. Without documentation of the individual local adverse events for each test reagent, it is difficult to draw the conclusion that no local events were due to Spherusol. The causative agent for systemic adverse events can not be determined such that all systemic adverse events should be assigned to the skin test reagents and controls collectively. Please acknowledge.
11. Since five of the subjects enrolled in Study S104-2 were skin test negative to both Candin and Trichophyton, as well as the saline placebo and Spherusol (section 11.4.2), these subjects may be excluded from the analysis of reactions to Spherusol in the non-endemic area despite the normal lymphocytic profiles. One of the subjects who did not react to positive controls had a positive reaction to thimerosal (Subject -(b)(6)-). Thus, 60 subjects were enrolled to the study, 55 subjects had skin test reactions to the positive controls and are evaluable. Of the 55 evaluable subjects, one subject (-(b)(6)-) had a positive reaction to Spherusol. Therefore 54/55 (98%) of subjects in the non-endemic area did not react to Spherusol. Please revise your text, package insert and tables to reflect this analysis of the data including re-calculation of the confidence intervals.
12. We note the letter from Dr. Kernerman attached to the May 28, 2010 submission to your license application. The information contained in the letter regarding subject reactions following administration of Spherusol should be included as part of the narrative of safety findings for Study S104-2. Please revise the study report to include this

information. Please include which skin test reagent elicited the local reactions that were classified as dermatitis by the attending physician, but as ulceration by the subjects.

13. One subject [-(b)(6)-] with reported ulceration at one of the skin test sites was seen by a physician and instructed to apply Elocon (Mometasone Topical) to the area. This appears to meet the definition of a severe adverse event (needs medical attention). Please revise the study report to capture this case of ulceration as a severe adverse event.
14. Please provide an overall summary of safety data for the studies administering Spherusol to provide the following information:
 - a. Number of subjects who received the skin test in all trials;
 - b. Commonly occurring local and systemic adverse events over 7 days following administration;
 - c. An analysis of the timing for the occurrence of AEs for each study and the studies overall (e.g., “For the twelve subjects with a previous history of pulmonary histoplasmosis, the majority of local adverse events occurred within 48- 72 hours following administration of the Spherusol skin test antigen.”); and
 - d. Narrative information on the on all severe adverse reactions, local or systemic, which occurred during the conduct of each study.

We request that you submit the above information as soon as possible, but before May 31, 2011. Please note that our review of your responses may generate additional clinical and labeling comments.

If you have any questions regarding the above comments, please contact either Ms. Holly Wieland or Dr. Jon Daugherty at 301-796-2640.