DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Meeting Response Memorandum

Our Reference: CRMTS #7260
Ref #STN 125335/0

Division of Blood Applications

TODAY'S DATE: November 17, 2009 **PAGES:** 5

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SUBJECT: Summary of FDA Internal Meeting

PRODUCT: Centruroides (Scorpion) Immune F(ab)2 Intravenous (Equine)

We have completed our review of your information package for Centruroides (Scorpion) Immune F(ab)2 Intravenous (Equine) and are providing the following responses to the questions you posed in the package. Although we continue to reserve November 18, 2009 11:00 am–12:30 pm for a telecom with you regarding this product, if you find that our attached responses and advice are sufficiently clear and complete to obviate the need for further discussion, please inform us as soon as possible so that the meeting time may be cleared. Alternatively, if you have questions regarding specific responses or advice, please inform us so that the appropriate members of the review team can provide clarification during the reserved meeting time.

THANK YOU

Questions from the Applicant/Applicant:

Clinical

Applicant Question 1: Regarding CR 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 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.

b. *The signs of "respiratory compromise" were observed in 3 subjects (2 in Anascorp arm and 1 in placebo arm) and subsided within 2 hours. Its components, "upper respiratory compromise," "other respiratory compromise," and "pulse oximeter <90%," are not informative because the degree of compromise or the actual pulse oximeter reading are not known. The observed "other respiratory compromise" in this study is described as "respiratory acidosis" without actual data presented to substantiate severity. Thus, we cannot*

verify any of the "respiratory compromise" signs from the information submitted. Please address the fact that because all signs of "respiratory compromise" in the 3 study subjects subsided within 2 hours of treatment no effectiveness can be inferred for Anascorp in the treatment of "respiratory compromise." Efficacy, if established, is primarily driven by the data on "pathological agitation."

Discussion Points:

Protocol AL-02/03 did not include a statistical analysis of respiratory compromise, because the intention was to demonstrate overall efficacy of the antivenom, not to characterize the severity of the disease or separate out any of the components. It was also essential to minimize the impact of know confounders. Had the primary endpoint depended on a more inclusive definition of respiratory compromise, including specific oxygen saturation levels and/or use of supplemental oxygen, the study would have required a much larger sample size, and this was not feasible given the rarity of the condition. We would like to have further discussion with the Agency about the primary efficacy endpoint and "respiratory compromise" of scorpion envenomation.

FDA Response to Applicant Question 1b:

Since the primary endpoint was dependent on the presence or absence of individual components for “pathological agitation” or “respiratory compromise,” meeting the efficacy endpoint for ‘pathological agitation” may be sufficient to establish efficacy.

c. *For the treatment of a serious and life-threatening condition, the product should demonstrate effect on mortality or major morbidities. You did not demonstrate efficacy in AL-02/03 on "respiratory compromise" or any life-threatening manifestations of scorpion envenomation because this study does not seem to have enrolled the most severe cases of scorpion envenomation to demonstrate success in reducing mortality or major morbidity. Please be advised that you need to conduct a study on subjects with more serious manifestations if your product claim includes treatment of a serious and life-threatening condition.*

Discussion Points:

The neurotoxic syndrome has been historically managed in the intensive care setting because it is serious and life-threatening. The prospective Anascorp protocols, overall, included as close as possible to 100% of U.S. patients with medically important manifestations of scorpion sting. By treating patients within the first hours of the syndrome, these studies prevented prolonged lCU admissions during which most of the severe manifestations of envenomation would have manifested. Historical comparisons, with Protocol AL-03/06 as well as with reports unrelated to this BLA, demonstrate amply that scorpion envenomation is serious and life-threatening. We feel this is a treatment of a serious and life-threatening condition and that efficacy was determined. We would like to have further discussion with the Agency about this point.

FDA Response to Applicant Question 1c:
We agree**.**

Applicant Question 2: Regarding CR item 62:
In all the clinical studies presented, subject follow-up after discharge is based on telephone interview and not in-person visits or laboratory tests. In pediatric patients, the information from phone contact would likely be second-hand and this adds to the uncertainty about the accuracy of the follow-up safety data. Please address the impreciseness of such data collection, particularly with reference to the inability to confirm a diagnosis for serum sickness in at least 10 subjects in AL-03/07.

Discussion points:
We did not encounter enough evidence of classic serum sickness in this study to prove that it occurs at all, following use of the study drug. The cases abstracted in section 5.3.5 of the Integrated Summary of Safety, which were culled out as the highest-likelihood cases in the dataset, did not include a single example with the entire classic symptom complex. We would like to understand what additional information is necessary, if any at all.

FDA Response to Applicant Question 2:
The potential for serum sickness exists and this will have to be stated in the label

Applicant Question 3: Regarding CR item 63:
The use of antihistamines or corticosteroids is not specifically prohibited in the protocol of most clinical studies and there may be other confounding concomitant medications such as benzodiazepines and narcotics. Please address how you can adequately evaluate safety in the presence of these mitigating or confounding factors.

Discussion Points:
Given the severity and emergency nature of the disease, it was not practical or feasible to exclude patients who received potentially confounding medications. The relatively large number of patients enrolled in Protocol AL-03/07, however, means that it would be possible to do a retrospective comparison between those who did and those who did not receive confounding medications. We would like to understand whether this is necessary and if so to discuss the analysis with the Agency.

FDA Response to Applicant Question 3:
The use of medications that may have reduced the adverse events due to the product will need to be stated in the label.

Applicant Question 4: Regarding CR 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.