



Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

STATISTICAL REVIEW AND EVALUATION BLA

BLA/Supplement Number: 125354/005

Product Name: *Coccidioides immitis* Spherule-Derived Skin Test Antigen

Indication(s): For detection of delayed type hypersensitivity to
Coccidioides immitis

Applicant: Allermed Laboratories, Inc.

Date(s): Letter Date: May 26, 2009
Action Due Date: March 27, 2010

Review Priority: Standard

Statistical Branch: FDA/CBER/OBE/DB/VEB

Primary Statistical Reviewer: Jingyee Kou, Ph.D. _____
Mathematical Statistician Date

Concurring Reviewer (1): Tammy Massie, Ph.D. _____
Lead, Bacterial & Allergenic Team Date

Concurring Reviewer (2): A. Dale Horne, Dr. PH _____
Chief, Vaccine Evaluation Branch Date

Medical Office/Division: OVRR/DVRPA

Clinical Reviewer(s): Ann Schwartz, MD

Project Manager: Holly Wieland, RN, MPH
Jon Daugherty, Ph.D.

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The reviewer recommends a letter including the following statistical comments be sent to the applicant.

The review considers the responses to CBER question #40, #41, and #42 are not adequate.

In your responses to these questions, you requested that the protocol entitled “Statistical Protocol for Skin-test ---(b)(4)--- Dose/Response Study” dated 9/28/2001 be withdrawn from the BLA consideration. Furthermore, you requested that a new study report completed by -----(b)(4)-----, entitled “Statistical Evaluation of dose-Response Study of Spherusol-Derived Coccidioidin Skin Test Antigen (Study Protocol S101A, Amended on June 19, 2002)” be used for the BLA consideration.

In your BLA submission, neither document was provided. The original statistical protocol was provided in the original IND submission. If there is a need to change the analysis plan, concurrence by CBER is required well before the study completion. Furthermore, revisions to the protocol after study inception typically should be minor or administrative in nature. Revisions in data collection or analysis may impact sample size requirements and type I error rates. Please provide a detailed timeline as to when ---(b)(4)--- started his employment and when the analysis protocol was revised. If --(b)(4)-- was employed after the study was completed, his analysis would be considered to be post-hoc. Usually this type of analysis for pivotal trials would not be permitted to support licensure. Please submit a revised report for this study to include:

- a) Time line of the statistical protocol development and -----(b)(4)----- employment
- b) Rationale for changing the method used in analyzing the data
- c) ----(b)(4)----- analysis in detail
- d) References for supporting the new method

CBER will review the revised report in order to determine whether the result from the new analysis is acceptable to replace the old report.

The reviewer considers the response to CBER question #43 is not adequate.

You stated that the data are not available. However, the value -(b)(4)- was used as the standard for establishing the final dose. Please provide any information, such as reports, articles, or other reference material (in its entirety) that can substantiate this claim.

The reviewer considers the responses to CBER questions #44, #45, #46, and #47, are adequate.

1.2 Brief Overview of Clinical Studies

Not applicable.

1.3 Major Statistical Issues and Findings

Please see section 2.1.

2. INTRODUCTION

2.1 Overview

This submission contains the responses from the applicant to CBER's Complete Response (CR) letter dated March 26, 2010.

The statistical reviewer has reviewed the responses from the applicant to the statistical questions raised by the reviewer in the CR letter. The reviewer has the following comments:

CBER Question:

40. In this study, you have collected induration response data from 20 subjects, each of whom received 5 different dose concentrations. After eliminating the placebo dose, the highest dose due to incomplete data, and one subject for no data, you plotted the mean induration response of 19 subjects for each of the 3 doses against the dose concentration. In section VII, Data Analysis, you state: "The dose-response curve was analyzed by linear regression and it was determined that a dose of 1.27 µg corresponded to a mean response of 22 mm." We have the following comments:

a. Please provide a rationale for using the mean induration response as the dependent variable. Note that by taking the mean, you have arbitrarily reduced the variation within each dose.

b. Please provide a rationale or justification illustrating how you determined that the relationship between induration response and dose is linear.

41. In section VII, Data Analysis, you state: "Based on our experience with other skin test antigens, we believe that a 20% variance in the induration response associated with cellular hypersensitivity is indicative of equipotency."

In the same section, you obtained an acceptable range of 17.6 to 26.4 mm by subtracting and adding 4.4 mm (20% of 22 mm) to 22 mm which was considered the corresponding mean response for the dose concentration 1.27µg from the linear regression. Then using the same

data and the SAS MIXED procedure, you fit a mixed linear model. In the same section, you state: “From the ... model, the estimated mean induration for a 1.27 concentration is 22.24mm and the associated 95% confidence interval computed through the MIXED procedure is between 19.383 and 25.091 mm.

The 95% confidence limits fall well within the acceptable range of 17.6 and 26.4.” We have the following comments:

a. Please provide documentation to support your statement that 20% variance in induration response associated with cellular hypersensitivity is indicative of equipotency for this product.

b. You use the same data to determine an acceptable range and to fit the mixed linear model. Please provide data from independent sources to support your claim that the mean induration response corresponding to a dose concentration of 1.27 µg is about 22 mm. Please also provide independent sources to support your proposed acceptable range. For example, these independent sources may be either historical data or information in the published literature.

42. This study was conducted under IND -(b)(4)-. When you submitted the original submission to the IND (received by CBER on December 12, 2001), you included a document titled “Statistical Protocol for Skin-Test --(b)(4)--- Dose/Response Study” as part of the study protocol. In this document, a detailed analysis plan was provided. We have determined that you did not follow the steps outlined in that document and you did not submit the document to the current BLA. We request that you re-analyze your data following the steps outlined in the statistical protocol and submit the results as well as the statistical protocol to the BLA. Furthermore, we consider the following four subjects should not be included in the analysis:

- Subject ID (b)(6): Due to results that could not be determined.*
- Subjects ID --(b)(6)---: These two subjects responded to the placebo, thimerosal, which makes other results uninterpretable since the reactions might be due to the thimerosal in the placebo.*
- Subject (b)(6): Due to the subject having a non-linear response with increasing dose, which does not satisfy the criterion for inclusion in the analysis.*

Reviewer’s comment:

The reviewer considers the responses to CBER question #40, #41, and #42 are not adequate.

In your responses to these questions, you requested that the protocol entitled “Statistical Protocol for Skin-test ---(b)(4)--- Dose/Response Study” dated 9/28/2001 be withdrawn from the BLA consideration. Furthermore, you requested that a new study report completed by -----(b)(4)-----, entitled “Statistical Evaluation of dose-Response Study of Spherosol-

Derived Coccidioidin Skin Test Antigen (Study Protocol S101A, Amended on June 19, 2002)” be used for the BLA consideration.

In your BLA submission, neither document was provided. The original statistical protocol was provided in the original IND submission. If there is a need to change the analysis plan, concurrence by CBER is required well before the study completion. Furthermore, revisions to the protocol after study inception typically should be minor or administrative in nature. Revisions in data collection or analysis may impact sample size requirements and type I error rates. Please provide a detailed timeline as to when ----(b)(4)--- started his employment and when the analysis protocol was revised. If ---(b)(4)--- was employed after the study was completed, his analysis would be considered to be post-hoc. Usually this type of analysis for pivotal trials would not be permitted to support licensure. Please submit a revised report for this study to include:

- e) Time line of the statistical protocol development and -----(b)(4)----- employment
- f) Rationale for changing the method used in analyzing the data
- g) ----(b)(4)----- analysis in detail
- h) References for supporting the new method

CBER will review the revised report in order to determine whether the result from the new analysis is acceptable to replace the old report.

CBER Question:

43. In the afore-mentioned statistical protocol, you state: “The mean induration response from the -----(b)(4)----- data was -(b)(4)-.” Please submit the --(b)(4)-- ----- data to the BLA to enable our independent verification of this result.

Reviewer’s comment:

The reviewer considers the response to CBER question #43 is not adequate.

You stated that the data are not available. However, the value -(b)(4)- was used as the standard for establishing the final dose. Please provide any information, such as reports, articles, or other reference material (in its entirety) that can substantiate this claim.

Reviewer’s comment:

The reviewer considers the responses to CBER questions #44, #45, #46, and #47, are adequate.

2.2 Data Sources

“Response to FDA BLA Review Letter Dated March 26 2010.pdf”

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Not applicable.

3.2 Evaluation of Safety

Not applicable.

3.3 Gender, Race, Age and Other Special/Subgroup Populations

Not applicable.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

Please see section 2.1.

4.2 Conclusions and Recommendations

Please see section 2.1.

APPENDICES (IF NEEDED)

None

DISTRIBUTION LIST

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