



Official Meeting Summary

Meeting ID #: CRMTS #7260
Application type and number: BLA 125335/0
Product name: Centruroides (Scorpion) Immune F(ab')₂ Intravenous (Equine)
Firm: Instituto Bioclon, S.A. de C.V.
Meeting type: Type C
Meeting category: BLA, Other
Meeting date & time: November 18, 2009, 11:00 a.m. – 11:45 a.m.
Meeting format: Teleconference
Meeting Chair/Leader: Basil Golding, M.D.
Meeting Recorder: Debbie Cordaro
 Aaron Josephson

FDA Attendees:

Basil Golding, M.D., Director, Division of Hematology, OBRR
 Hon-Sum Ko, M.D., Medical Officer, Division of Hematology, OBRR
 Robert Fisher, Ph.D., Staff Fellow, Division of Hematology, OBRR
 Jessica Kim, Ph.D., Mathematical Statistician, Division of Biostatistics, OBE
 Xue (Mary) Lin, Ph.D., Visiting Scientist, Division of Biostatistics, OBE
 Dorothy Scott, M.D., Chief, Laboratory of Plasma Derivatives, Division of Hematology, OBRR
 Nisha Jain, M.D., Acting Chief, Clinical Review Branch, Division of Hematology, OBRR
 Michael Kennedy, Ph.D., Team Lead, Division of Hematology, OBRR
 Debbie Cordaro, Regulatory Project Manager, Division of Blood Applications, OBRR
 Aaron Josephson, Consumer Safety Technician, Division of Blood Applications, OBRR
 Michael Yoler, Contractor, Division of Blood Applications, OBRR

Instituto Bioclon, S.A. de C.V. (Bioclon) Attendees:

Juan Lopez de Silanes, Président, Instituto Bioclon, S.A. de C.V.
 Walter Garcia Ubbelohde, M.D., Medical Director, Instituto Bioclon, S.A. de C.V.
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 Leslie Boyer, M.D., Medical Director, Arizona Poison and Drug Information Center
 Jude McNally, R.PH. ABAT, Medical Science Liaison, Rare Diseases Therapeutics, Inc.
 Milton Ellis, President, Rare Disease Therapeutics, Inc.
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Background and Objectives:

Instituto Bioclon, S.A. de C.V. (Bioclon) submitted their original biologics license application (BLA) for the use of Centruroides (Scorpion) Immune F(ab')₂ Intravenous (Equine) in the treatment of clinically important signs of scorpion envenomation on January 21, 2009. On July 23, 2009, FDA issued a complete response (CR) letter. Bioclon submitted a meeting request and

meeting materials on September 15, 2009 (attachment 1). The purpose of the meeting is to discuss four of the clinical items in the letter.

FDA provided their proposed responses to the firm on November 17, 2009 (attachment 2). After reviewing the proposed responses, Bioclon notified FDA on November 17, 2009, of their decision to limit the agenda for this meeting to questions 1a and 4 (attachment 3).

Discussion:

FDA asked Bioclon if they intended to request another meeting to discuss additional clinical issues. The applicant stated they did not anticipate needing another meeting to discuss clinical issues. For this meeting, Bioclon had one comment regarding question 1a and requested for clarification about the response to question 4. All other responses required no discussion.

Clinical

Applicant Question 1:

[Regarding CR Letter item 66]

The primary efficacy endpoint was to demonstrate resolution of clinically important systemic signs of scorpion envenomation within four hours for patients treated with Anascorp. The "Severity Evaluation" document in the study protocol's Appendix 1 does not grade and only lists "clinically important systemic signs of scorpion envenomation" under components of (1) respiratory compromise and (2) pathological agitation.

- a. *As indicated in this protocol, judgment of the resolution of the clinical signs was left to the Investigator's discretion. Clinical signs are non-specific for envenomation and not entirely objective and there is considerable confounding by concomitant medication(s), especially in the case of "pathologic agitation." In 3 of the 7 placebo-treated subjects, the Investigator provided an assignment for resolution at 4 hours different from what the systemic signs would have dictated. Please address the validity in the evaluation of primary endpoint in this study.*

Discussion Points:

The choice of an ungraded, binary endpoint for this study was deliberate, to enable a clear distinction between starkly different outcomes in the two groups in a low "n" study. Interaction between midazolam dosing and assessment of the primary endpoint was anticipated from the outset of the study, but ethical study design precluded withholding of sedative medication. For this reason, the investigator was required to take oversedation into account before rendering judgment so to whether pathological agitation was present. The time delay of 4 hours between administration of study drug and assessment of the primary endpoint ensured the robustness. We would like to discuss this point further with the Agency.

FDA Response to Applicant Question 1a:

We agree with several of the points in the “Discussion Points”. However, the CR Letter Item requests that you address the validity of the primary endpoint evaluation, because the Investigator’s subjective decision could override the findings from the components for “pathological agitation” and “respiratory compromise.” Please provide information on how the primary endpoint was previously validated.

Additional discussion:

Bioclon commented that they did not previously validate the primary endpoint; however, they now have data to support the validity of the primary endpoint that will be submitted in their response to the CR letter. Bioclon considers respiratory compromise and pathological agitation one aggregate endpoint.

FDA stated that because the data submitted in the application were primarily based on the evaluation of pathological agitation and there were very few patients with documented respiratory compromise, Bioclon should revise the package insert to reflect the indication actually studied in the pivotal clinical trial. Bioclon agreed to revise the package insert to document both what they studied and the appropriate indication for use.

Applicant Question 4:

[Regarding CR Letter item 77]

In the BLA submission, you did not provide an up-to-date study report of AL-03/07. Although you included an interim report covering the period May 23, 2005, through September 23, 2006, a span of 16 months, together with a Statistical Report covering the period up to June 2008, an additional 21 months, there should be one up-to-date interim study report covering the entire period up to at least June 2008, so that the information and dataset in the Statistical Report can be reconciled with the submitted study report data. In addition, the dataset was submitted piecemeal in relation to periods between May 2005 and June 2008. Please submit an up-to-date study report that contains all the appropriate documentation together with a complete dataset for evaluation. A "Statistical Report" alone will not fulfill regulatory requirements.

Discussion Points:

We do not feel there is a need for a new study report. All data have been presented to the Agency in the BLA submission. We would like to discuss the necessity of a new study report.

FDA Response to Applicant Question 4:

We are not asking for a new study report. Instead we are asking for an up-to-date report. You are required to submit all relevant previous human experience using your product to the BLA.

Additional discussion:

Bioclon previously interpreted FDA's answer as asking for a completely new study report for AL-03/07. They had concerns that FDA's request would require a great deal of effort to redo the report, especially because this is an open-label study not necessarily intended to study efficacy. Bioclon commented that they submitted the data in the BLA. FDA contended that Bioclon needs to integrate the data submitted piecemeal in the BLA.

Bioclon clarified they used a June 2008 cutoff for the data and explained the data from August 2005 through June 2008 is comprised of three components. They broke this information out because the starting dose was one vial and almost all subjects in that group received three vials. Bioclon amended the protocol and from October 2006 through June 2007, the initial dose was three vials. The change in June 2007 was because a new validated ---(b)(4)--- was installed, and the subjects between July 2007 and June 2008 received product made with the new equipment. Three hundred thirteen subjects received product made from the new ---(b)(4)--- .

Bioclon asked what FDA meant by an up-to-date report. Bioclon confirmed that the study is ongoing and added that they submitted a treatment protocol to their investigational new drug file (IND) in August 2009. Because the firm is still collecting data, FDA stated that Bioclon is required to submit all safety information to the BLA. FDA agreed to Bioclon's proposal to submit data after a new cutoff date in a supplemental safety report.

Bioclon noted they are not receiving cost recovery at this time and does not intend to request cost recovery because the State of Arizona is providing the product (Anascorp) free of charge to all subjects. Bioclon submitted the treatment protocol for the purpose of reducing the burden of data collection; they would only collect safety data to submit. FDA responded that they will review the protocol and convey comments.

FDA reminded Bioclon that when they submit the safety data, they must also provide an integrated analysis not in its separate components. Over 500 subjects were treated up to June 2008 and since then several hundred additional subjects have been treated, totaling over 1,000 subjects. Bioclon prefers not to use resources to re-enter all 1,000 subjects and perform a reanalysis. FDA repeated that the applicant is responsible for integrating all safety data. FDA's role is to verify the analysis submitted. This integrated safety report is to include all studies, including AL-03/07. The package insert will include the safety data from all studies. FDA acknowledged that it requires several months for a firm to analyze data and agreed that it is reasonable for Bioclon to establish a cutoff of June 2009 for their data to be included in the integrated safety analysis, which will include the safety data of AL-03/07.

Post-meeting comment:

If the date of resubmission is delayed, the cutoff date for the integrated safety report must be adjusted to no more than 90 days prior to resubmission.

Decisions made and/or agreements reached:

See above.

Issues requiring further discussion:

None

Action items:

The firm will prepare their response to the CR letter.

Attachments/Handouts:

1. Meeting materials submitted 15-Sep-09 DCC L# 473016, STN 125335/0/28
2. FDA's proposed responses to the questions (enclosed)
3. Bioclon's notification of change to agenda.

END