Clinical Review Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: May 6, 2011

To: To File (BLA STN 125335/0)

From: Hon-Sum Ko, Medical Officer, HFM-392

Through: Nisha Jain, Branch Chief, HFM-392

CC: Debra Cordaro, RPM, HFM-370

Applicant: Rare Disease Therapeutics, Inc.

Product: Centruroides (Scorpion) Immune F(ab')2 Intravenous (Equine)
Trade name: Anascorp®

Subject: **"**Mid-cycle" Review of Resubmission as Complete Response to CR Letter of 7/23/09

Recommendations:

The Applicant's responses to Clinical Items in the CR Letter of 7/23/09 require resolution of some issues which should be conveyed in an Information Request. The following comments should be conveyed:

1. Your response to item 67.b. of the CR Letter does not explain the choice of 0.2 as a clinically meaningful difference. As stated in the CR item, while it may be acceptable to have a difference of 0.2 for treatment of a serious and life-threatening condition, if "the endpoint is vague and the venom toxicities exhibited by the subjects under study are not life-threatening, such as agitation in the absence of respiratory or other serious manifestations, there should be a much bigger difference in order to be certain of a meaningful therapeutic benefit." Please address your choice of clinically meaningful difference in light of the severity of envenomation in the subjects studied in your pivotal trial, AL-02/03.

2. CR Letter item 71 asks for addressing the serum antivenom assay which is an -(b)(4)- but not measuring neutralizing activity in serum, whereas your response explains the potency testing for Anascorp. Please support your serum antivenom assay by providing its correlation with neutralization activity.

3. In your response to CR Letter item 73, you describe the evolution of the designing of Studies AL-03/06, AL-02/04, AL-02/05, and AL-02/06. You have not addressed the CR item issue about lack of pre-specified hypotheses-testing in these "controlled" studies based on AL-03/06 historical data, which showed *success rate without antivenom treatment in the order of around 0.4*, as 58.8% of subjects in AL-03/06 still had clinical signs at the end of 4 hours, whereas protocols AL-02/04, AL-02/05, and AL-02/06 *assumed historical control success rate of 0.7 to 0.8*. Please address the CR item.

4. Table 5.4.3 of the Integrated Summary of Safety lists 48 serious adverse events (SAEs) in 41 subjects (41/1534, or 2.7%; with 5 adults [5/330, or 1.5%], and 36 pediatric patients [36/1204, or 3.0%]). However, section 5.1 of the report also states: "Thirty-four (2.2%; 34/1534) patients experienced a total of 39 serious adverse events. The incidence of patients experiencing SAEs in the adult and pediatric populations are 1.2%; 4/330 and 2.5%; 30/1204, respectively." Please resolve this discrepancy.

5. Although we shall be conveying to you more comprehensive comments to your draft package insert, the following are labeling and promotional issues arising from your responses to the CR Letter items:

- In your response to CR Letter item 62, you state that the WARNINGS AND PRECAUTIONS section in the draft label has been revised to mention 3 patients exhibited symptoms suggestive of an acute hypersensitivity reaction and eight patients exhibited symptoms suggestive of a Type III immune response; no patient manifested the full serum sickness syndrome. These may be underestimates because of the use of premedications and concomitant medications, as well as the suboptimal follow-up procedures for serum sickness. Please include such information to provide perspective to the prescriber.
- In your response to CR Letter item 63, you have provided language for the DRUG INTERACTIONS section of the package insert concerning adverse event rates with benzodiazepines and opiates or phenylpiperidines. The wording has been revised in your latest draft package insert submitted on 3/18/11, which states in bold: "**It is not necessary to administer concomitant sedation for the treatment of scorpion envenomation, and the use of sedatives may increase the risk of adverse events.**" As the patients who require concomitant sedation may be sicker than those who do not, it may be premature to conclude that use of sedation may increase the risk of adverse events. Moreover, the focus of the CR Letter item is on antihistamines and corticosteroids which may mask acute hypersensitivity reactions to the equine product. Please address their effects in labeling.
- In your response to CR Letter item 66.b., you propose to have the Indications and Usage section to be revised to: "*Anascorp is an equine-derived F(ab)2 antivenin indicated for the management of patients with clinically important signs, primarily driven by data on pathological agitation, of scorpion envenomation*". You also recognize the Agency's position concerning the nonverifiability of "respiratory compromise" in the subjects enrolled in your pivotal trial, and our request to have more specific language in the Indications and Usage section. Because of the fact that your pivotal study data on reversal of clinical signs are purely based on pathological agitation, labeling should be revised to that effect: "*Anascorp is an equine-derived F(ab)2 antivenin indicated for the management of pathological agitation in patients with scorpion envenomation.*"
- CR Letter item 66.c. asserts that the pivotal clinical trial did not enroll subjects with sufficient disease severity to support a claim for the product to be a treatment of a serious and life-threatening condition, and no benefit for mortality or major morbidity has been demonstrated. Efficacy, if demonstrated in this study, is limited to subjects not showing life-threatening manifestations of envenomation. Although there may be a potential for the product to be a treatment for a serious and life-threatening condition, please be reminded that because the pivotal study did not include subjects showing life-threatening manifestations of envenomation, ***promotional claims to the effect that efficacy has been established for the product to be intended for a serious and life-threatening condition would be inappropriate***. In fact, your response to CR Letter item 72 recognizes that the product may have a role in preventing "prolonged ICU admissions during which most of the severe manifestations of envenomation would have manifested" instead of *treating* a serious and life-threatening condition. As such, you are actually agreeing with the CR Letter item for "the ***potential*** role of antivenom in scorpion envenomation as being primarily in the shortening of the neuromuscular effects of envenomation or reduction in the use of concomitant medications, rather than providing benefit on mortality or irreversible morbidity."
- In addition, the Clinical Studies section contains data from chart review (AL-03/06) as "historical control". Labeling should be based on data from adequate and well-controlled trials, and the use of AL-03/06 data should be avoided. Similarly, data from uncontrolled studies AL-02/04, AL-02/05, AL-02/06, and AL-03/07 should be removed from Figure 1 of the draft label, because the studies are not blinded and subject to bias. As well, the Clinical Studies section contains a paragraph and a Table (Table 4) on serum levels of venom. Because of issues relating to the validity of the binding assay for

Executive Summary

BLA STN 125335 was submitted by Instituto Bioclón S.A. de C.V. in January, 2009, and the clinical data consist of information from the following studies:

Study Number, Study Title and Study Report Number (in Parentheses)	# Subjects using Alacramyn[1]
AL-02/03. Prospective, randomized, double-blind, controlled study of Alacramyn vs placebo in pediatric patients with systemic signs of scorpion sting envenomation in Arizona, U.S. (CSR XE-C-02)	**8**[2]
AL-03/06. Historical control: establishment of natural history of scorpion envenomation in the absence of antivenom treatment in pediatric patients in Arizona, U.S. (CSR XE-C-03)	**0**
AL-02/04: Open label, confirmatory, controlled clinical study of Alacramyn in adult patients with scorpion sting envenomation (CSR-XE-C-04)[3]	**22**
AL-02/05: Open label, confirmatory, controlled clinical study of Alacramyn in pediatric patients with scorpion sting envenomation (CSR-XE-C-04)	**29**
AL-02/06: Open label, confirmatory, controlled clinical study of Alacramyn in pediatric patients with scorpion sting envenomation (CSR-XE-C-04)	**50**
AL-99/02. Randomized, double-blind, variable dose comparison of Alacramyn vs Birex in patients with Scorpion sting study in Mexico (CSR-XE-C-05)	**105**
Ongoing AL-03/07. Open treatment protocol for use of Anascorp in patients with scorpion sting envenomation in Arizona, U.S.A, (CSR XE-C-01)	**1425 as of September, 2010**

[1] Alacramyn is the tradename of the product in Mexico. In the U.S., the proposed proprietary name is "Anascorp".
[2] An additional 7 subjects used placebo.
[3] One report for three "studies": CSR-XE-C-04, for AL-02/04, AL-02/05, and AL-02/06

The relative importance of the different clinical trials is as follows:

Importance	Study/Studies	Utility in Review of Applicastion
1	AL-02/03. Prospective, randomized, double-blind, controlled study of Alacramyn vs placebo in pediatric patients with systemic signs of scorpion sting envenomation in Arizona, U.S.	Primary support of efficacy; study in pediatric subjects
2	AL-02/04, AL-02/05 and AL-02/06: Open label, confirmatory, controlled* clinical study of Alacramyn in (adult (AL-02/04) or pediatric (AL-02/05, AL-02/06)) patients with scorpion sting envenomation	Supportive phase 2/3 study in adults and pediatric subjects for safety
	AL-03/06. Historical control: establishment of natural history of scorpion envenomation in the absence of antivenom treatment in pediatric patients in Arizona, U.S. [retrospective chart review]	Conducted after completion of AL-02/04, AL-02/05, and AL-02/06 and lack of pre-specified hypothesis to serve as historic control. No data on Anascorp use to support safety or efficacy
3	Ongoing AL-03/07. Open treatment protocol for use of Anascorp in patients with scorpion sting envenomation in Arizona, U.S.A,	Open label treatment protocol for patients of any age, which can be used to support safety
4	AL-99/02. Randomized, double-blind, variable dose comparison of Alacramyn vs Birex in patients with Scorpion sting study in Mexico	Comparison with product not licensed in U.S. not useful to support efficacy; potential to support safety

*The applicant considers AL-02/04, AL-02/05, and AL-02/06 as "controlled", because of the potential use of data from AL-03/06 for historic control comparison. The combined total in these three trials of ~100 subjects is similar in size to that of AL-03/06.

Efficacy:

Among the 15 patients enrolled in an adequate and well controlled pivotal trial, AL-02/03 comparing Anascorp with placebo, one patient in each group did not have detectable serum venom levels. Of the remaining 13 patients with scorpion envenomation, there is a clinically relevant difference (95% confidence level lower bound of 50%) in resolution of the signs of

enveomation by the end of 4 hours between treatment groups with Anascorp and placebo. However, the subjects enrolled were primarily children showing signs of pathological movement rather than respiratory distress or other life-threatening manifestations of envenomation. Hence, the efficacy of Anascorp is based on less severe forms of envenomation in children, which needs to be addressed in labeling.

Safety:
The Applicant has presented safety data from over 1500 patients stung by scorpion and treated with Anascorp. Given the fact that the product is of F(ab')2 from horses, the safety profile of Anascorp in these study subjects is acceptable, with vomiting, pyrexia, rash, nausea, pruritus, and headache being the most common adverse events, and low rates of acute allergic reactions (3 of 1534 patients) and possible serum sickness (13 of 1534 patients), but no reports of full serum sickness syndrome. Because of the use of concomitant medications and sedation as well as the limitations in follow-up procedures, the true incidence of acute allergy reactions and serum sickness syndrome is uncertain.

Other Significant Issues:
- Anascorp has been granted orphan product designation on 1/13/09 for "the treatment of scorpion envenomation requiring medical attention."
- Because of orphan product designation, PREA requirements do not apply.
- There are no issues arising from BIMO inspections.
- The Applicant has provided financial disclosure information and there are no issues arising from such information.

Conclusion and Recommendation:
- From a clinical standpoint, despite the data limitations in this application, the Applicant has demonstrated the safety and efficacy of Anascorp in the management of pathologic agitation in patients with scorpion envenomation. The limitations would have to be addressed in labeling.
- It is approvable upon clarification of some of the responses to the items in the CR Letter of 7/19/09 and revision of draft package insert.

Background
BLA STN 125335 was submitted by Instituto Bioclón S.A. de C.V. on 1/21/09, and the Applicant received a CR Letter on 7/23/09. The Applicant sought clarifications of the CR Letter comments from FDA and held telecons with the Reviewers in 2009 and 2010 to address selected issues in the letter. On January 31, 2011, Rare Disease Therapeutics, Inc., to which this application has been transferred from Instituto Bioclón S.A. de C.V., submitted a response to the CR Letter, and the response has been deemed to be complete. The new Applicant has since also submitted revised labeling with a new draft package insert on 3/17/11.

Applicant Response to FDA Comments in CR Letter of 7/23/09
The following provides Items 60 to 78 in the CR Letter of 7/23/09, which pertain to clinical issues in the original submission, and the Applicant's response to each item.

60. We note that your study reports in the Clinical Section (Item 8) of this BLA do not bear

RESPONSE
Signature pages for all clinical study reports included in the BLA are enclosed.

Comment *The "signature pages" are presented and are all signed on 10/22/09 by Walter Garcia Ubbelohde, MD, who is both author of all the reports and Sponsor's Responsible Medical Officer of Bioclon. Although this approach is not ideal, the Applicant has submitted the material requested in this item.*

61. Please address the lack of adequate dose-ranging studies in establishing the proposed dose (3 initial vials, with repeat at 30- to 60-minute intervals up to 5 vials; more if envenomation is severe) in the draft package insert. You should have a systematic approach to dosing based on pharmacokinetics, body mass, and the use of concomitant medications in the clinical development program for the product. Please also address the lack of GCP documentation for your human PK data.

RESPONSE
Dosing:
Dosing of antivenom treatment is based on the amount of neutralizing antibody fragments needed to bind the amount of venom injected by the scorpion. As this venom burden is unknown to the treating clinician empiric dosing and titration is necessary. Pharmacokinetic studies of venom and antivenom in other species demonstrate that there is not a linear dose-response that can be used to determine a meaningful minimal effective dose. It has been shown that higher than the minimum effective doses provide faster and permanent neutralization of circulating toxins by accommodating for redistribution of toxins from extravascular to vascular compartments.

Comment *Although not ideal, this may be considered an acceptable response, since antibodies are usually to be given in excess to cover the unknown quantity of venom causing intoxication, and PK data play a minor role in the management of such patients.*

PK study:
The PK study published in Toxicon 2005; 46:797-805 using Anascorp was conducted before the IND -(b)(4)- was in place, nevertheless the study was approved by the local IRB and all healthy volunteers signed informed consent before entering the study. Unfortunately source documents were not properly stored, CRFs were not available and the analytical method used to measure the Anascorp plasma level to calculate the PK parameters was not validated. For this reason we decided to conduct a well controlled PK study with Anavip which has physicochemical properties identical to Anascorp and is expected to have the same pharmacokinetic behavior.

Comment *This response concerning unavailability of source documents for GCP in the Anascorp PK study is unsatisfactory. The Applicant states that the study on Anavip can provide the same PK information as for Anascorp. This has not been supported by submission of physicochemical properties of the two products for comparison. Since the distribution of*

digested material has major impact on PK, it would be important to know that these products ***have comparable distribution*** *of various fragments and IgG, as well as Anascorp having distribution of the fragments and IgG in different lots* ***consistent with those in the Anavip product lot in the PK study****. It is not adequate simply to say that Anascorp and Anavip are expected to have the same PK behavior because of "identical" physicochemical properties. However, as stated above, since dosing is expected to be in excess, the PK parameters do not play a significant role in dosing. Thus, although the response is unsatisfactory, no further request may be necessary.*

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.

RESPONSE

Clarification on CR question 62 was requested as part of the November 18, 2009 Type C meeting. **See CRMTS 7260**, Meeting Response Memorandum dated November 17, 2009.

The sponsor provided the following discussion points regarding this question:

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.

The FDA made the following comments:

The potential for serum sickness exists and this will have to be stated in the label.

New wording from sponsor:

Package Insert language added to Section 5: Warnings and Precautions:

The possible risks and side effects associated with the administration of heterologous animal proteins in humans include anaphylactic and anaphylactoid reactions, and delayed allergic reactions (late serum reaction or serum sickness). Although none of the patients in the clinical studies of Anascorp experienced a severe anaphylactic reaction or delayed allergic reactions such as serum sickness, the possibility of an anaphylactic reaction or delayed allergic reactions should be considered.

Comment *The Applicant has not addressed the impreciseness of their data collection, which is the essence of the item. "We did not encounter enough evidence ….." because the data collection was not adequate. The fact that the "highest-likelihood cases" did not have "a single example with the entire classic symptom complex" can easily be explained on the basis of inadequate follow-up. Nevertheless, as this can be addressed by labeling, no further requests are necessary. The labeling proposed by the Applicant has actually been revised in a submission dated 3/17/11 (Amendment 40) to: "The possible risks and side effects associated with the administration of heterologous animal proteins in humans include anaphylactic and anaphylactoid reactions, and delayed allergic reactions (late serum reaction or serum sickness). Three patients exhibited symptoms suggestive of an acute hypersensitivity reaction and eight patients exhibited symptoms suggestive of a Type III immune response; no patient manifested the full serum sickness syndrome."*

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.

RESPONSE

Clarification on CR question 63 was requested as part of the November 18, 2009 Type C meeting. **See CRMTS 7260**, Meeting Response Memorandum dated November 17, 2009.

The sponsor provided the following discussion points regarding this question:

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.

The FDA made the following comments:

The use of medications that may have reduced the adverse events due to the product will need to be stated in the label.

New wording from sponsor:

Package Insert language added to Section 7: Drug Interactions:

Studies of drug interactions have not been conducted with Anascorp, although over 40% (42%; 279/663) of patients received benzodiazepines prior to or during Anascorp administration; of these patients, 44% experienced an adverse event, compared to 27% of patients who did not receive benzodiazepines. Narcotics (opiates and phenylpiperidines) were used in more than 20% of patients (15% and 9.8%, respectively) and the concomitant use of an opiate was also associated with a higher incidence of patients with AEs (62%) compared to those not receiving opiates (29%).

It is unclear if the use of some medications used prior to or during Anascorp administration reduces adverse events associated with the product.

Comment *The Applicant has not addressed the masking of adverse events with confounding medications like corticosteroids and antihistamines, as requested in this item. Instead, they point out that patients receiving benzodiazepines or narcotics had higher incidence of adverse events. This higher incidence is unexplained, but possibly due to such patients being sicker. The labeling language given in the response has been revised in a submission dated 3/17/11 (Amendment 40) to:*

> *"Studies of drug interactions have not been conducted with Anascorp, although over 37% (37.5%; 576/1534) of patients received benzodiazepines prior to or during Anascorp administration; of these patients, >37% experienced an adverse event, compared to 21% of patients who did not receive benzodiazepines. Narcotics (opiates and phenylpiperidines) were used in more than 25% of patients (18% and 15%, respectively) and the concomitant use of an opiate was also associated with a higher incidence of patients with AEs (37%) compared to those not receiving opiates (25%).* ***It is not necessary to administer concomitant sedation for the treatment of scorpion envenomation, and the use of sedatives may increase the risk of adverse events.****"*

Significantly this revision has removed "It is unclear if the use of some medications used prior to or during Anascorp administration reduces adverse events associated with the product." Unless

the Applicant analyzes adverse events in patients who did or did not receive corticosteroid or antihistamine, the potential for masking adverse events cannot be ruled out. However, as with benzodiazepines and narcotics, it would still be uncertain whether patients who used corticosteroids or antihistamines were sicker. Thus, it would be more appropriate to state the uncertainty in labeling.

64. In several of the clinical studies, including the pivotal trial (AL-02/03), you use the decline in serum venom levels by a binding assay after Anascorp treatment as an endpoint for efficacy. Please address the issue that in the absence of assay validation to detect active venom when antivenom is present the venom levels in Anascorp-treated subjects would be un-interpretable.

RESPONSE

The (b)(4) used to measure venom levels in plasma samples of patients was validated according to ICH guidelines Q2A and Q2B for its accuracy, precision, specificity, detection limits, quantitation limits, linearity and range of venom not bound to the antivenom. The validation did not address the activity of venom that is not bound to antivenom and thus measurable by our (b)(4) system. Nevertheless, the potency testing **(BLA STN 125335/0 Volume 4, Item 4, pages 20-85)** used to establish the antivenom specifications shows that when venom and antivenom are mixed at different proportions, the toxic effect of the constant venom amounts measured by ---(b)(4)--- is inversely related to the amount of antivenom added to the mixture, thus only unbound venom is exerting its toxic effect.

Comment *The Applicant concedes that their "validation did not address the activity of venom that is not bound to antivenom and thus measurable by (their) (b)(4) system." Instead, the relationship between -------(b)(4)------ and the amount of antivenom in a venom-antivenom mix in the potency assay is put forth to justify the lack of validation of the binding assay in the presence of antivenom. These are very different assays and it is not appropriate to use results of the potency assay for cross-validation of the binding assay. Moreover, the binding assay uses serum which has other potential interference effects. There are two subjects, (b)(6) (Anascorp) and (b)(6) (placebo), who did not have detectable venom in serum throughout the course of study. Although it is quite possible that there was no envenomation, however, because of the lack of this validation, it is uncertain whether most of the venom in Subject (b)(6) had already been tissue-bound, and the small quantity of remaining venom in serum was further masked by subsequent antivenom administration or not.*

This issue is unresolved, but venom level is a supportive endpoint, while primary efficacy is based on clinical endpoints. However, the draft label contains a whole paragraph and a Table (Table 4) on serum venom levels. Because of the assay issues discussed above, the venom levels may be misleading and should not be included in labeling.

65. In some clinical studies, including AL-02/03 and AL-03/07, the study report states that the maximum protein content of the Anascorp used was (b)(4). This differs from the specifications for release. Please confirm that the same formulation was used for your clinical studies as the one proposed for marketing.

RESPONSE

Product specification submitted in the IND (b)(4) in 2002 stated that the maximum protein content of Anascorp® was (b)(4). The specifications for protein content for Anascorp®

changed to ----------(b)(4)---------- based on a retrospective analysis of (b)(4) Anascorp® lots, although the product formulation has remained the same. Bioclon's research and development team have validated the analytical method. Current methodology reflects more accurately the determinations of the products' composition and purity. The protein content in Anascorp® is analyzed using the -------(b)(4)---------. Validation process for the -------(b)(4)---------- was included in the BLA, Item 4, Chemistry section, Volume 1.4, appendix 9, page 167.
----------(b)(4)----------.

------(b)(4)-------

Drug Product lots of Anascorp used in all the clinical studies complied with the specifications submitted in the BLA**,** see **BLA STN 125335/0, Item 8, Volume 8, page 50** for the batch number and Certificates of Analysis for the Anascorp® Drug Product used in the clinical trials**.**

Comment *The Applicant uses specification of --------(b)(4)------ protein content. It is unclear why it is necessary to use such high levels like ---(b)(4)--- for specification, when the measured levels consistently are at or below (b)(4). Such specification may be acceptable for protein content but not for antivenom potency, which should be at or above a defined level. Since potency and protein content are related, the divergence in specification is intriguing. The CMC Reviewer is aware of the issue.*

Study AL-02/03:

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 severity 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.

RESPONSE
Clarification on CR question 66(a) was requested as part of the November 18, 2009 Type C meeting. See **CRMTS 7260**, Meeting Response Memorandum dated November 17, 2009.
The sponsor provided the following discussion points regarding this question:
The choice of an upgraded, 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.

The FDA made the following comments:

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.

Final Sponsor Response:

The Agency is correct in its observation that concomitant sedation can obscure agitation. Because this was a potential confounder for the primary endpoint, study design deliberately addressed this question by requiring blinded physician judgment and documentation of reasoning to support the validity of the endpoint determination.

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. "Pathological agitation" in the case of scorpion envenomation is a syndrome neurologically very different from other "agitation" patterns commonly seen in pediatrics, and it is considered pathognomonic by University of Arizona pediatric faculty. Before sedative drugs are administered to newly-arrived patients, the diagnosis is obvious.

Interaction between midazolam and the primary endpoint was anticipated from the outset of the study, but ethical study design precluded withholding of sedative medication. Without taking sedation into account, we might have had patients in whom oversedation at the 4-hour time point made it impossible to distinguish presence or absence of medically important signs of envenomation. For this reason, the investigator was required to take oversedation into account. The time delay of 4 hours between administration of study drug and assessment of the primary endpoint ensured the robustness of this distinction, as follows:

- In the Anascorp-treated group, 5 of 8 patients responded to treatment so rapidly that no additional midazolam was required, at all, following administration of study drug. Three of 8 (#----------(b)(6)----------) received additional midazolam, in the range of 0.2 to 0.3 mg/kg, during the first hour after receiving study drug, but they required no sedation after one hour. As a consequence, 8 of 8 in the treated group reached the 4-hour observation point having been unsedated for at least 3 hours; and absence of the clinical syndrome in this group was crystal clear. Please note that in no case did a subject in this group experience a return to agitation after syndrome resolution: once neurotoxicity has resolved, it stays resolved, consistent with the expected mechanism of action of antivenom.
- Among the placebo recipients, 6 of 7 were still requiring sedation at the 4-hour point, implying a risk that toxicity assessment might be falsely negative owing to suppression of movements by midazolam. Please note that the manufacturer of midazolam recommends an intravenous infusion rate of 0.06-0.12 mg/kg/hour for sedation generally, but that children in our placebo group received an average of 1.8 mg/kg over a 4-hour period. Despite this extremely high dosing, 4 of the 6 still on midazolam exhibited break-through pathological agitation at the assessment time point. The other two (#------(b)(6)---) had transient suppression of agitation when the 4-hour time point was assessed, but subsequent observations revealed that toxicity was indeed ongoing. In subject #(b)(6), a total of 0.66 mg/kg of midazolam was administered between study baseline and 4 hours; and additional infusion

- The third patient for whom investigator judgment differed from systemic signs was the study's sole outlier. This child received midazolam only until 2.5 hours after receiving study drug, because pathological agitation resolved. As stated in the clinical study report, section 11.4.1.1: "The placebo-treated patient (Patient #(b)(6)) in whom resolution of signs was evident at 4 hours was the oldest (10.3 years) and the heaviest (42 kg) patient in the study, suggesting that the greater volume of distribution of scorpion venom may have contributed to earlier spontaneous resolution of the syndrome. The investigator attributed jerky eye movements occurring in this patient at the 4-hour time point to the effect of midazolam."
- The primary endpoint was resolution of clinically important systemic signs of scorpion envenomation, within 4 hours for patients treated with Anascorp, and this was supported by the secondary endpoint that Anascorp-treated patients would require significantly less benzodiazepine sedation than controls, for control of agitation. Both separately and combined, these endpoints provide strong support for the efficacy of Anascorp.

Comment *The Applicant does not address the validity of the evaluation of the primary endpoint, but rather explains the discrepancies between Investigator designation of having "clinically important signs of envenomation" and actual data of clinical signs on the basis of sedative use. The Investigator overall evaluation subverts the actual findings in three placebo subjects:*

- *Subject (b)(6): Due to the requirement of continuous midazolam infusion and need for additional bolus dose over 7 hrs after initiating treatment, it is believed that patient was experiencing ongoing venom effect despite lack of symptoms at the 4 hour time point.*
- *Subject (b)(6): Patient was sedated at 4 hour time point, but physician note states that agitation and nystagmus were present, decreasing one hour after 4 hour time point. Last documented symptom was shakiness/tremor as per nursing note, over 12 hours after initiating treatment.*
- *Subject (b)(6): At the 4 hr time point, patient had jerky eye movements, but Investigator overall evaluation was negative for "clinically important signs of envenomation" because the jerky eye movements were thought to be due to midazolam effect.*

Perhaps the primary endpoint should be renamed to be "Investigator overall evaluation of envenomation effect" instead of "Investigator overall evaluation of clinical important signs of envenomation", because the Investigator is at liberty to determine envenomation effect taking into consideration midazolam action and other potential factors. Certainly this overall evaluation may be more prone to bias, as a need for midazolam by the 4th hour could suggest that the subject was using placebo and thus causes unblinding. If one would attribute jerky eye movement to midazolam effect, then abnormal eye movement may not be considered a reliable sign of envenomation in the presence of midazolam. However, it is noted that 100% of the subjects had used benzodiazepine sedation prior to study product administration.

For placebo subjects (b)(6)and (b)(6), it may be reasonable to consider them still under venom effect with manifestations controlled by midazolam at 4 hours, as they required continuation of sedative or showed clinical signs of envenomation after 4 hours. For placebo subject (b)(6), it is unclear whether attribution of jerky eye movement to midazolam effect could be valid or not. This is one of the two patients without detectable serum venom at any time during the study.

Unless there was a failure in the assay for serum venom or all venom from the scorpion had become tissue-bound, the abnormal eye movement may not be due to venom effect.

Therefore, although the Applicant has not addressed the validity of the primary endpoint in relation to clinical signs, it appears that this is no longer necessary because the thrust of the evaluation was not clinical signs but overall venom effect. There is a certain amount of subjectivity in the evaluation of overall venom effect in the presence of midazolam, but the evaluation may be verified by subsequent developments in the patient with respect to continued sedative requirements or recurrence of clinical signs. No further requests are needed on this item.

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."

RESPONSE

Clarification on CR question 66(b) (*Applicant Question 1*) was requested as part of the November 18, 2009 Type C meeting. **See CRMTS 7260**, Meeting Response Memorandum dated November 17, 2009.

The sponsor provided the following discussion points regarding this question:

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.

The FDA made the following comments:

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.

FDA stated that the indications for use need to be more specific.

Current indication statement:

Anascorp is an equine-derived $F(ab)_2$ antivenin indicated for the management of patients with clinically important signs of scorpion envenomation.

Revised indication statement:

Anascorp is an equine-derived F(ab)2 antivenin indicated for the management of patients with clinically important signs, primarily driven by data on pathological agitation, of scorpion envenomation.

Comment *The Indications and Usage statement should be revised to be specific about pathological agitation rather than "clinically important signs" because no efficacy on any other clinical signs or a constellation of such signs has been demonstrated.*

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.

RESPONSE

Clarification on CR question 66(c) (*Applicant Question 1*) was requested as part of the November 18, 2009 Type C meeting. See **CRMTS 7260**, Meeting Response Memorandum dated November 17, 2009.

The sponsor provided the following discussion points regarding this question:

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 magnifications of scorpion sting. By treating patients within the first hours of the syndrome, these studies prevented prolonged ICU 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.

The FDA made the following comments:

We agree.

Comment *The Applicant cites FDA agreement to their discussion points in November 2009. It is unclear to what extent FDA agreed. This Reviewer would agree that the product is a potential treatment of a serious and life-threatening condition. The CR item asserts that the pivotal clinical trial did not enroll subjects with sufficient disease severity to support a claim for the product to be a treatment of a serious and life-threatening condition, and no benefit for mortality or major morbidity has been demonstrated. Efficacy, if demonstrated in this study, is limited to subjects not showing life-threatening manifestations of envenomation.*

The Applicant's discussion points did not mention that they would make a claim for treatment of a serious and life-threatening condition, and the draft package insert (revised) does not contain such language. However, the Applicant should be reminded that because their pivotal study did not include subjects showing life-manifestations of envenomation, promotional claims to the

effect that efficacy has been established for the product to be intended for a serious and life-threatening condition would be inappropriate.

67. In the original submission of this protocol to BB-IND (b)(4), you proposed a sample size of at least 12 subjects to discern a significant difference between treatments assuming expected success proportions of 0.85 for the Anascorp treatment and 0.10 for the comparator group. The finalized study protocol for AL-02/03 does not pre-specify a hypothesis for a given difference in success rate between treatment arms. However, the Statistical Analysis Plan dated September 22, 2005, states that the product will be declared superior to placebo if the difference in success rates is 0.2 or greater. An appropriate hypothesis should be based on the lower bound of the 95% confidence interval for the difference in success rates between treatment arms. If the endpoint is vague and the venom toxicities exhibited by the subjects under study are not life-threatening, such as agitation in the absence of respiratory or other serious manifestations, there should be a much bigger difference in order to be certain of a meaningful therapeutic benefit. Please address:

    a. The inconsistencies in your assumptions of treatment effect; and

RESPONSE

The amended study protocol of November 2003 for AL-02/03 stated that treatment proportions would be calculated and clinically interpreted. The study was not designed to achieve the usual levels of statistical significance but only to achieve the necessary information for a descriptive examination of the antivenom effect of Anascorp.

Comment *The Applicant has not addressed the inconsistency regarding assumptions of treatment effect. In fact, it is contradictory to cite the November 2003 protocol to state that the "study was not designed to achieve the usual levels of statistical significance but only to achieve the necessary information for a descriptive examination of the antivenom effect of Anascorp" while the statistical analysis plan (SAP) of 2005 requires a success rate difference of at least 0.2 to declare superiority. Moreover, the original protocol assumed a difference of 0.75 (success rate of 0.85 for Anascorp and 0.10 for placebo). The rationale for the three positions has not been explained.*

    b. Why a difference of 0.2 can be regarded as clinically meaningful, considering your assertion that Anascorp is indicated for the treatment of a serious and life-threatening condition when a placebo success rate is estimated to be 0.1.

RESPONSE

The statistical analysis plan of September 2005 stated the systemic sign responses would be presented using frequencies and percentages. Anascorp would be declared clinically superior to placebo if the Anascorp success percentage were at least 20% greater than the placebo success percentage.

Comment *The response does not explain the choice of 0.2 as a clinically meaningful difference. As stated in the CR item, while it may be acceptable to have a difference of 0.2 for treatment of a serious and life-threatening condition, if "the endpoint is vague and the venom toxicities exhibited by the subjects under study are not life-threatening, such as agitation in the absence of respiratory or other serious manifestations, there should be a much bigger difference in order to be certain of a meaningful therapeutic benefit."*

The lower bound of the 95% confidence interval for the difference in success rates is greater than 0.2, both in the entire ITT population, and among envenomated subjects (35.7% and 50.1%, respectively).

Success Rates at the End of 4 hrs (No Pathological Agitation or Respiratory Compromise)

	Anascorp	Placebo	Difference (Anascorp – placebo) and 95% C.I.
Entire ITT population	8/8 (100%)	1/7 (14.3%)	85.7% (35.71%, 99.64%)
Envenomated subjects	7/7 (100%)	0/6 (0)	100% (50.14%, 100%)

Although these data are based on the subjects studied, who were not with the most severe forms of envenomation, the success rate difference of 35.7% or 50.1% between Anascorp and placebo is probably clinically meaningful.

68. The placebo is said to be lyophilized material to be reconstituted with normal saline, but the finalized protocol dated November 30, 2003, states it is normal saline (page 7 of protocol, BLA vol. 1.8, page 194). Please provide detailed information on the nature of the placebo.

RESPONSE **Response needs clarification** Placebo used in the clinical studies contained in the BLA consists of (b)(4) glycine, lyophilized and then reconstituted with normal saline. The November 30, 2003 protocol study outline cover page is incorrect. Placebo is not normal saline as noted in Section 7.0 (Study Drug), Step 7.2 (Clinical Formulation of Placebo) of Clinical Protocol (**BLA STN 125335/0 Volume 1.8, page 203, page 16 of protocol**), which note that Instituto Bioclon S.A. de C.V. prepared a lyophilized placebo, indistinguishable from the active drug, to be reconstituted with normal saline.

Comment *Issue resolved*

69. Please address the imbalance between treatment arms in:

a. The subjects' age (and hence maturity and body mass);

RESPONSE

Although the patients in the placebo group tended to be slightly older and to weigh correspondingly more than the patients in the antivenom group, these differences were primarily due to outlier values for one patient, who, at 10 years of age and 42 kg, was 4 years older and 17 kg heavier than any other child in the study. The one placebo recipient in whom there was spontaneous resolution of the syndrome within 4 hours was this oldest and heaviest child. Smaller children, with a smaller body mass in which the injected venom is distributed, tend to have more severe reactions than do larger children or adults; so if antivenom were ineffective then the smaller, younger antivenom recipients in this imbalanced population should have had worse, not better, outcomes. Exclusion of the outlier from the analysis would accentuate apparent treatment efficacy. The fact that this imbalance falls this means that the odds were against study success; so clinical interpretation of the study outcome is therefore strengthened.

Comment *Although the outlier quoted in this response (Subject (b)(6)) did not have detectable serum venom levels, and hence the envenomation is questionable, making the discussion in the response difficult to interpret, the analysis excluding the two subjects without detectable serum*

venom levels ((b)(6) (Anascorp) and (b)(6) (placebo)) still shows a success rate difference of 100% (lower bound 95% C.I. 50%)(see above).

b. The time between scorpion sting and administration of test product; and

RESPONSE

We anticipated that a prolonged delay from sting to study enrollment might predispose patients toward spontaneous resolution of the syndrome, and that in a small study this phenomenon could interfere with demonstration of efficacy. Published reports and preliminary chart reviews suggested that nearly all critically ill patients required ongoing observation and midazolam treatment for greater than 9 hours (see reference below); so we established an outer limit of 5 hours from sting time, as an exclusion criterion for participation in this 4-hour study. As it turned out, the placebo group had a slightly longer interval between sting and study enrollment than did the antivenom group. This is most likely a reflection of variation in the multiple factors involved in patient transport from the scorpion-habitat neighborhoods on the outskirts of Tucson to the urban ICU setting. The difference was so small that it is unlikely that there was any impact on the primary endpoint. The fact that this imbalance chanced to fall the way that it did, however, means that the odds were against study success; so clinical interpretation of the study outcome is therefore strengthened.

Comment *Delay in treatment may be expected to give a worse outcome if the treatment is efficacious, but in this case the "treatment" delay occurs in the placebo group. However, the Applicant contends that delay in treatment predisposes to spontaneous resolution of the syndrome. At the same time, delay in treatment may result in the administration of more midazolam, which confounds the interpretation of clinical signs. Hence, the effect of delay in treatment is complicated and hard to be certain. Since the time delay from "envenomation" to enrollment between the two groups is small, and given the small sample size in this study, it would be very difficult to determine the bias introduced by the longer interval between scorpion bite and treatment in the placebo group.*

c. The median dose of midazolam sedation administered prior to study enrollment.

RESPONSE

Small doses of midazolam (relative to those that can be administered in the ICU setting) were given in transport vehicles and in the emergency department, prior to study enrollment. Midazolam is used in this situation because of its very short half-life, so that ventilatory suppression – if it occurs – will be very brief; and for this reason multiple small doses (several per hour) are commonly administered. Patients with longer delays from sting to study enrollment receive larger cumulative doses of midazolam for this reason; and as expected the placebo group therefore received slightly more midazolam overall than did the antivenom group. By study design, children were excluded if they received greater than 0.3 mg/kg of midazolam during the hour prior to study enrollment. This was a safety measure intended to prevent ventilatory failure if pathologic agitation were suddenly reversed while an excessive dose of midazolam was still in effect. All patients in both groups received less than or equal to 0.3 mg/kg of midazolam during the hour prior to enrollment

Comment *The Applicant has not addressed the bias introduced by more midazolam use before enrollment in the placebo group. Although the response states that the placebo group received slightly more midazolam, and that both groups received less than or equal to 0.3 mg/kg in the hour prior to enrollment, the actual use in the placebo group prior to enrollment was not just "slightly more", as shown in the following Table:*

Total dose of midazolam before study drug infusion (mg/kg)	Treatment Groups	
	Anascorp N=8	Placebo N=7
Mean (SD)	0.2 (0.1)	0.5 (0.7)
Median	0.2	0.3
Min, Max	0.1, 0.4	0.1, 2.0

The midazolam confounding effect is substantial, and caused the Investigator to reverse the presence/absence of "clinically important signs of envenomation" in 3 of the 15 subjects. Thus, it is important to address the bias due to greater use of midazolam in one of the groups.

70. Two of the subjects had no detectable venom in serum at any time during the study (one in each treatment arm) and two other subjects did not have serum venom assayed (both in Anascorp arm). Thus, there were only 11 subjects with documented envenomation in this study (5 in Anascorp arm and 6 in placebo arm). Please reanalyze your data for subjects with documented envenomation.

RESPONSE

The primary end point of this study was to demonstrate resolution of clinically important systemic signs of scorpion envenomation within four hours for patient treated with Anascorp. Blood venom level was a secondary endpoint and was stated that the venom blood levels with decrease within one hour after Anascorp treatment.
Further, if you examine the data from those patients that did have measurable venom levels it can be seen that in the Anascorp treated patients the blood venom level in the Anascorp treated patients did decrease (none detected) in one hour after treatment while the placebo treated patients had significant elevated venom levels even out to 4 hours. In addition if you look at the clinical results, related to the primary end point, 100% of the Anascorp treated patients did not have clinically significant signs of scorpion envenomation four hours after treatment. Further, all other parameters measured were consistent with this outcome.
As such we do not think that a reanalysis of the data of only those patients with demonstrable venom levels is appropriate nor will it change the outcome of the primary endpoint.

Comment *The Applicant has declined to reanalyze the data using only envenomated subjects. However, an analysis of such subjects (including two subjects without venom sampling done, but assumed to be enveomated; see above under the comment to response on item 67b) still shows success rate difference of 100% between Anascorp and placebo groups (95% C.I. 50%).*

71. Please address the fact that the serum antivenom assay is a binding assay for equine F(ab')2 and may not necessarily be demonstrating serum activity in neutralizing scorpion venom.

RESPONSE

The potency testing **(BLA Volume 4, Item 4, pages 20-85)** used to establish the antivenom specifications shows that when venom and antivenom are mixed at different proportions, the toxic effect of the constant venom amounts measured by -----(b)(4)----- is inversely

related to the amount of antivenom added to the mixture, thus only unbound venom is exerting its toxic effect.

Comment *The Applicant is not addressing the CR item. The CR item asks for addressing the serum antivenom assay which is an (b)(4), whereas the response explains the potency testing for Anascorp. See comment on Applicant response to CR item 64.*

Studies AL-03/06, AL-02/04, AL-02/05, and AL-02/06:

72. In AL-03/06, a study based on chart review of patients with scorpion sting but not antivenom treatment, approximately 30% of "envenomated" subjects showed some form of respiratory compromise. It appears to confirm, as in the pivotal trial (AL-02/03), that scorpion envenomation in young children is predominated by neuromuscular toxicity as manifested by "pathological agitation." There were no deaths or serious adverse events using standard of care and it is not clear how "respiratory compromise" contributes to morbidity, which appears to be readily reversible with supportive care. Please address the potential role of antivenom in scorpion envenomation as being primarily in the shortening of the neuromuscular effects of envenomation or reduction in the use of concomitant medications, rather than providing benefit on mortality or irreversible morbidity.

RESPONSE

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 ICU admissions during which most of the severe manifestations of envenomation would have manifested.

Comment *The Applicant is using the same argument as in the response to CR item 66c. See comment on their response to that item. The Applicant concedes that the product may have a role in preventing "prolonged ICU admissions during which most of the severe manifestations of envenomation would have manifested" instead of treating a serious and life-threatening condition. As such, the Applicant is de facto agreeing with the CR item for "the potential role of antivenom in scorpion envenomation as being primarily in the shortening of the neuromuscular effects of envenomation or reduction in the use of concomitant medications, rather than providing benefit on mortality or irreversible morbidity."*

73. Although you consider the open-label studies, AL-02/04, AL-02/05, and AL-02/06, as "controlled," using the natural history study, AL-03/06, as historic control, we cannot consider this appropriate because:

    a. AL-03/06 was completed (July 2007) after completion of these three "controlled" trials (October 2006); and

    b. The protocols for these "controlled" studies were finalized before AL-03/06 was initiated.

Please address the lack of pre-specified hypotheses-testing in these "controlled" studies, which were intended to incorporate the historic data from AL-03/06 as "control" to establish efficacy.

RESPONSE

The development of the concepts for using historic data for comparison with the data in the "Controlled" studies Al-02/04, Al-02/05, Al-02/06 was discussed with the Agency at a post-BB-IND -(b)(4)- meeting on September 27, 2002 and the rational and details of the concept was subsequently submitted to the Agency on January 10, 2003 (**S005**).

Additionally, the retrospective (historical) study concept and discussion about statistical power and hypothesis was described and submitted to BB-IND -(b)(4)- in **S006** on May 28, 2003 which included a protocol, a discussion about the trials and the use of an ethically acceptable control group. It contained two clinical trial protocols, a double blind study and other open trials.

It also contained a draft of a prospectively designed retrospective chart review protocol of envenomation in the Tucson, Arizona area, treated at the University Medical Center and Tucson Medical Center between 1993 and 2002 without antivenin. This study was designed to describe the natural course of scorpion envenomation, when the standard of care at the time was sedation and no antivenin was administered (non available). It was our stated suggestion that this retrospective study could act as a control to the open studies. Further, in the discussion of the research plan of these protocols the statistical considerations were stated and discussed in comparison to the open studies. Subsequently, the retrospective study (AL-03/06, amended in **S010**, June 2, 2004) and the open studies (AL-02/04 & 05 & 06) were amended and a statistical hypothesis included in the protocols submitted to the above noted BB-IND in **S009, S010**, and **S013**.

Protocol AL-02/04 was finalized and dated May 29, 2003 (**BLA 125335, Vol. 1.12 p. 201**).

Protocol AL02/05 was amended (November 30, 2003) and submitted on January 23, 2004 in **S009** and protocol AL-02/06 was submitted on August 30, 2004 as **S013** to the above noted BB-IND.

However it is important to note that these studies were discussed together in S006 dated May 28, 2003, along with a prospective, well designed, retrospective protocol (historical study) addressing the comparison to open studies and a rational why this historical study protocol design and data collection would be appropriate for the comparison to the open studies as well as act as a control for all open studies.

Comment *The Applicant describes the evolution of the designing of Studies AL-03/06, AL-02/04, AL-02/05, and AL-02/06, but has failed to address the CR item about lack of pre-specified hypotheses-testing in these "controlled" studies, which were intended to incorporate the historic data from AL-03/06 as "control" to establish efficacy.*

Study AL-99/02:

74. Please address the reconstitution of Anascorp in AL-99/02 (in 5 mL normal saline) as being different from that in the pivotal trial, AL-02/03 (10 mL saline, section 9.4.2 of study report), or the proposed use in the draft package insert for this BLA submission (5 mL sterile water).

RESPONSE

The AL-99/02 study was conducted prior to the IND submission. Anascorp AL-02/03 and all studies subsequent to IND submission have followed the reconstitution procedures described in the AL-02/03 Clinical Study Protocol section 9.1. "For each vial

approximately 5 ml of normal saline will be injected into the study drug vial using standard sterile procedure."

Comment *The Applicant does not address the differences between reconstitution methods in different studies, or even the difference between the AL02/03 clinical study report and its protocol. Instead, draft labeling has been changed to conform to having reconstitution with 5 mL normal saline and not 5 mL sterile water. Issue resolved.*

75. Please address the fact that the adverse event reporting in AL-99/02 is defined by relatedness to Anascorp treatment, making the database incomplete because of non-reporting of events deemed "not related."

RESPONSE

The AL-99/02 study was conducted prior to the IND submission. Three of 105 patients (ID #---(b)(6)---) reported transient adverse events. All adverse events were reported, although these adverse events were not listed as related vs. non-related. The study investigators did not assess causality.

Comment *The Applicant states in the response that the Investigators did not assess causality and all adverse events were reported. This is in contrast to the study report:*

- *The synopsis of the report states: "Safety will be evaluated by the: (o)ccurrence of any adverse event reported by the attending personal* ***and deemed to be related*** *to the antivenom use", and*
- *Section 4.1 of the report states: "Safety was evaluated by comparing the incidence of adverse events* ***related to*** *antivenom use"*

This response is inaccurate*, but since Study AL99/02 has a multitude of problems in the collection of safety data, such as masking of adverse events by the use of antihistamines or corticosteroids, inadequate follow-up, etc., selection by causality attribution may be only one of many. Indeed, the data listings for this study do not even give any information on the three subjects who developed adverse events.* ***As such, it is not possible to make any firm conclusions on safety in the use of Anascorp in this study.*** *In fact, in the updated integrated Summary of Safety, the Applicant has excluded the 105 subjects in AL-99/02 treated with Anascorp in the evaluation of event rates. This issue about evaluation of only related adverse events in AL99/02 will not be further pursued.*

76. Please note that since the comparator to Anascorp (Birex) is not a licensed product in the U.S., AL-99/02 is not adequate to support efficacy of Anascorp in scorpion envenomation.

RESPONSE

Study AL-99/02 was conducted in 1999 and was not intended to support efficacy for the BLA STN 125335/0. This study was not conducted under the current IND (BB-IND -(b)(4)-). Only the Anascorp results of this study were presented in the BLA (see Volume 1.15, page 002, CSR XE-C-05), for completeness of data collected and to show that based on these results as well as post-approval efficacy results in Mexico, the Sponsor was encouraged to open an IND to begin the study of Anascorp in the United States.

In the Anascorp portion of AL-99/02, dealing specifically with the 105 Alacramyn (Anascorp's name in Mexico) recipients, nearly all patients experienced clinical recovery by 3 hours after start of treatment, and 90% recovered after receiving 3 or fewer vials of Alacramyn. These results were the basis for choosing the dose used in pivotal study AL-

02/03. In addition, comparison of these findings with U.S. case series describing the untreated syndrome lead to the choice of the primary endpoint of the pivotal trial, that is, presence or absence of the medically important signs of envenomation, 4 hours following study baseline.

Comment *The Applicant concedes that AL99/02 was not intended to support efficacy for BLA STN 125335/0. The response is primarily about the utility of this study during product development (choice of product dose and primary endpoint as well as its timing in the pivotal study), and requires no further comment.*

Study AL-03/07:

77. In this 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.

RESPONSE

Clarification on CR question 77 was requested as part of the November 18, 2009 Type C meeting. **See CRMTS 7260**, Type C Meeting Response Memorandum dated November 17, 2009 and Official Meeting Summary dated December 18, 2009. Question 77 was also discussed on January 21, 2010, **see CRMTS 7330** and during a teleconference on June 3, 2010. The following decisions were agreed upon and have been provided in this complete response letter.

It was agreed if the resubmission was delayed; the cutoff date for the integrated safety report must be adjusted to no more than 120-130 days prior to resubmission. As agreed, incorporating this cutoff date requirement, a new study report for study AL-03/07 is provided (XE-C-13). This report contains all data from August 2005 – September 2010. Also incorporating this cutoff date requirement, an up-to-date Integrated Summary of Safety (XE-ISS-012) is provided. This report contains comparisons/integration of all new data through September 2010, along with critical safety tables for all other studies that were included in the BLA.

Comment *An updated safety report for AL03/07 and an updated Integrated Summary of Safety have been submitted (see review of these reports in Appendices I and II of this memo). The overall safety profile of Anascorp in the treatment of scorpion envenomation appears to be acceptable.*

78. Please address the lack of clinical laboratory testing to evaluate safety in AL-03/07.

RESPONSE

Clinical laboratory testing was not performed in the study described as AL-03/07 "Open Treatment Protocol for Use of Anascorp in Patients with Scorpion Sting Envenomation"

since it was only designed to provide study drug to envenomated patients in Arizona in compliance with the request of the Governor of Arizona and while the documentation submitted to the FDA to support a Biological License Application was under review for Licensure.
Further, clinical laboratory safety data was collected in all studies conducted with Anascorp (AL-02/03, AL-02/04, AL-02/05 and AL-02/06). Blood was collected for clinical chemistry and hematology testing to be performed and in some patients serum antigen levels were evaluated and utilized to assess the safety and efficacy of Anascorp. Thus, it was not deemed necessary to perform clinical laboratory testing in AL-03/07 since this work was performed in other controlled and open studies and AL-03/07 was opened to compassionately supply product to all areas in Arizona that have a scorpion envenomation problem since no approved treatment or scorpion antivenin is available at this time.

Comment *Response acceptable*

Conclusions

The Applicant has presented responses to clinical items in the CR Letter of 7/23/09. The following can be concluded from the data in the original submission and current response:

- Among the 15 patients enrolled in an adequate and well controlled pivotal trial, AL-02/03, comparing Anascorp with placebo, one patient in each group did not have detectable serum venom levels. Of the remaining 13 patients with scorpion envenomation, there is a clinically relevant difference (95% confidence level lower bound of 50%) in resolution of the signs of enveomation by the end of 4 hours between treatment groups with Anascorp and placebo. However, the subjects enrolled were primarily children showing signs of pathological movement rather than respiratory distress or other life-threatening manifestations of envenomation. Hence, the efficacy of Anascorp is based on less severe forms of envenomation in children, which needs to be addressed in labeling.
- The Applicant has presented safety data from over 1500 patients stung by scorpion and treated with Anascorp. Given the fact that the product is of F(ab')2 from horses, the safety profile of Anascorp in these study subjects is acceptable, with vomiting, pyrexia, rash, nausea, pruritus, and headache being the most common adverse events, and low rates of acute allergic reactions (3 of 1534 patients) and possible serum sickness (13 of 1534 patients), but no reports of full serum sickness syndrome. Because of the use of concomitant medications and the limitations in follow-up procedures, the true incidence of acute allergy reactions and serum sickness syndrome is uncertain.

Labeling

In the response to CR Letter comments, the Applicant has made several suggestions for labeling. The following should be conveyed to the Applicant to be addressed:

- In your response to CR Letter item 62, you state that the WARNINGS AND PRECAUTIONS section in the draft label has been revised to mention 3 patients exhibited symptoms suggestive of an acute hypersensitivity reaction and eight patients exhibited symptoms suggestive of a Type III immune response; no patient manifested the

full serum sickness syndrome. These may be underestimates because of the use of premedications and concomitant medications, as well as the suboptimal follow-up procedures for serum sickness. Please include such information to provide perspective to the prescriber.

- In your response to CR Letter item 63, you have provided language for the DRUG INTERACTIONS section of the package insert concerning adverse event rates with benzodiazepines and opiates or phenylpiperidines. The wording has been revised in your latest draft package insert submitted on 3/18/11, which states in bold: "It is not necessary to administer concomitant sedation for the treatment of scorpion envenomation, and the use of sedatives may increase the risk of adverse events." As the patients who require concomitant sedation may be sicker than those who do not, it may be premature to conclude that use of sedation may increase the risk of adverse events. Moreover, the focus of the CR Letter item is on antihistamines and corticosteroids which may mask acute hypersensitivity reactions to the equine product. Please address their effects in labeling.

- In your response to CR Letter item 66.b., you propose to have the Indications and Usage section to be revised to: "Anascorp is an equine-derived F(ab)2 antivenin indicated for the management of patients with clinically important signs, primarily driven by data on pathological agitation, of scorpion envenomation". You also recognize the Agency's position concerning the nonverifiability of "respiratory compromise" in the subjects enrolled in your pivotal trial, and our request to have more specific language in the Indications and Usage section. Because of the fact that your pivotal study data on reversal of clinical signs are purely based on pathological agitation, labeling should be revised to that effect: "Anascorp is an equine-derived F(ab)2 antivenin indicated for the management of pathological agitation in patients with scorpion envenomation."

- CR Letter item 66.c. asserts that the pivotal clinical trial did not enroll subjects with sufficient disease severity to support a claim for the product to be a treatment of a serious and life-threatening condition, and no benefit for mortality or major morbidity has been demonstrated. Efficacy, if demonstrated in this study, is limited to subjects not showing life-threatening manifestations of envenomation. Although there may be a potential for the product to be a treatment for a serious and life-threatening condition, please be reminded that because the pivotal study did not include subjects showing life-threatening manifestations of envenomation, promotional claims to the effect that efficacy has been established for the product to be intended for a serious and life-threatening condition would be inappropriate. In fact, your response to CR Letter item 72 recognizes that the product may have a role in preventing "prolonged ICU admissions during which most of the severe manifestations of envenomation would have manifested" instead of treating a serious and life-threatening condition. As such, you are actually agreeing with the CR Letter item for "the potential role of antivenom in scorpion envenomation as being primarily in the shortening of the neuromuscular effects of envenomation or reduction in the use of concomitant medications, rather than providing benefit on mortality or irreversible morbidity."

In addition, the draft label contains data in the Clinical Studies section from chart review (AL-03/06) as "historical control". Labeling should be based on data from adequate and well-controlled trials, and the use of AL-03/06 data should be avoided. Similarly, data from uncontrolled studies AL-02/04, AL-02/05, AL-02/06, and AL-03/07 should be removed from Figure 1 of the draft label, because the studies are not blinded and subject to bias. As well, the Clinical Studies section contains a paragraph and a Table (Table 4) on serum levels of venom. Because of issues relating to the validity of the binding assay for serum venom levels (CR Letter item 64), e.g., interference by antibodies and correlation with activity, these venom level data may be misleading and should not be included in labeling.

Recommendations

- From a clinical standpoint, this application is approvable upon clarification of some of the responses to the items in the CR Letter of 7/19/09 and revision of draft package insert.

Appendix I. Review of Study AL03/07 Updated Safety Report

Title of Study: Treatment Protocol for Use of Anascorp™ in Patients with Scorpion Sting Envenomation

Investigators/Study Center(s):
- This was a multicenter study with 25 sites.
- The principal investigator was Dr. Leslie Boyer of University Medical Center, Tucson, AZ.

Study Period: initiation: 23 May 2005, and last patient follow-up visit: 29 September 2010

Phase: 2/3

Objectives:
- Primary endpoint: to evaluate the adverse events (AEs) profile of scorpion envenomation patients immediately after treatment with Anascorp, at 24 hours post-treatment, and 14 days post-treatment.
- Secondary endpoint: to identify resolution of systemic signs of scorpion envenomation after treatment with Anascorp.

Design:
- Patients diagnosed with systemic scorpion sting symptoms who met selection criteria were enrolled. Baseline history and physical examination were obtained, symptoms of systemic scorpion envenomation were documented, vital signs were recorded and concomitant medications and demographic data were collected. Patients were then administered Anascorp IV and evaluated for symptom resolution.
- Treatment emergent AEs including acute hypersensitivity reactions and delayed serum sickness were monitored. When clinically significant signs of envenomation were absent for at least 30 minutes, a final physical assessment was performed and the patient was discharged. Patients were contacted at 24 hours and 14 days after Anascorp treatment for a follow-up interview to assess symptoms suggestive of ongoing venom effect, delayed serum sickness or any other AEs; as necessary, patients with ongoing symptoms or events were referred for appropriate care.

Number of Patients (Planned and Analyzed):
- Up to 150 patients per year were to be treated with Anascorp until U.S. marketing approval or discontinuation of the study deemed to be appropriate. At the time of finalization of the Statistical Analysis Plan, 858 patients were expected. Enrollment was extended by an additional year, and a total of 1426 patients were analyzed.

Eligibility Criteria:
- Inclusion: a) Males and females of any age presenting for emergency treatment with clinically important systemic signs of scorpion sting envenomation, and b) Devoid of known allergy to horse serum
- Exclusion: known allergy to horse serum

Test Product, Dose and Mode of Administration, and Duration of Treatment:
- Anascorp was diluted in 20 to 50 mL normal saline and was intravenously administered over 10 minutes or as permitted by IV access. The initial dose was changed from one vial to three vials in accordance with Amendment 1 to the protocol. Subsequent single vial doses of Anascorp, up to a total of five vials, were administered at 30 minute intervals as indicated by the patient's condition until resolution of symptoms. Duration of treatment was up to 2.5 hours.

Criteria for Evaluation:
- Efficacy: The resolution of systemic scorpion sting signs and symptoms was evaluated. Additional efficacy endpoints analyzed were time from study drug infusion to resolution of envenomation and to discharge, presence of specific symptoms at follow-up, effect of concomitant medications and duration of hospitalization.

- Safety: Adverse events (AEs), vital signs, and concomitant medications were assessed. The intensity of an AE is a relative estimate made by the investigator:
  - Mild: transient and easily tolerated by the patient and requires no special treatment
  - Moderate: causing patient discomfort that may be ameliorated by simple therapeutic measures
  - Severe: incapacitating, simple therapeutic measures cannot ameliorate the event.

Statistical Methods:

- Efficacy: The presence (yes/no) of selected signs and symptoms of envenomation (i.e., abnormal eye movement, increased secretions, respiratory distress, thrashing of limbs, and other) was recorded and patients were categorized as being a patient success or not a patient success. A patient was considered to be a patient success at a particular time point if that patient exhibited no signs or symptoms at that time point. Otherwise, the patient was not considered a patient success. Selected intervals of duration (e.g., time from study drug infusion to resolution, time from study drug infusion to discharge) were summarized by Age Group and Overall.
  The presence of each sign and symptom was summarized using incident counts and percentages for Age Group and Overall by time point (Baseline, Discharge). Ninety-five percent (95%) confidence intervals (CIs) for each sign and symptom were generated and displayed based on binomial distributions.
- Safety:
  - Exposure. Study drug exposure was summarized using descriptive statistics for Age Group and Overall for the following endpoints: duration of actual study drug administration, total time of study drug administration, volume administered and the number of vials received. In addition, number of vials received was also summarized with incident counts and percentages using the following categories: less than or equal to 2 vials, 3 vials, 4 vials, 5 or more vials.
  - Adverse Events. All AE summaries were restricted to TEAEs. *Although the primary objective of the study was to evaluate AEs immediately after, 24 hours after, and 14 days after treatment with Anascorp, these analyses were not performed for all AEs; only acute hypersensitivity was evaluated immediately after the start of infusion and specific AEs were evaluated at the two follow-up time points*. Ninety-five percent (95%) CIs for endpoints of interest from the analyses described above were generated and displayed based on binomial distributions.
    At the 24-Hour and Day 14 follow-up evaluations, all TEAEs were recorded. In addition, existence of specific AEs (i.e. itching, rash, petechia, arthralgia, myalgia, nausea, vomiting, dehydration, chest pain, hematuria, possible serum sickness, and other) was queried and recorded: for each of these specific AEs, responses of Yes, No, or Missing were summarized.
    - Medical review of suspected cases of patients with acute hypersensitivity reaction was performed to determine actual cases.
    - Possible or probable cases of serum sickness, included in an overall summary of AEs, were identified programmatically and by medical review of all relevant data (including investigator comments) collected on the CRFs.
    - Summaries of acute hypersensitivity/serum sickness were included in an overall summary.
  - Vital Signs. Vital signs were summarized using descriptive statistics at Baseline and Discharge: changes and percent change from Baseline were summarized.

Patient Enrollment and Disposition:

	Adult (> 18 years)	Pediatric (0-18 years)	Overall
Patients enrolled	308	1118	1426
ITT population	307	1118	1425
Patients who did not receive drug	1	0	1
Completed study Yes	292 (95.1%)	1048 (93.7%)	1340 (94.0%)
No	15 (4.9%)	70 (6.3%)	85 (6.0%)
Primary reason for discontinuation			
Lost to follow-up	15 (4.9%)	70 (6.3%)	85 (6.0%)

Efficacy Results:

- As this is an open-label study with no hypothesis testing, the data are not adequate to support efficacy. Nevertheless, for the 1396/1425 patients with available data, the mean time from Anascorp infusion to resolution was 1.42 hours and the maximum time was 20.5 hours. This did not appear to

- Only 5 patients were readmitted to the hospital within 14 days after treatment. During the 14-day follow up period, the most common ongoing symptoms were “other” (11.6%), rash (3.6%), itching (2.8%), vomiting (1.8%), and nausea (1.3%); follow-up data were not available for 6.0% of patients.

Safety Results:

- Exposure. Patients received a mean total dose of 3.59 vials, with most receiving 3 (48.1%) or 4 (36.0%) vials of Anascorp. Within the pediatric group, weight distribution remained similar regardless of dose level, whereas in the adult group, dose levels roughly correlated with weight categories. Patients who received a total dose of 1 or 2 vials had the highest incidence of TEAEs (42.5%). In patients who received 3, 4 or 5 vials, a trend of increasing TEAE incidence (24.5%, 28.3%, and 35.8%, respectively) with increasing dose was observed. Changes from an initial dose of 1 to 3 vials and from the old to the new lyophilizer improved the safety profile of the Anascorp treatment regimen. Nearly twice the incidence of TEAEs was observed in patients enrolled prior to the initial dose change (49.2% [95% CI 39.8-58.5] change to 26.1% [95% CI 23.7-28.6]) and lyophilizer change (43.1% [95% CI 37.3-48.9] change to 24.0% [95% CI 21.5-26.6]).
- ALL Adverse Events. Overall, 399/1425 patients (28.0%) experienced a total of 717 TEAEs, with similar incidences in adult (31.6%) and pediatric (27.0%) patients. The most frequently reported TEAEs were vomiting (4.7%), pyrexia (4.1%), rash (2.8%), nausea and pruritus (2.2% each), headache and rhinorrhoea (2.0% each), myalgia (1.7%), fatigue (1.6%), cough (1.5%), diarrhoea (1.2%), and lethargy (1.1%). Pyrexia, rash, and rhinorrhoea were reported more frequently in the pediatric group than in the adult group. Nausea, headache, and myalgia were reported more frequently in adults than in pediatric patients. All other common TEAEs occurred with similar incidences in both study populations. As to severity, patients reporting TEAEs experienced mild TEAEs most frequently (17.7%); 8.3% and 1.9% of patients reported moderate or severe TEAEs, respectively. Most of the commonly reported AEs were mild or moderate. Severe vomiting, fatigue, and diarrhoea were each reported by 0.1% of patients.
- Adverse Events with at least Possible Relationship to Treatment. Overall, 143 patients (10.0%) reported at least 1 TEAE with a possible or probable relationship to treatment, or one that was not assessable. The most common treatment-related TEAEs were vomiting and pyrexia (1.8% each), rash (1.5%), and nausea (1.1%). Treatment-related vomiting and rash occurred with similar incidences in adult and pediatric patients. Pyrexia occurred with a higher incidence in pediatric patients, whereas nausea was reported more frequently in adults. As to severity, treatment-related moderate or severe TEAEs were reported in 4.4% of patients, with a slightly higher incidence in adults (6.5%) than in pediatric patients (3.8%): vomiting, rash, and pyrexia (0.6% each) and pruritus, diarrhoea, and headache (0.3% each) were reported most frequently by all patients; headache was reported by adults only; rash and pyrexia were more common in pediatric patients; and diarrhoea, rash macular, rash pruritic, fatigue, nausea, and anorexia were reported by pediatric patients only.
- Vital Signs at Discharge. Most patients with available data had improvements in vital signs. The most common vital signs TEAE was pyrexia (4.1%), and “other” (orthostatic hypotension, hyperthermia, tachycardia, and body temperature increased: each reported by 1 or 2 patients).
- Deaths, Discontinuations, and SAEs. No deaths or discontinuations due to TEAEs were reported. Overall, 31/1425 patients (2.2%) experienced 36 treatment-emergent SAEs total (adult 1.3% and pediatric patients 2.4%). The majority of SAEs were moderate or severe and most were not related to treatment. *Moderate or severe SAEs of respiratory distress and sedation (each in a total of 0.4% overall) were observed exclusively in pediatric patients; all were considered not related to treatment*. Five of 1425 patients (0.4% overall, 1 adult and 4 pediatric) experienced a total of 9 SAEs considered possibly related or of unknown relationship to treatment (stridor, lethargy, endotracheal intubation, eye swelling, vomiting, nausea, mental state changes, lipase increased, and dehydration). All related SAEs resolved during study, except for one (lipase increased), with unknown outcome.
- Specific Monitored AEs – acute hypersensitivity and serum sickness:
  - Three patients (0.2%) had symptoms consistent with possible acute hypersensitivity.

- Thirteen patients (0.9%) had possible serum sickness, including 6 (0.4%) identified by programmatic evaluation of follow-up symptoms and 8 (0.6%) by medical review of CRF data; 1 with both methods.
  - Of these 13 patients with possible serum sickness, 8 (4 adult, 4 pediatric) were concluded to have a Type III immune response after medical review (all possible cases identified by medical review; one adult also identified programmatically and another adult also identified as having a serum sickness AE).
  - The remaining 5 patients (all pediatric; possible cases identified programmatically) included 3 with likely viral infections; 1 with a cold and skin irritation unrelated to treatment; and 1 with symptoms related to a broken bone.
  - Although no patients in the study had symptoms consistent with full serum sickness syndrome, medical review of the data indicated that Type III immune responses occurred after treatment with Anascorp in a small number of patients (8/1425, 0.6%).

Comment *This is an open-label study for expanded access of Anascorp, and the primary use of the study data is for support of safety, since the efficacy data cannot be considered adequate because of study design. However, the collection of safety data is also not ideal because of the lack of laboratory testing or actual visits for follow-up (by phone contact after discharge from hospital). Thus, although the study has included a large number of subjects, because of the above limitations, its regulatory utility is limited. Despite this, the study appears to show that the equine F(ab')2 product, Anascorp, is well tolerated, with low rate of acute hypersensitivity reactions, while a full-scale serum sickness syndrome has not been observed.*

The most frequent adverse events considered to be treatment-related were: vomiting, pyrexia, rash, and nausea (occurring in > 1% of patients). They resolved during the study and were generally manageable with other therapy or required no action.

Appendix II. Review of Integrated Summary of Safety (ISS) Report (XE-ISS-12)

This Integrated Summary of Safety is based on safety data from the following studies:

Protocol # Investigators Publications	**Location Product Code**	**Design**	**Treatment Doses**	**Number Entered Each Treatment**	**Age Range in years (mean)**	**% M/F (B/W/H/O)[1]**
AL-99/02 Multicenter	Mexico Product codes not available	Double-blind, randomized, comparison vs. Birmex (antivenom)	Alacramyn: 1 – 6 vials Birmex: Unknown	Alacramyn: 105 Birmex: 143	3 – 87 (32.0)	65 / 35 (0 / 0 / 248 / 0)
AL-02/03 Boyer, Leslie	Arizona B-2M-01	Double-blind, randomized, placebo-controlled	Anascorp: 3 vials	Anascorp: 8 Placebo: 7	Anascorp: 1 – 6 (2.0) Placebo: 1 – 10 (3.0)	Anascorp: 50 / 50 (0 / 3 / 3 / 2) Placebo: 43 / 57 (1 / 4 / 1 / 1)
AL-02/04 Vera Castro, America	Mexico B-5F-11	Open-label	Anascorp: 2 – 4 vials	Anascorp: 22	19 – 55 (33)	36 / 64 (0 / 0 / 22 /0)
AL-02/05 Osnaya Romero, Neydi	Mexico B-2M-01 or B-5F-11	Open-label	Anascorp: 3 – 10 vials	Anascorp: 29	0.9 – 9 (3.0)	55 / 45 (0 / 0 / 29 /0)
AL-02/06 Multicenter	Arizona B-2M-01, B-5F-11, or B-6B-01	Open-label	Anascorp: 3 – 4 vials	Anascorp: 50	0.6 – 51 (4.3)	61 / 39 (0 /10/5/35)
AL-03/07 Multicenter	Arizona B-2M-01, B-5F-11, B-6B-01, B-6E-15, B-5M-02, P-6M-03, P-8H-01-A, P-8H-01-B, or B-0D-21	Open-label	Anascorp: 1 – 5 vials	Anascorp: 1425	0.03 – 90.5 (14.8)	52 / 48 (32/797/ 393/203)
Vazquez H et al. Pharmacokinetics of a $F(ab')_2$ scorpion antivenom in healthy human volunteers	Mexico B-0J-04	Open-label	Anascorp: 1 vial	Anascorp: 8	17 – 26 (22.6)	75 / 25 (0 / 0 / 8 / 0)
Vazquez H et al. Pharmacokinetics of a $F(ab')_2$ scorpion antivenom administered intramuscularly in healthy human volunteers	Mexico B-0J-04	Open-label	Anascorp: 1 vial	Anascorp: 6	19 – 33 (23.7)	86 / 14 (0 / 0 / 6 / 0)

1B/W/H/O = Black/White/Hispanic/Other. Other includes Native American

Extent of Exposure

Product exposure in the Anascorp studies is summarized in the following Table:

Protocol number	**99/02**	**99/02**	**02/03**	**02/04**	**02/05**	**02/06**	**02/06**	**03/07**	**03/07**	**03/07***	**03/07***
Age group	<16 yrs	≥16 yrs	<18 yrs	≥18 yrs	<18 yrs	<18 yrs	≥18 yrs	≤18 yrs	>18 yrs	≤18 yrs	>18 yrs
N	24	65	8	22	29	49	1	84	34	1034	273
Initial dose	1 – 3	1 – 2	3	2	3	3	3	1	1	3	3
Total dose Mean	1.8	1.6	3	2.7	3.7	3.1	3	2.7	3.5	3.6	3.9
Standard deviation	0.9	1.0	0	0.9	0.7	0.2	0	0.9	1.0	0.7	0.8
Total dose Median	2	1	3	2	4	3	3	3	3	3	4
Minimum	1	1	3	2	3	3	3	1	2	3	3
Maximum	4	6	3	4	10	4	3	5	5	5	5

Baseline Demographics

Demographics of study subjects is presented as follows:

Protocol Number	**99/02 ANA N=105**	**02/03 ANA N=8**	**02/03 PBO N=7**	**02/04 ANA N=22**	**02/05 ANA N=29**	**02/06 ANA N=49[1]**	**03/07 ANA N=1425**	**03/06 Historical N=97**
Age (yrs)								
Mean (SD)	32.0 (NA)	2.0 (1.8)	4.3 (3.0)	33.8 (10.9)	3.0 (2.2)	4.3 (3.2)	14.8 (21.4)	3.92 (3.26)
Median	29.0	1.0	4.0	33.0	2.1	3.7	4.8	3.0
Range	3 to 87	1 to 6	1 to 10	19.8 to 55.7	0.9 to 9.1	0.6 to 12.9	0.03 to 90.5	0.6 to 15.6
Gender								
Male	68 (65%)	4 (50%)	3 (43%)	8 (37%)	16 (55%)	30 (61%)	744 (52%)	52 (54%)
Female	43 (35%)	4 (50%)	4 (57%)	14 (64%)	13 (45%)	19 (39%)	681 (48%)	45 (46%)
Race								
White	0	3 (37.5%)	4 (57%)	0	0	9 (18%)	797 (56%)	32 (33%)
Black	0	0	1 (14%)	0	0	0	32 (2.2%)	0
Hispanic	100%	3 (37.5%)	1 (14%)	22 (100%)	29 (100%)	5 (10%)	393 (27.5%)	9 (9.3%)
Native American	0	1 (12.5%)	1 (14%)	0	0	UNK	122 (8.6%)	5 (5/2%)
Other	0	1 (12.5%)	0	0	0	1 (2.0%)	81 (5.7%)	1 (1.0%)
Unknown	0	0	0	0	0	34 (69%)	0	50 (52%)
Weight (kg)[2]								
Mean (SD)	NA	11.9 (4.0)	18.8 (11.7)	62.4	13.7 (6.6)	18.9 (10.1)	30.1 (25.2)	17.5 (11.0)

1Excludes one adult protocol violator: 51.8 year old white female weighing 56.7 kg.
2N=21 for 02/04, N=1353 for 03/07, and N=95 for 03/06 for weight
ANA = Anascorp; PBO = placebo
NA = Not available

Adverse Event Data

A total of 1,653 subjects received Anascorp in clinical trials: 14 healthy volunteers and 1639 patients who presented for emergency treatment with "clinically important signs of scorpion envenomation". There were 105 patients who participated in study AL-99/02, where there were no case report forms (CRFs), and all that is known about their adverse events is that they were transient.

- Of the remaining 1,534 patients, 27% (421/1534) reported at least one treatment-emergent adverse event (TEAE). No patients died or discontinued study participation for AEs. The most frequent adverse events observed in the studies are shown in the following Table:

	Anascorp N (%)	**Historical Control N (%)**	**Placebo N (%)**
N=	1534	97	7
Patients reporting ≥1 adverse event	421 (28)	38 (39)	1

Preferred Term				
	Vomiting	72 (4.7)	7 (7.2)	0
	Pyrexia	63 (4.1)	6 (6.2)	1 (14)
	Rash	41 (2.7)	1 (1.0)	1 (14)
	Nausea	32 (2.1)	0	0
	Pruritus	31 (2.0)	0	0
	Headache	29 (1.9)	0	0
	Rhinorrhoea	28 (1.8)	0	0
	Myalgia	25 (1.6)	0	0
	Fatigue	24 (1.6)	0	0
	Cough	22 (1.4)	0	0
	Diarrhoea	20 (1.3)	0	0
	Lethargy	17 (1.1)	0	0
	Intubation	2 (0.1)	5 (5.2)	0
	Hypoxia	1 (0.1)	4 (4.1)	0
	Pneumonia aspiration	3 (0.2)	4 (4.1)	0
	Stridor	2 (0.1)	3 (3.1)	0
	Hospitalisation	3 (0.2)	2 (2.1)	0
	Hallucination	0	2 (2.1)	0
	Blood potassium decreased	0	2 (2.1)	0
	Lumbar puncture	0	2 (2.1)	0
	Accident	0	2 (2.1)	0
	Respiratory acidosis	1 (0.2)	0	1 (14)

The frequent symptoms such as vomiting, pyrexia, rash, nausea, etc. may have been related to the envenomation, use of sedative medication, or to concurrent illness during the two week period between treatment and follow–up evaluation. In contrast, the most frequently occurring AEs in historical control patients not treated with antivenin also included vomiting (7.2%; 7/97), pyrexia (6.2%; 6/97), as well as respiratory AEs such as intubation (5.2%; 5/97), hypoxia (4.1%; 4/97), aspiration pneumonia (4.1%; 4/97), and stridor (3.1%; 3/97).

- Four adverse events (0.6%) were considered to be 'definitely' related to study drug. Two of these were infiltration of the IV through which the Anascorp was being delivered, one was local reaction at the IV site, and one was possible serum sickness manifesting as a rash without myalgias or arthralgias.
- In addition, 103 patients had adverse events that the investigator considered 'possibly' related to study drug and 47 patients experienced AEs that were coded as 'not assessable'. Of the events "possibly" related to Anascorp, there were 5 "severe" adverse events (5 of the 33 "severe" events in the database): one patient had a body rash that was possibly serum sickness, one patient had intermittent diarrhea, one patient had intermittent body aches during the first two days after the sting, one patient had vomiting for two days, and one patient was intubated after possible aspiration. Other than the intubation, the adverse events in all five patients resolved without the need for treatment.
- There were two pediatric patients and one adult patient who had symptoms during or immediately following Anascorp use that were suggestive of an acute allergic reaction. One pediatric patient with stridor was treated with diphenhydramine, epinephrine, and solumedrol. The other pediatric patient was treated with diphenhydramine, corticosteroids, and famotidine. The adult patient was treated only with diphenhydramine. In all 3 cases, symptoms resolved within one hour.
- There were 13 patients in clinical trials that were identified either programmatically or through medical review to have possible serum sickness. After the details of their cases were reviewed by the principal investigator, 8 patients were considered to have had a "Type III"

- Table 5.4.3 of the ISS provides a listing of serious adverse events (SAEs). The majority of SAEs were moderate or severe, and most were not related to treatment. All patients recovered without sequelae. The following is an excerpt from that Table, giving the SAE preferred terms and SOCs, subject IDs, age, weight, sex, and age:

System Organ Class Preferred Term	ID #	Age (yrs), Weight (kg)	Sex, Race
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Respiratory distress	(b)(6)	1.4, 12.3	F, O
Respiratory distress	(b)(6)	1.1, 10.0	F, W
Respiratory distress	(b)(6)	5.2, 12.0	F, W
Aspiration	(b)(6)	1.7, 16.0	M, B
Stridor	(b)(6)	3.8, 15.9	M, B
Respiratory distress	(b)(6)	0.33, 5.0	F, W
Respiratory distress	(b)(6)	6, 23.6	M, W
Pneumonia aspiration	(b)(6)	2.7, 15.9	M, W
Respiratory failure	(b)(6)	3, 14.0	M, W
Aspiration	(b)(6)	5.9, 17.5	F, W
Respiratory distress	(b)(6)	0.5, 9.3	F, H
Respiratory distress	(b)(6)	1.4, 10.2	M, W
Aspiration	(b)(6)	0.8, 9.6	F, W
Pneumonia aspiration	(b)(6)	2.0, 14.5	F, W
Hypoxia	(b)(6)	0.75, 9.1	M, W
Respiratory distress	(b)(6)	0.75, 9.1	M, W
Respiratory distress	(b)(6)	1.4, 10.0	M, W
Respiratory distress	(b)(6)	0.8, 11.0	M, W
NERVOUS SYSTEM DISORDERS			
Sedation	(b)(6)	4.2, 17.2	M, W
Ataxia	(b)(6)	2.9, 15.5	F, H
Sedation	(b)(6)	3.8, 22.0	F, H
Sedation	(b)(6)	2.8, 20.9	M, W
Sedation	(b)(6)	13, 58.9	M, W
Sedation	(b)(6)	8.9, 31.9	M, W
Lethargy	(b)(6)	73, 61.8	F, W
Lethargy	(b)(6)	0.2, 5.4	M, H
SURGICAL AND MEDICAL PROCEDURES			
Hospitalisation	(b)(6)	0.8, 10.0	M, W
Endotracheal intubation	(b)(6)	2.7, 15.9	M, W
Endotracheal intubation	(b)(6)	4.1, 24.4	M, W
Hospitalisation	(b)(6)	1.5, 10.0	F, W
Hospitalisation	(b)(6)	0.17, 5.3	M, W
GASTROINTESTINAL DISORDERS			
Vomiting	(b)(6)	6.2, 18.5	M, W
Vomiting	(b)(6)	5.6, 22.0	M, W
Vomiting	(b)(6)	5.8, 18.0	M, W
Nausea	(b)(6)	5.8, 18.0	M, W
PSYCHIATRIC DISORDERS			
Agitation	(b)(6)	2.1, 10.9	M, H
Agitation	(b)(6)	46, 115.5	M, H
Mental status changes	(b)(6)	5.8, 18.0	M, W
Agitation	(b)(6)	1.9, 11.9	M, H
EYE DISORDERS			
Eye swelling	(b)(6)	3.8, 15.9	M, B
Eye movement disorder	(b)(6)	20, 60.0	M, H
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Pyrexia	(b)(6)	1.0, 8.2	F, O

Pyrexia	(b)(6)	5.8, 18.0	M, W
INFECTIONS AND INFESTATIONS			
Pneumonia	(b)(6)	0.8, 8.8	F, H
Cellulitis	(b)(6)	3.25, 13.5	F, O
METABOLISM AND NUTRITION DISORDERS			
Dehydration	(b)(6)	5.8, 18.0	M, W
INJURY, POISIONING AND PROCEDURAL COMPLICATIONS			
Venomous sting	(b)(6)	31, 61.3	F, H
INVESTIGATIONS			
Lipase increased	(b)(6)	62, 65.3	F, W

M=male, F=female, O other, W=White, B=Black, H=Hispanic.

Comment *The Table lists 48 SAEs in 41 subjects (2.7%; 41/1,534, with 5 adults [5/330, or 1.5%], and 36 pediatric patients [36/1204, or 3.0%]). However, section 5.1 of the report also states: "Thirty-four (2.2%; 34/1534) patients experienced a total of 39 serious adverse events. The incidence of patients experiencing SAEs in the adult and pediatric populations are 1.2%; 4/330 and 2.5%; 30/1204, respectively." This discrepancy needs to be resolved.*

- Demographic subset analysis:
  - The younger age groups (up to 5 years of age) were more likely to be affected severely by the envenomation, and had the highest incidences of vomiting, pyrexia, rash, rhinorrhea, respiratory distress, and aspiration. AEs that were reported more frequently by older patients included more subjective complaints such as fatigue, pruritus, headache, nausea, and musculoskeletal / peripheral nerve symptoms (e.g., arthralgia, myalgia, hypoesthesia, stiffness, pain).
  - Female patients had higher incidence of AEs than males.
  - Patients >65 years of age had a higher incidence of neurological adverse events than those ≤65 years. However, the elderly population did not have respiratory complaints, compared to >5% of the younger population.
  - Of the 3 major race categories, White / Caucasian patients reported a higher incidence of adverse events than both Hispanics and Other / Native Americans (33% vs. 22% and 18%, respectively). When Hispanics are broken out into U.S. vs. Mexican patients, only 16% (16%; 8/51) of Mexican Hispanic patients reported an AE compared to 23% (23%; 93/401) of U.S. Hispanic patients.
  - Patients weighing 10 kg or less had the highest overall incidence of AEs.

Comment *The demographic subset analyses are post-hoc; they may be useful to generate hypotheses for testing, but are not able to support any conclusions by themselves.*

Clinical Laboratory

There are no consistent patterns of clinical laboratory changes observed in the studies conducted on Anascorp.

Foreign Marketing Experience

Anascorp is registered in Mexico and Colombia under the name Alacramyn®. It has been available in these countries since 1998. The number of patients treated with Alacramyn / Anascorp is not known, but the numbers of vials sold were: ----------(b)(4)----------, for 2008, 2009, and 2010, respectively. In the past 12 years, there were 3 spontaneous adverse events recorded in Mexico:

- One patient was a 23 year old female who received 4 vials of Alacramyn and metamizole. She was discharged 2 hours after treatment. Two days later, she returned to the hospital with an erythematous, pruritic rash on the back of her left hand. After treatment with chlopheniramine, the symptoms resolved without sequelae.
- A 19 year old male received 5 vials of Alacramyn. Thirty minutes later, he developed rash and pruritus. After treatment with an unknown antihistamine, the symptoms resolved without sequlae.
- A patient of unknown age and sex developed chest tightness, palpitations, mild frontal headache, and dyspnea after receiving Alacramyn. There is no further information on treatment or outcome.

Overall Comments on the Updated ISS

- *There have been 1639 patients who received Anascorp in clinical studies, among whom 105 were in AL99/02, which only collected data on adverse event considered to be treatment-related. However, the safety data collection appears to be suboptimal in most of the studies because of the lack of live follow-up visits, and in some of them, lack of clinical laboratory data as well.*
- *The most common adverse events observed in Anascorp clinical studies were vomiting, pyrexia, rash, nausea, pruritus, and headache. However, these symptoms could also be related to envenomation or the use of sedative medication.*
- *Among the reported adverse events, 3 patients experienced acute allergic reactions, and 13 patients had clinical manifestations suggestive of possible serum sickness, but there were no reports of a full serum sickness syndrome. Because of the limitations in follow-up procedures, the true incidence of serum sickness syndrome is uncertain.*
- *The overall safety profile of Anascorp in the treatment of scorpion envenomation appears to be acceptable.*