Clinical Review Memorandum

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

Date: July 8, 2009

To: To File (BLA STN 125335/0)

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

Through: Nisha Jain, Acting Branch Chief, HFM-392

CC: Debra Cordaro, RPM, HFM-370

Applicant: Instituto Bioclón, S.A. de C.V., Mexico, D.F.

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

Subject: Final Review

Recommendations:

A. At this time, Bioclón has not provided substantial evidence to support effectiveness of Anascorp in the treatment of "clinically important signs of scorpion envenomation." I recommend issuing a CR Letter with the following comments to Bioclón.

B. CR Letter Comments

Overall Clinical Comments

1. We note that your study reports in the Clinical Section (Item 8) of this BLA do not bear signatures of the responsible parties. For instance, the pages for "Signature of Sponsor's Responsible Medical Officer" have the wording "not applicable." Please submit signed clinical study reports or documentation that "a responsible medical officer" was responsible for eqch clinical study report.

2. 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. There should be a systematic approach to dosing based on pharmacokinetics, body mass, and the use of concomitant medications in the clinical development program for the product.

3. In all of the clinical studies presented, subject follow-up after discharge is based on telephone interview and not actual 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.

4. 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 benzodiazepams and narcotics. Please address how safety can be adequately evaluated in the presence of these mitigating or confounding factors.

5. In several of the clinical studies, including the pivotal trial, AL-02/03, the decline in serum venom levels by a binding assay after Anascorp treatment is used 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 uninterpretable.

6. 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 has been used for your clinical studies as the one proposed for marketing.

Study AL-02/03

7. The primary efficacy endpoint was to demonstrate resolution of clinically important systemic signs of scorpion envenomation within 4 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.

- As indicated in this protocol, judgment of the resolution of the clinical signs was left at the discretion of the Investigator. 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 out 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.
- 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, as 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, none of the "respiratory compromise" signs are verifiable from the information submitted. Please address the fact that since 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."
- For the treatment of a serious and life-threatening condition, the product should demonstrate effect on mortality or major morbidities. In AL-02/03, no efficacy has been demonstrated 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 a study on subjects with more serious manifestations would be needed if your product claim includes treatment of a serious and life-threatening condition.

8. In the original submission of this protocol to IND (b)(4), at least 12 subjects were proposed as sample size 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 being studied are not life-threatening, such as agitation in the absence of respiratory or other serious manifestations, then 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 (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 has been estimated to be 0.1.

9. The placebo is said to be lyophilized material to be reconstituted with normal saline, but the finalized protocol dated 11/30/03 states it is normal saline (p.7 of protocol, BLA vol 1.8, p.194). Please provide detailed information on the nature of the placebo.

10. Please address the imbalance between treatment arms in:
- the subjects' age (and hence maturity and body mass),
- the time between scorpion sting and administration of test product, and
- the median dose of midazolam sedation administered prior to study enrollment.

11. 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.

12. 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.

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

13. 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 would appear 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.

14. 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, this cannot be considered as 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.

AL-99/02

15. 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).

16. 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".

17. 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.

AL-03/07

18. In this BLA submission, you have not provided an up-to-date study report of AL-03/07. Although you have included an interim report covering the period 5/23/05 to 9/23/06, 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.

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

Executive Summary Instituto Bioclón, S.A. de C.V. submits BLA STN 125335 in support of its new product, Centruroides (Scorpion) Immune F(ab')2 Intravenous (Equine), with tradename of Anascorp® for the indication of management of patients with clinically important signs of scorpion envenomation. The clinical data to support BLA submission consist of one "pivotal" controlled trial (AL-02/03) and 5 open-label studies (AL-99/02, AL-02/04, AL-02/05, AL-02/06, and AL-03/07), together with a chart review retrospective study not involving use of Anascorp (AL-03/06).

AL-02/03 was a double-blind, randomized, placebo-controlled, two-center trial in Arizona in pediatric patients with "clinically important signs" of scorpion envenomation. It enrolled 15 subjects (8 in Anascorp arm and 7 in placebo arm) and showed that the "clinically important signs" subsided within 4 hours in all subjects in the Anascorp arm, but only in 1 of 7 subjects in the placebo arm. However, the patients in this study were mostly enrolled on the basis of "pathological agitation" rather than the more serious and life-threatening manifestations of scorpion envenomation. In addition, patients in the Anascorp arm were younger than those in the placebo arm, and their elapsed time between sting and treatment with test product appears to be shorter than that in the placebo arm. The use of Anascorp was well tolerated in this study.

The open label studies AL-99/02, AL-02/04, AL-02/05, AL-02/06, and AL-03/07 provide additional data to support safety in the use of Anascorp for the management of scorpion envenomation. They have together constituted a database of over 600 subjects (by June 2008) and shown that Anascorp was well tolerated in patients with scorpion envenomation. However, although an attempt was made to identify serum sickness syndrome in AL-03/07 by the Principal Investigator, no firmly established cases have been documented.

In conclusion, this submission has provided clinical data to support the safety of Anascorp despite uncertainties regarding the occurrence of serum sickness on follow-up. However, effectiveness in the management of patients with "important signs of scorpion envenomation" is primarily driven by sings of "pathological agitation", and there are uncertainties in the objectiveness of the evaluations. At this time, I recommend a CR Letter for the applicant to address these uncertainties before final decision on product licensure.

Background

Instituto Bioclón, S.A. de C.V. submits BLA STN 125335 in support of its new lyophilized product, Centruroides (Scorpion) Immune F(ab')2 Intravenous (Equine), with tradename of Anascorp® for the management of patients with clinically important signs of scorpion envenomation.

Anascorp® is a sterile preparation of scorpion venom-specific binding fragments, presented as a lyophilized powder in a 10 ml vial. Each vial of lyophilized white powder contains sufficient F(ab')2 to neutralize ≥150 mouse LD50 of Centruroides venom. Anascorp® antivenom contains Centruroides venom-specific binding fragments, enzymatically derived from equine anticentruroides immunoglobulin. The antibodies are obtained from horses (b)(4)immunized with venom of Ce*ntruroides sp*. and then cleaved by pepsin to form F(ab')2 fragments. The F(ab')2 content is ≥85% and Fab content is ≤7%. The product contains ≤5% whole IgG and -----(b)(4)-----.

Anascorp is available in 10 mL single dose vials of a sterile, pyrogen-free lyophilized powder that appears to be a porous solid white to pale yellow color. When up to 10 mL of saline is added, the powder dissolves rapidly and the resulting liquid appears to be a clear, colorless solution. ----------(b)(4)----------.

In the U.S., envenomation by neurotoxic scorpions occurs in the southwestern States, particularly in Arizona. The sting may produce mild envenomation, more common in adults and consist mainly of local pain. It resolves without specific treatment in the course of hours to days. Severe envenomation, more common in small children, may involve neuromotor hyperactivity, pulmonary edema and ventilatory compromise, occasionally resulting in death (Connor, 1995). This results from the actions of specific ion channel toxins in the scorpion venom, which stimulate or potentiate action potentials throughout the peripheral nervous system. All medically important scorpions in North America fall within one genus (*Centruroides)*, and they contain analogous ion channel toxins.

In 2004, the Toxic Exposure Surveillance System (TESS) reported 14,950 scorpion stings in the United States, with outcome data available for 3,195. Of these, 85% (2,718) were coded as mild, 12.7% (398) as moderate and 0.4% (13) as major. The AAPCC criteria define major effects as life threatening or resulting in significant residual disability or disfigurement; and moderate effects are more pronounced, more prolonged or more systemic in nature than minor effects. No deaths were reported. Six percent of all reported stings (907 of 14,950) were treated in a health care facility (Watson et al., 2005).

Although AAPCC data are not reported geographically, other sources indicate that the great majority of moderate to severe envenomations occur in Arizona (Berg and Tarantino, 1991; Rachesky et al., 1984; Rimsza et al., 1980). A retrospective review of calls to the Arizona Poison and Drug Information Center showed systemic neurotoxicity in 5% of adults and 80% of children under age 2 stung by scorpions (Likes et al., 1984).

There has never been an approved and marketed therapy in the United States for the treatment of scorpion envenomation. The only previously available U.S. scorpion antivenom, a goat whole-IgG immunoglobulin preparation provided since 1965 by Arizona State University under the State of Arizona, ceased being produced in 2000.

Current Submission

This submission is a paper submission, and follows the format of FDA Form 356h. The indication in the proposed package insert is "the management of patients with clinically important signs of scorpion envenomation."

Financial certification and disclosure information (Form 3454) covering the clinical studies in this submission have been submitted in vol 1, pp 174-182 (Item 19), including Form 3455 for Dr. Leslie Boyer.

In vol 1 of this submission, page 184, is the applicant's acceptance letter for Orphan Product Designation (#00-1359). As this application is for an orphan indication, Instituto Bioclón S.A. de C.V. has not attempted to address formally the submission of pediatric assessment data under PREA. However, the majority of subjects in the clinical studies were below 16 years of age, with approximately 80% below 18 years of age.

In a separate submission, Instituto Bioclón S.A. de C.V. requested priority review of this application for Anascorp. There is no currently marketed product licensed for the management of symptomatology arising from scorpion envenomation. It is reasonable to grant this request, because licensure will lead definitely to an improvement over the current management of scorpion envenomation.

Review of Clinical Studies Reported in BLA 125335/0

The clinical data section contains the clinical study reports for these trials:

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)	**554 as of June 08**

[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; may 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.

Study AL-02/03: Prospective, Randomized, Double-Blind, Controlled Study of Anascorp vs. Placebo in Pediatric Patients with Systemic Signs of Scorpion Sting Envenomation [initiated 6/18/04, completed 8/26/05]

Investigator(s): Leslie Boyer, MD; Andreas A. Theodorou, MD

Study center(s): The University of Arizona Health Sciences Center, Arizona Poison and Drug Information Center, Tucson, Arizona; Tucson Medical Center, Tucson, Arizona

Objectives:
The primary efficacy endpoint was to demonstrate resolution of clinically important systemic signs of scorpion envenomation within 4 hours for patients treated with Anascorp.

Secondary endpoints were to demonstrate that -
(1) patients treated with Anascorp will require significantly less benzodiazepine sedation for control of agitation than controls; and
(2) venom blood levels will decrease within one hour after Anascorp treatment, while the placebo group will have elevated blood venom levels for several hours.

Design: Prospective, randomized, double-blind, controlled, multicenter Phase 3 study to demonstrate the efficacy and safety of Anascorp in the treatment of systemic manifestations of scorpion sting. A minimum of 12 patients were to be randomized in a 1:1 treatment ratio of Anascorp to placebo. Male and female patients 6 months to 18 years of age who presented for emergency treatment within 5 hours of scorpion sting with clinically important systemic signs of severe scorpion sting envenomation were included.

Study Flow Chart*

Procedure	Screen	Baseline	Treatment Period	After Treatment Initiation			Discharge	7 Days 14 Days Follow-Up
				1 Hr	2 Hrs	4 Hrs		
Informed Consent	X							

Inclusion/ Exclusion	X							
Medical History / PE Demographics Scorpion Information		X						
Severity Evaluation[1,2]		X		X	X	X	X[2]	
Vital Signs[2]		X		X	X	X[2]	X[2]	
Physical Assessment and Symptom Assessment[2]		X		X	X	X[2]	X[2]	
Pulse Oximeter[3]		X[3]	X	X	X	X	X	
Sedation Protocol[4]			X	X	X	X	X	
Study Drug Infusion[5]			X[5]					
Laboratory Tests: Hematology Chemistry Urinalysis		X				X		
Laboratory Tests: Venom level and Antivenom level		X		X		X		
Follow-Up Questionnaire								X
Concomitant Medications		X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X

*Reflects changes per Protocol Amendment 2 (3 September 2004).

1. Refer to Appendix 1 in protocol (Appendix 16.1.1) for Severity Evaluation of scorpion envenomation
2. Vital signs, severity evaluation, and physical assessment and symptom assessments were to be performed for all study patients at 4-hour discharge. If patient remained hospitalized after the 4-hour observation, these assessments were to be performed at hospital discharge or at 24 hours after treatment if hospitalization continued
3. Pulse oximeter initiated at baseline, prior to start of study drug infusion.
4. Refer to Appendix 3 in protocol (Appendix 16.1.1) for sedation protocol procedures.
5. Study Drug Infusion Procedures: Upon enrollment into the study, patient received 3 vials of Anascorp and was evaluated 1 hour after start of study drug infusion (blood was drawn for venom and anti-venom levels, vital signs, severity evaluation, physical and symptom assessments). During the following 3 hours, midazolam drip was continued, if indicated, for agitation. If patient was symptom free 1 hour after study drug treatment, patient remained in clinic for the 2 and 4 hour observations prior to discharge. Patients still requiring midazolam sedation and/or exhibiting clinically important systemic signs of scorpion envenomation were given standard of care for the duration of the clinical symptoms. Blood was drawn for venom and anti-venom levels at 4 hours. Patient was evaluated at 4 hours and time of discharge or at 24 hours, if hospitalization continued (refer to Flow Chart and Section 9.1 Overall Study Design and Plan: Description).

Patients who arrived at the participating center presenting with a scorpion sting were evaluated with respect to the inclusion/exclusion criteria. Because they were treated on an emergency basis, informed consent was obtained as soon as a scorpion sting diagnosis had been verified and the inclusion/exclusion criteria reviewed. Only patients with “clinically important systemic signs of severe scorpion sting envenomation” were included in the study; patients with mild or moderate envenomations were not included. Baseline measures included severity evaluation of the scorpion sting, vital signs (blood pressure, heart rate, temperature, and respiration), physical and symptom assessments, medical history, physical examination, concomitant medications, scorpion sting information, demographics, and laboratory tests (hematology, chemistry, venom and antivenom levels, and urinalysis). If the urine sample could not be obtained at entry, the patient was not excluded from the study. Continuous pulse oximetry was initiated.

If pathological agitation was severe, midazolam sedation (standard of care) was initiated when the treating physician deemed it necessary. Standard of care was not withheld pending study drug readiness. Concomitant medications were allowed as needed. Midazolam dosing followed an agreed-upon protocol (see below).

Prior to discharge at 4 hours, repeat lab work, severity evaluation, physical and symptom assessments, and vital signs were completed. All patients received these assessments whether they were discharged 4 hours after receiving study drug or at a later time. Patients still requiring midazolam sedation and/or manifesting clinically important systemic signs of scorpion envenomation were treated with standard of care for the duration of clinical symptoms. Those remaining for extended care underwent final study assessments (severity evaluation, vital signs, physical and symptom assessments) at time of hospital discharge or at 24 hours after study drug infusion if hospitalization continued. No additional laboratory testing was performed beyond the 4-hour assessment period

All patients were monitored for signs and symptoms of adverse events, including acute hypersensitivity reactions (anaphylactic and/or anaphylactoid reactions) and delayed serum sickness. All patients who received study drug were included in the final analyses.

All patients who participated in the study were contacted by phone 7 and 14 days after treatment by the research nurse for a follow-up interview to assess symptoms suggestive of ongoing venom effect, delayed serum sickness, and any other adverse events reported by the patient.

Eligibility Criteria:
Inclusion Criteria
• Males and females 6 months to 18 years of age
• Presenting for emergency treatment with systemic signs of scorpion sting envenomation
• Signed written Informed Consent by patient or legal guardian
• No participation in a clinical drug trial within the last month or concomitantly

Exclusion Criteria
• Allergy to horse serum
• Use within the past 24 hours of drugs expected to alter immune response: H1 or H2 blockers, corticosteroids, epinephrine*
• Use of any antivenom within the last month or concomitantly
• Underlying medical conditions that significantly alter immune response
• Allergy to midazolam
• Pregnant and nursing women (sic)
• > 0.3 mg/kg of body weight of midazolam administered during the hour prior to study drug infusion
• Concurrent medical condition involving a baseline neurologic status mimicking envenomation (chorea, tardive dyskinesia, uncontrolled epilepsy)

The protocol stipulates that only patients with clinically important systemic signs of scorpion sting envenomation were supposed to be included, and baseline measures were to include severity evaluation of the scorpion sting. The study report indicates that by most objectively evaluable components of grading scales commonly in use in the U.S. and Mexico (e.g., Curry scale), these patients met criteria for severe envenomation. Patients with mild or moderate envenomations were not included.

Comment The "Severity Evaluation" document in protocol's Appendix 1 does not grade severity and only lists "clinically important systemic signs of scorpion envenomation" as (1) respiratory compromise: pulmonary edema, incoordinate ventilatory efforts, pulse oximeter <90% and upper airway compromise due to excessive secretion, and (2) pathological agitation: abnormal eye movements, thrashing of limbs, loss of ability to ambulate and fasciculation. Both pulmonary edema and fasciculations are not considered "clinically important" unless other signs are present.

Test Products, Dose and Mode of Administration, Batch Number: A nurse or pharmacist not involved in patient evaluation prepared the study drug (Anascorp or placebo): 3 vials Anascorp or placebo were administered in a total volume of 50 mL IV via peripheral vein with the use of infusion pump, over ≥10 minutes, or as permitted by IV access (net pump rate of 300 mL/hr). Standard of care precautions during infusion of serum products, including anthistamines, corticosteriods, and epinephrine, were available but not administered unless clinically indicated. During infusion, the patient was monitored for changes in heart rate, blood pressure, respiratory distress, oxygen saturation, and cutaneous manifestations of allergic reaction. The lot number used for the study drug was B-2M-01.

For an individual patient, the study started at hospital admission and ended at time of hospital discharge, or at 24 hours after start of study drug infusion if hospitalization continued. Patients off midazolam and no longer manifesting clinically important systemic signs of envenomation were discharged at 4 hours after receiving study drug, or 2 hours following cessation of midazolam drip, whichever occurred later.

Patients still requiring midazolam sedation and remaining for extended care underwent final study assessments at the time of discharge or at 24 hours after receiving study drug, if hospitalization continued. The outcome at 7 days and 14 days after discharged was assessed by telephone interview.

Lyophilized placebo to be reconstituted with normal saline was provided for administration in a similar manner. The lot number used for placebo was -----(b)(4)-----.

Comment The placebo is said to be lyophilized material to be reconstituted with normal saline, but the protocol dated 11/30/03 says it is normal saline in its Study Outline (p.7 of protocol, BLA vol8, p.194). The real nature of the placebo needs to be substantiated.

If at any time urticaria, respiratory distress, or changes in vital signs suggestive of acute allergic reaction were observed, infusion was stopped and appropriate interventions made, in accordance with standard of care, and both the investigator and the attending physician were notified. As to midazolam:

- Patients off midazolam sedation after receiving study drug and no longer manifesting "clinically important systemic signs" of scorpion envenomation were discharged at 4 hours, or 2 hours following cessation of midazolam drip, whichever occurred later. All patients who had received midazolam continued to be monitored for sedation and for renewed agitation for at least 2 hours following cessation of the drip.
- Patients still requiring midazolam sedation and/or manifesting clinically important systemic signs of scorpion envenomation were treated with standard of care for the duration of clinical symptoms.
- Patients remaining for extended care underwent final study assessments at time of hospital discharge or at 24 hours after study drug infusion if hospitalization continued.

No additional laboratory testing was performed beyond the 4-hour assessment period.

Standard of Care
If, upon admission or any time thereafter, pathological agitation was severe, IV midazolam sedation (standard of care) was initiated when the treating physician deemed it necessary.

For the first 60 minutes, the patient was evaluated not less than every 15 minutes and treated with midazolam (0.05 mg/kg to 0.2 mg/kg per dose IV) as needed to reduce agitation. A continuous midazolam infusion was subsequently initiated at a dose of 0.1 mg/kg/hour, when appropriate. During the continuous infusion, the patient was evaluated not less than every 15 minutes. At each interval the patient was to be assessed and had subsequent additional midazolam (standard of care) dose administration (if any) based on an agreed upon protocol in routine use by pediatric intensivists at the treatment sites.

The midazolam (standard of care) dose was based on an agreed-upon protocol in routine use by pediatric intensivists at the treatment sites, as shown below. Changes in the treatment actions detailed in the following table were allowed if the treating physician deemed clinically necessary.

Midazolam Treatment Based on Patient Assessment	
Patient Assessment	**Treatment Action**
Continued to have pathological agitation but was calm and not at immediate risk of injury (adequately controlled without excessive sedation)	Continued current midazolam infusion dose
Continued to have pathological agitation and was severely frightened or appeared at risk of physical injury (agitation was not adequately controlled)	IV bolus of midazolam (0.05 mg/kg – 0.2 mg/kg) administered, and continuous infusion increased by 0.05 mg/kg/hour
Difficult to arouse, no respiratory depression (too sedated)	Infusion decreased by 0.05 – 0.1 mg/kg/hour
Had ventilatory depression regardless of systemic signs of envenomation	Midazolam infusion immediately stopped and airway managed as needed
No pathological agitation in past 15 minutes	Midazolam discontinued

Selection of Doses in the Study The selection of Anascorp dose (3 vials) was based on a randomized, double-blind, variable dose comparison of Anascorp with Birmex, an antivenom produced by

the Mexican government (AL-99/02). The choice of Anascorp dose used in this study was flexible, with as much study medication allowed as was deemed clinically necessary. Of the 105 Anascorp recipients in this study, 90% recovered after receiving three or fewer vials of Anascorp.

Comment AL-99/02 was conducted primarily to compare Anascorp and Birmex, and not intended to be a formal dose-ranging study. The rationale of using 3 vials has not been properly established.

Efficacy and Safety Measurements Assessed
Data collected at baseline prior to study drug infusion included the following:

1. Demographic information (age, race, sex, ethnic background)
2. Medical history (including current and past scorpion sting information, current concomitant medications, prior antivenom use)
3. Physical examination (including head, eyes, ears, nose, and throat; lymphatics; bronchopulmonary; cardiovascular; gastrointestinal; genitourinary; neurologic; musculoskeletal; dermatologic; psychological; and other systems)
4. Severity evaluation for respiratory compromise and pathological agitation
5. Vital signs (blood pressure, heart rate, temperature, respiratory rate, height, and weight)
6. Physical assessment (sialorrhea, abdominal distention, vomiting, priapism, cranial nerve dysfunction [blurred vision, wandering eye movements, hypersalivation, trouble swallowing, tongue fasciculation, problems with upper airway, slurred speech], somatic skeletal nerve dysfunction [jerking extremities, restlessness, severe involuntary shaking and jerking that may be mistaken for a seizure disorder])
7. Symptom assessment (pain at sting site, pain remote from the sting site, paresthesias remote from sting site, nasopharyngeal pruritis, pharyngeal foreign body sensation, transient blindness, retrosternal pain, dyspnea)
8. Laboratory tests (hematology, chemistry, urinalysis, serum venom level)

Safety evaluations included adverse events (AEs), vital signs, clinical laboratory assessments (hematology, chemistry, and urinalysis), medical history, and physical examinations. All patients were monitored for acute hypersensitivity reactions (anaphylactic and/or anaphylactoid reactions), ongoing venom effect, and delayed serum sickness. They were contacted by telephone 7 and 14 days after Anascorp treatment for symptoms suggestive of ongoing venom effect, delayed serum sickness and other AEs. In the event that symptoms or AEs were discovered, patients were referred for appropriate care and AE forms completed.

Efficacy Variables
The primary efficacy variable was the resolution of "clinically important signs of scorpion envenomation" within 4 hours for patients treated with Anascorp. Clinically important components of the scorpion envenomation syndrome were divided into Pathological Agitation and Respiratory Compromise categories for separate documentation at each time point.

- Components of Pathological Agitation: abnormal eye movements, thrashing of limbs, loss of ability to ambulate, and presence of muscle fasciculations. All but fasciculations were considered clinically important and therefore contributed to the overall toxicity determination.
- Components of respiratory compromise: pulmonary edema, incoordinate ventilatory effort, upper airway compromise, hypoxemia (pulse oximetry reading < 90% saturation), and other respiratory compromise. All but pulmonary edema contributed to the overall toxicity determination. Pulmonary edema was considered a supporting finding only, excluded from the assessment of treatment efficacy because prolonged time to resolution of pulmonary edema might in theory have exceeded the binding phase of antivenom treatment, thereby obscuring therapeutic effect.

The primary endpoint was defined as a binary variable (syndrome present or syndrome absent) based on the presence or absence of key respiratory and neuromotor components. *The resolution of the syndrome was determined by study physician and nurse at each time point, with a primary study endpoint at 4 hours.* This investigator judgment was derived from review of the Respiratory and Pathological Agitation data, in the context of concurrent patient management. *Investigators were permitted to determine that*

toxicity was present, in the absence of overt pathological agitation, if ongoing dosing of sedative before and after the study time point indicated that the underlying movement disorder was still present but under transient pharmacological control. Similarly, they were permitted to judge that toxicity was not present, if the sole indicator of the syndrome was readily explained by a comorbid condition (e.g., if respiratory failure was present due to prior aspiration, but other ongoing signs of direct toxicity were no longer present).

Comment The choice of the primary endpoint (i.e., presence or absence of the medically important signs of envenomation 4 hours following study baseline) was based on results from Mexican clinical data (AL-99/02) demonstrating that nearly all patients experienced clinical recovery by 3 hours after start of treatment. Because data from published U.S. series were insufficient for use as formal historical controls, Anascorp was compared to Placebo in this study. As indicated in this protocol, the Investigator is given liberal leeway in judgment of the resolution of the clinical signs.

The secondary endpoint (dose of midazolam administered to patients following study enrollment) was chosen as a consequence of the clinical-care requirement suggested by the pediatric intensivists at both treatment sites. It was reasoned that successfully-treated children might require far less sedation than Placebo recipients. An additional secondary endpoint (venom blood levels) was chosen to provide a surrogate measure of treatment success. On the basis of quantitative serum venom levels obtained in study AL-99/02, it was predicted that venom levels would decrease within 1 hour after study enrollment among Anascorp recipients, but that Placebo recipients would continue to manifest elevated venom levels for many hours while the clinical syndrome persisted. For all patients, 1.5 ml of blood was drawn at baseline and at 1 and 4 hours after start of initial study drug infusion. Samples were sent to the ----------(b)(4)---------- for venom and antivenom measurements.

> Plasma venom and antivenom levels were determined using an ----------(b)(4)---------- for *Centruroides sculpturatus venom and F(ab')2 fragment from Anascorp antivenom.* Analyses were obtained using validated ----------.

Comment The antivenom assay is a binding assay for equine F(ab')2 and may not be demonstrating activity vs venom in the serum.

Statistical and Analytical Plans
The Statistical Analysis Plan is dated 22 September 2005.

General Analysis Considerations and Sets Continuous variables were summarized using counts, means, medians, standard deviations, minimums, and maximums. Categorical variables were summarized using frequencies and percentages.

The ITT population included all patients who were randomized, received study drug, and had at least one post-baseline evaluation of systemic signs of scorpion envenomation. The safety population included all patients who were randomized and received any study drug.

Patient Disposition, Demographics, and Baseline Characteristics Patient disposition was tabulated and summarized for all randomized patients by treatment group. Summaries include the number of randomized patients, the number of patients completing the study, and the primary reason for discontinuation. Data listings are presented by site and patient.

Demographic variables (age, sex, and race) and baseline characteristics (weight, height, medical history abnormalities, physical examination abnormalities, vital signs) were summarized by treatment group. At baseline, the patient's medical history was recorded before study drug was infused. Details were provided for any abnormalities that did exist.

Scorpion sting information obtained at baseline included (a) the date and time of scorpion sting, (b) the time of onset of clinically important systemic signs of scorpion envenomation, (c) date and time of arrival at hospital, (d) the occurrence of any prior scorpion stings, (e) prior use of antivenom, (f) identification of body part of scorpion sting, (g) whether the scorpion was collected, (h) whether the scorpion species had been identified, and (i) the location where the patient was stung.

Primary Efficacy Analysis The primary endpoint was the resolution of clinically significant systemic signs of scorpion envenomation within 4 hours. The systemic sign responses were presented using frequencies and percentages. Anascorp was to be declared clinically superior to placebo if the Anascorp success percentage was ≥20% than the Placebo success percentage.

Comment No formal hypothesis testing has been stated in the statistical plan. It is also unclear what is meant by "clinically superior" if the success percentages differ by ≥20%. The difference should be based on the distance between the lower 95% C.I. limit for the Anascorp success rate and the upper limit for the Placebo rate. The clinical significance of the 20% difference would depend on the severity of the condition being treated. With a hard endpoint for a serious condition, such as death or stroke, even a small difference may be clinically meaningful. If the endpoint is vague and the venom toxicities exhibited by the subjects being studied are not life-threatening, such as agitation in the absence of respiratory or other serious manifestations, then there should be a much bigger difference in order to be certain of a clinically meaningful therapeutic benefit.

Secondary Efficacy Analyses

- Midazolam dose was calculated and evaluated as a secondary efficacy endpoint. Total dose, maximum rate per hour, and duration of midazolam use in Anascorp- and Placebo-treated patients were compared and examined for treatment effect.
- Venom blood levels would decrease within one hour after Anascorp treatment, while the placebo group would have elevated blood venom levels for several hours. Within the Anascorp-treated group, a paired t-test was used to compare the serum blood levels at 4 hours with baseline levels. Within the placebo-treated group, the serum blood levels were clinically examined for elevation. The serum venom levels were summarized at each hourly evaluation. Serum reaction responses were categorized and summarized.
- Patient symptoms (respiratory compromise, pathologic agitation, physical assessments, and symptom assessments) were presented at baseline. Baseline responses were categorically compared with responses at each hour using frequencies and percentages. At each hourly evaluation, the symptoms were tabulated and summarized.

Safety Analysis All randomized patients who received any study drug were included in the safety analyses. Patient reasons for premature discontinuation of the study were listed and categorized.

Follow-Up Evaluations At 7 days and 14 days post-hospital discharge, telephone contact was made with the patient, parent/guardian, or other person regarding possible rehospitalization of the patient (a reportable SAE) or the development of specific symptoms since hospital discharge. The list-specific symptoms included itching, rash, petechiae, arthralgia, myalgia, nausea, vomiting, dehydration, chest pain, hematuria, and possibility of serum sickness. The responses included "no" and "yes." If "yes," the details were documented on the adverse event form.

Comment There is no provision as to in how much detail serum sickness would be sought, and if diagnosed, how it would be managed.

Sample Size At least 12 evaluable patients were to be enrolled in the study in a 1:1 treatment ratio. This sample size was determined based on the hypothesis that at 4 hours, all patients receiving Anascorp would be free of symptoms while at the same timepoint, no patients in the placebo group would be free of symptoms. Although the study was not designed with this statistical objective owing to the small sample sizes expected in the participating sites, this rationale was the basis for enrolling a minimum of 12 patients.

Changes in the Conduct of the Study

The original protocol dated 30 November 2003 was amended three times.

- Protocol Amendment #1 (dated 22 June 2004): The number of vials contained in each carton was changed from (b)(4) vials to 3 vials to accurately reflect the protocol design.

- Protocol Amendment #2 (dated 03 September 2004): To clarify that all discharge assessments were to be performed and documented for all study patients at the 4-hour time point. These assessments included severity evaluation, vital signs, physical and symptom assessments, and laboratory tests (hematology, chemistry, urinalysis, venom and anti-venom levels). If the patient remained hospitalized, the following assessments were to be conducted at hospital discharge or at 24 hours after treatment: severity evaluation, vital signs, and physical and symptom assessments. No additional laboratory testing was required at the time of discharge or at 24 hours after treatment, if hospitalization continued.

- Protocol Amendment #3 (dated 14 December 2004): The exclusion criterion of "use within the past 24 hours of drugs expected to alter immune response, H1- or H2- blockers and corticosteroids" was removed to allow the use of H1- or H2- blockers and corticosteroids within the 24 hour period prior to hospital admission. The basis for this amendment was low patient enrollment due to prior use of antihistamines and/or corticosteroids.

Comment Because antihistamines can inhibit acute allergic reactions, a full evaluation of allergic reactions to study drug in the acute safety period may be difficult in patients receiving these agents prior to hospital admission.

DISPOSITION OF PATIENTS

Randomization of Patients

Anascorp (N=8)	Placebo (N=7)
----------(b)(6)----------	----------(b)(6)----------

Patient Disposition: All Randomized Patients

Disposition Parameters	Treatment Groups		Total N=15, n (%)
	Anascorp N=8, n (%)	Placebo N=7, n (%)	
Safety Analysis Population[1]	8 (100)	7 (100)	15 (100)
ITT Population[2]	8 (100)	7 (100)	15 (100)
Completed Study[3]			
Yes	8 (100)	6 (86)	14 (93)
No	0 (0)	1 (14)	1 (7)
Primary Reason for Discontinuation			
Lost to follow-up	0 (0)	1[4] (14)	1 (7)

1 All randomized patients who received ≥ 1 dose of study treatment, 2 All randomized patients, 3 Patient completion of study included Day 14 follow-up. 4 One patient in the Placebo group (Patient #(b)(6)) discontinued the study due to inability to reach her parents for 7 and 14 day follow-up evaluations.

Two investigational sites were initiated and enrolled patients in the study:

Dr. Leslie Boyer (11 subjects)
The U of Arizona Health Sciences Center
Arizona Poison and Drug Information Center
1501 N Campbell Ave
Tucson, AZ 85724

Dr. Andreas A. Theodorou (4 subjects)
Tucson Medical Center
5301 E Grant Road
Tucson, AZ85712

PROTOCOL DEVIATIONS

Two patients (13%), both in the Anascorp group, were identified as having protocol deviations. In both patients, the deviation was inadvertent failure to record patient observations every 15 minutes during the first 1 hour despite continuous observation for the first 4 hours after envenomation.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic Characteristics

Disposition Parameters	Treatment Groups	
	Anascorp (N=8)	Placebo (N=7)
Age (years)		
Mean (SD)	2.0 (1.8)	4.3 (3.0)
Min, Max	1, 6	1, 10
Sex, n (%)		
Male	4 (50.0)	3 (42.9)
Female	4 (50.0)	4 (57.1)
Race, n (%)		
African American/Hispanic	1 (12.5)	0 (0.0)
Black	0 (0.0)	1 (14.3)
American Indian	1 (12.5)	0 (0.0)
Caucasian	3 (37.5)	4 (57.1)
Hispanic	3 (37.5)	1 (14.3)
Native American	0 (0.0)	1 (14.3)
Weight (kg)		
Mean (SD)	11.9 (4.0)	18.8 (11.7)
Min, Max	8,20	8, 42
Height (cm)*		
Mean (SD)	80.7 (4.67)	136.0 (0.0)
Min, max	77, 84	136-136

*Anascorp (N=2), Placebo (N=1)

Comment Patients in the Anascorp group were younger (mean age 2.0 vs 4.3 years) and correspondingly smaller than those in the Placebo group. How this might have impacted evaluation has not been addressed.

Baseline Characteristics

- The distribution of medical history abnormalities was similar between patients in the Anascorp and Placebo groups, with abnormalities of the head, eyes, ears, nose, and throat the most common (50.0% for Anascorp recipients vs 57.1% for Placebo recipients).
- The distribution of physical examination abnormalities was similar between groups as well, with 100.0% of patients in each group experiencing baseline neurological abnormalities.
- Baseline vital signs were comparable between treatment groups, although mean systolic blood pressure, diastolic blood pressure, and heart rate were slightly higher in the Anascorp group compared with the Placebo group.
- None of the patients had experienced prior scorpion stings or previously used antivenom. The scorpion was collected and identified in one case (Patient #(b)(6) in Placebo group - *Centruroides Exilicada*).
- Anascorp recipients presented to the hospital and for study enrollment (134.9 and 207.9 minutes) slightly sooner than did Placebo recipients (149.0 and 223.4 minutes). However, patients in both groups developed symptoms at a similar time following scorpion envenomation (29.2 vs 30.0 minutes).
- Overall, the baseline severity of signs of scorpion envenomation between groups was similar.

Baseline Severity of Scorpion Envenomation and Prior Midazolam use

Characteristic	Treatment Groups	
	Anascorp N=8	Placebo N=7
Respiratory Compromise, n (%)		
Pulmonary edema	0 (0.0)	0 (0.0)
Incoordinate ventilatory efforts	0 (0.0)	0 (0.0)
Upper airway compromise	1 (12.5)	0 (0.0)
Pulse oximeter < 90%	1 (12.5)	1 (14.3)

Other respiratory compromise Any respiratory compromise	0 (0.0) 2 (25.0)	0 (0.0) 1 (14.3)
Pathological Agitation Abnormal eye movement Thrashing of limbs Loss of ability to ambulate Fasciculation	 8 (100.0) 8 (100.0) 2 (25.0) 4 (50.0)	 7 (100.0) 7 (100.0) 3 (42.9) 5 (71.4)
Total dose of midazolam before study drug infusion (mg/kg) Mean (SD) Median Min, Max	 0.2 (0.1) 0.2 0.1, 0.4	 0.5 (0.7) 0.3 0.1, 2.0

Comment The inclusion criteria required presence of systemic signs of envenomation, and so milder cases with only local effect of the venom would not have been enrolled. The symptomatology considered as clinically important in this study is primarily based on respiratory compromise and pathological agitation, but at baseline, most of the envenomation "severity" is due to pathological agitation, which was to include "abnormal eye movement", limb thrashing, "loss of ability to ambulate", and fasciculation (if other signs coexist). These signs are nonspecific and not totally objective. Since patients could have already received midazolam prior to presentation, and were allowed to be administered midazolam after test product infusion, the utility of pathological agitation signs for primary evaluation is not optimal.

Other Baseline Physical Assessment*

	Sialorrhea	Abnormal Distention	Vomiting	Priapism	"Cranial Nerve Dysfunction"	"Somatic Skeletal Nerve Dysfunction"
Anascorp (N=8)	2 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (100.0%)	8 (100.0%)
Placebo (N=7)	3 (42.9%)	2 (28.6%)	2 (28.6%)	0 (0.0%)	7 (100.0%)	7 (100.0%)

*All patients with baseline physical assessments.

Comment This degree of baseline dysfunction in physical assessment is consistent with this degree of severe envenomation. However, it is unclear how the cranial or somatic skeletal nerve dysfunction manifested in the study subjects from such description. The applicant should be asked to provide narratives from the study subjects for further assessment.

Prior to hospital admission, six Anascorp recipients (75%) and six Placebo recipients (85.7%) used concomitant medications. The most common concomitant medications were midazolam (7 patients), acetaminophen (3 patients), and ibuprofen (2 patients). In addition, after the removal of the exclusion criteria regarding use of H1 or H2 blockers or corticosteroids within the previous 24 hours per Protocol Amendment #3, 3 patients (2 Anascorp recipients and 1 Placebo recipient) were enrolled who had received the H1 blocker diphenhydramine prior to hospitalization. Sedatives other than midazolam used during the pre-enrollment period included lorazepam in 1 patient who received Anascorp and diazepam, lorazepam, and meperidine in 3 patients who received Placebo.

The median dose of midazolam sedation administered prior to study enrollment was higher in the placebo group (0.2 mg/kg for Anascorp recipients vs 0.3 mg/kg for Placebo recipients), and so was the mean dose (0.2 ± 0.1 mg/kg for Anascorp group and 0.5 ± 0.7 mg/kg for placebo group).

Comment The applicant attributes the difference to the effects of two patients in the Placebo group who were under medical care long enough to receive higher doses prior to study enrollment. Patient #(b)(6) had received two midazolam doses (5.4 mg and 8.6 mg) and Patient #(b)(6) had received 4 mg midazolam prior to study enrollment. Midazolam use in the hour immediately prior to receiving study drug was comparable between groups and was in all cases at or below 0.3 mg/kg, the maximum dose permitted by study criteria, for safety reasons. It is noted that although the time between envenomation and symptom onset was similar between arms, the Placebo recipients took longer to present to hospital and enroll in

the study. The elapsed time between envenomation and product administration has not been presented. There is potential for further imbalance between arms if this elapsed time shows disparity.

Concomitant Medications Concomitant medications administered during hospitalization to patients in the *Anascorp* group included single doses of racemic epinephrine for stridor (Patient #(b)(6)) and acetaminophen with codeine for pain (Patient #(b)(6)). Among *Placebo* recipients, Patient #(b)(6)received a single dose of permethrin for head lice and Patient #(b)(6)received a single dose of acetaminophen for restlessness.

EFFICACY RESULTS

Efficacy analyses were conducted on the ITT population for all parameters. Of the 15 patients randomized to the study, all were included in the ITT analysis set.

Analysis of Efficacy

1. Primary Efficacy Variable

The overall assessment of clinically significant signs represents a combination of the Pathological Agitation and Respiratory data as assessed by the investigator. Overall, none of the Anascorp-treated patients were considered to have clinically significant signs of scorpion envenomation 4 hours after treatment compared with 85.7% of Placebo-treated patients.

Comment The applicant suggests that because 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, the greater volume of distribution of scorpion venom might have contributed to earlier resolution than in other Placebo-treated subjects. The investigator attributed jerky eye movements occurring in this patient at the 4-hour time point to the effect of midazolam.

Overall Assessment of Clinically Significant Signs of Scorpion Envenomation

Resolution of Symptoms	Treatment Groups	
	Anascorp (N=8)	Placebo (N=7)
Baseline, n (%)	8 (100.0)	7 (100.0)
Hour 1, n (%)	4 (50.0)	7 (100.0)
Hour 2, n (%)	1 (12.5)	6 (85.7)
Hour 4, n (%)	0 (0.0)	6 (85.7)
24 Hour Discharge, n (%)	0 (0.0)	0 (0.0)

Comment At the 4-hr time-point, 0 of 8 Anascorp recipients and 6 of 7 Placebo recipients showed "clinically important signs of envenomation" under a 15-minute overall assessment by the physician. In fact, even at the 2-hr time-point, the difference between the Anascorp arm and the placebo arm was 1 in 8 vs 6 in 7. However, these data are not consistent with the tables below on pathological agitation and respiratory compromise, which shows 5 placebo subjects having had evidence of pathological agitation and none of them showing respiratory compromise. For further discussion, see below.

Of the components of pathological agitation, *limb thrashing* and *abnormal eye movements* were present in 100.0% of patients in both groups at baseline, despite prior use of benzodiazepine sedation in all cases. These findings resolved within 4 hours for all patients in the Anascorp-treated group, but were still present at 4 hours in 57.1% of Placebo-treated patients. *Loss of ability to ambulate* resolved within 4 hours for all patients in both groups. Overall, any pathological agitation (except fasciculation) was present in all patients in both groups at baseline, but resolved in 50.0% and 100.0% of Anascorp-treated patients by 1 hour and 4 hours after study drug infusion, respectively. In contrast, five Placebo-treated patients (71.4%) continued to experience any pathological agitation (except fasciculation) at 4 hours after infusion.

Clinically Significant Signs of Scorpion Envenomation: Pathological Agitation

Characteristic	Treatment Groups	
	Anascorp N=8	Placebo N=7
Abnormal eye movement, n (%)		
Baseline	8 (100.0)	7 (100.0)

Hour 1	2 (25.0)	6 (85.7)
Hour 2	1 (12.5)	5 (71.4)
Hour 4	0 (0.0)	4 (57.1)
24 Hour Discharge	0 (0.0)	0 (0.0)
Thrashing of limbs, n (%)		
Baseline	8 (100.0)	7 (100.0)
Hour 1	3 (37.5)	5 (71.4)
Hour 2	1 (12.5)	6 (85.7)
Hour 4	0 (0.0)	4 (57.1)
24 Hour Discharge	0 (0.0)	0 (0.0)
Loss of ability to ambulate, n (%)		
Baseline	2 (25.0)	3 (42.9)
Hour 1	0 (0.0)	1 (14.3)
Hour 2	0 (0.0)	1 (14.3)
Hour 4	0 (0.0)	0 (0.0)
24 Hour Discharge	0 (0.0)	0 (0.0)
Fasciculation, n (%)		
Baseline	4 (50.0)	5 (71.4)
Hour 1	1 (12.5)	3 (42.9)
Hour 2	1 (12.5)	1 (14.3)
Hour 4	0 (0.0)	1 (14.3)
24 Hour Discharge	0 (0.0)	0 (0.0)
Any pathological agitation (except fasciculation), n (%)		
Baseline	8 (100.0)	7 (100.0)
Hour 1	4 (50.0)	6 (85.7)
Hour 2	1 (12.5)	6 (85.7)
Hour 4	0 (0.0)	5 (71.4%)
24 Hour Discharge	0 (0.0)	0 (0.0)

For components of respiratory compromise, one patient experienced *upper airway compromise* (#(b)(6), Anascorp arm), two patients experienced *pulse oximeter < 90%* (#(b)(6), Anascorp arm, and #(b)(6), Placebo arm), and one patient experienced other *respiratory compromise* (respiratory acidosis experienced by a Placebo-treated patient, #(b)(6)).

Clinically Significant Signs of Scorpion Envenomation: Respiratory Compromise

Characteristic	Treatment Groups	
	Anascorp N=8	Placebo N=7
Pulmonary edema, n (%)		
Baseline	0 (0.0)	0 (0.0)
Hour 1	0 (0.0)	0 (0.0)
Hour 2	0 (0.0)	0 (0.0)
Hour 4	0 (0.0)	0 (0.0)
24 Hour Discharge	0 (0.0)	0 (0.0)
Incoordinate ventilatory efforts, n (%)		
Baseline	0 (0.0)	0 (0.0)
Hour 1	0 (0.0)	0 (0.0)
Hour 2	0 (0.0)	0 (0.0)
Hour 4	0 (0.0)	0 (0.0)
24 Hour Discharge	0 (0.0)	0 (0.0)
Upper airway compromise, n (%)		
Baseline	1 (12.5)	0 (0.0)
Hour 1	1 (12.5)	0 (0.0)
Hour 2	0 (0.0)	0 (0.0)
Hour 4	0 (0.0)	0 (0.0)
24 Hour Discharge	0 (0.0)	0 (0.0)
Pulse oximeter < 90%, n (%)		
Baseline	1 (12.5)	1 (14.3)
Hour 1	0 (0.0)	0 (0.0)
Hour 2	0 (0.0)	0 (0.0)
Hour 4	0 (0.0)	0 (0.0)

24 Hour Discharge	0 (0.0)	0 (0.0)
Other respiratory compromise, n (%)		
Baseline	0 (0.0)	0 (0.0)
Hour 1	0 (0.0)	1 (14.3)
Hour 2	0 (0.0)	0 (0.0)
Hour 4	0 (0.0)	0 (0.0)
24 Hour Discharge	0 (0.0)	0 (0.0)
Any respiratory compromise (except pulmonary edema), n (%)		
Baseline	2 (25.0)	1 (14.3)
Hour 1	1 (12.5)	1 (14.3)
Hour 2	0 (0.0)	0 (0.0)
Hour 4	0 (0.0)	0 (0.0)
24 Hour Discharge	0 (0.0)	0 (0.0)

Comments

1. The signs of "respiratory compromise" were observed in only 3 patients (2 active, 1 placebo) and subsided within 2 hours. In fact, the terms "upper respiratory compromise", "other respiratory compromise", and "pulse oximeter <90%" are not very helpful, as the degree of compromise or how low a reading the pulse oximeter showed are not known. The "other respiratory compromise" is described as "respiratory acidosis" and occurred only at the 1-hr observation time for Patient #(b)(6) (Placebo arm), without actual data presented to substantiate how severe it was. Thus, none of the "respiratory compromise" signs are verifiable from the information submitted. Since all signs in the 3 patients subsided within 2 hours (possibly related to mildness of the observed signs), no effectiveness can be inferred for Anascorp in the treatment of "Respiratory Compromise." Efficacy is primarily driven by the data on "pathological agitation."

2. The case report forms for this study were obtained and reviewed to readjudicate success/failure in the use of Anascorp for scorpion envenomation. Since subjects (b)(6) (Anascorp) and (b)(6) (placebo) did not have detectable venom in serum, they should not be regarded as having had envenomation. The following table shows the presence/absence of the "important signs of envenomation" at the end of 4 hours, which is the time-point for primary analysis.

Hour 4 Clinically Important Signs of Scorpion Envenomation and Physician 15-Min Assessment

		Respiratory Compromise					Pathologic Agitation				Physician 15 min assessment on envenom-ation
		Pulm edema	Incoord-inate ventilation	Upper resp compro-mise	Pulsed oximeter <90%	Other resp compro-mise	Abnormal eye movement	Thrash-ing	Loss of ability to ambulate	Fasci-culatio n	
Anascorp	(b)(6)	-	-	-	-	-	-	-	-	-	-
	(b)(6)	-	-	-	-	-	-	-	-	-	-
	(b)(6)	-	-	-	-	-	-	-	-	-	-
	(b)(6)	-	-	-	-	-	-	-	-	-	-
	(b)(6)	-	-	-	-	-	-	-	-	-	-
	(b)(6)	-	-	-	-	-	-	-	-	-	-
	(b)(6)	-	-	-	-	-	-	-	-	-	-
	(b)(6)	-	-	-	-	-	-	-	-	-	-
Placebvo	(b)(6)	-	-	-	-	-	-	+	-	-	+
	(b)(6)	-	-	-	-	-	+	+	-	+	+
	(b)(6)	-	-	-	-	-	-	-	-	-	+*
	(b)(6)	-	-	-	-	-	-	-	-	-	+**
	(b)(6)	-	-	-	-	-	+	+	-	-	+
	(b)(6)	-	-	-	-	-	+	+	-	-	+
	(b)(6)	-	-	-	-	-	+	-	-	-	-***

Subjects (b)(6)and (b)(6) (highlighted in red) did not have detectable venom in serum at any time.

*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.
**Subject (b)(6): Patient sedated at 4 hour time point. Physician note states agitation & nystagmus present but decreasing one hour after 4 hour time point. Last documented symptom shaky/tremorous per nursing note over 12 hours after initiating treatment.
***Subject (b)(6): Attending physician stated jerky eye movements were due to midazolam effect.

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	**Adjudicated**	8/8 (100%)	1/7 (14.3%)	85.7% (35.71%, 99.64%)
	Worst case scenario	8/8 (100%)	3/7 (43.9%)	57.1% (10.89%, 90.10%)
Envenomated subjects	**Adjudicated**	7/7 (100%)	0/6 (0)	100% (50.14%, 100%)
	Worst case scenario	7/7 (100%)	2/6 (33.3%)	66.7% (14.33%, 95.67%)

Taking a worst-case scenario, the 95% C.I. lower bound of the difference between success rates would be lower than 20%, a difference postulated in the Statistical Analysis Plan for declaring superiority of Anascorp over placebo. However, if subjects (b)(6) and (b)(6) in the placebo arm are counted as failures, then the 95% C.I. lower bound would exceed 20%. It must be noted that (a) the success rates are entirely driven by signs of "pathological agitation", and (b) in the "envenomated subject" analysis, two subjects in the Anascorp arm (#(b)(6), #(b)(6)) actually had not been sampled for serum venom – for a truly valid comparison with documented envenomated subjects, there would only be 5 subjects in the Anascorp arm and 6 in the placebo arm.

2. Secondary Efficacy Variables

Midazolam Dosing

Midazolam Dosing

Parameter	Midazolam Dose (mg/kg)						
	Total Dose Prior to Baseline	Dose from Baseline to 1 hr	Dose from 1 hr to 2 hr	Dose from 2 hr to 4 hr	Dose from Baseline to 4 hr	Dose from Baseline to Discharge	Total Dose from Prior to Baseline through Discharge
Anascorp (N=8)							
Mean (SD)	0.2 (0.1)	0.1 (0.1)	0.0 (0.0)	0.0 (0.0)	0.1 (0.1)	0.1 (0.1)	0.3 (0.2)
Median	0.2	0.0	0.0	0.0	0.0	0.0	0.4
Min, Max	0.1, 0.4	0.0, 0.2	0.0, 0.0	0.0, 0.0	0.0, 0.2	0.0, 0.2	0.1, 0.5
Placebo (N=7)							
Mean (SD)	0.5 (0.7)	0.3 (0.4)	0.3 (0.3)	1.1 (1.3)	1.8 (1.6)	4.6 (5.8)	5.1 (5.6)
Median	0.3	0.1	0.2	0.8	1.2	3.4	3.9
Min, Max	0.1, 2.0	0.0, 1.1	0.0, 1.0	0.0, 3.9	0.1, 4.4	0.1, 16.7	0.3, 16.8

The study report gives the mean maximum rate for midazolam administration to be 0.1 ± 0.1 mg/kg/hr for the Anascorp group vs 0.8 ± 0.9 mg/kg/hr in the Placebo group.

Comment The following table gives the maximum rates for midazolam administration from information in the database. They are not consistent with the reported means in the study report.

Midazolam Maximum Infusion Rate

	Anascorp		Placebo	
	Patient	Rate (mg/kg/hr)	Patient	Rate (mg/kg/hr)
	(b)(6)	0.09	(b)(6)	0.08
	(b)(6)	0.12	(b)(6)	0.27
	(b)(6)	0.12	(b)(6)	0.54
	(b)(6)	0.22	(b)(6)	0.63
	(b)(6)	0.23	(b)(6)	0.80
	(b)(6)	0.27	(b)(6)	1.10
	(b)(6)	0.29	(b)(6)	2.67

	(b)(6) 0.31	
Mean	0.206	0.870

The average time from baseline until the last dose of midazolam for Anascorp patients was 22.5 minutes compared with 534 minutes (8.9 hours) for Placebo patients.

Scorpion Sting and Hospital Arrival Relative to Midazolam Dosing

Characteristic	Treatment Groups	
	Anascorp N=8	**Placebo N=7**
Time from sting to start of study drug infusion (baseline) (min)		
n	7	5
Mean (SD)	207.9 (68.5)	223.4 (33.4)
Min, Max	100, 310	192, 270
Time from sting to maximum midazolam dose (min)		
n	7	5
Mean (SD)	148.6 (83.4)	265.0 (129.2)
Min, Max	55, 310	53, 395
Time from sting to end of midazolam infusion (min)		
n	7	5
Mean (SD)	233.6 (75.2)	838.0 (266.4)
Min, Max	155, 370	370, 1095
Time from hospital arrival to start of study drug infusion (min)		
n	8	6
Mean (SD)	84.0 (50.8)	84.2 (30.1)
Min, Max	25, 161	47, 124
Time from hospital arrival to maximum midazolam infusion (min)		
n	8	6
Mean (SD)	24.5 (55.2)	82.5 (134.4)
Min, Max	-80, 100	-132, 260
Time from hospital arrival to end of midazolam infusion (min)		
n	8	6
Mean (SD)	106.5 (53.1)	667.2 (249.6)
Min, Max	35, 190	304, 964

Comment The information from the above table is not consistent with earlier information on hospital arrival time (Anascorp recipients presented to the hospital and for study enrollment (134.9 and 207.9 minutes) slightly sooner than did Placebo recipients (149.0 and 223.4 minutes)). From the table, using time from sting to end of midazolam infusion and time from hospital arrival to end of midazolam infusion, the derived time between sting and hospital arrival would be (234-107) min, or 127 min for Anascorp, and (838-667) min, or 177 min for Placebo, instead of 135 min for Anascorp and 149 min for Placebo.

Serum Venom Levels

The mean venom levels at baseline were similar in the Anascorp and Placebo groups, at 7.13 +/-4.56 ng/mL and 6.60 +/-10.14 ng/mL, respectively.

- Mean venom levels dropped below the limit of quantitation by 1 hour among all Anascorp recipients.
- Mean venom levels among Placebo recipients dropped to 2.65 +/- 3.03 ng/mL and 1.79 +/- 1.93 ng/mL at 1 hour and at end of study, respectively.

Serum venom levels were detectable, confirming the clinical diagnosis of scorpion envenomation, in 10 of the 12 patients (83%) for which baseline samples were available.

- One Anascorp recipient had no quantifiable venom in serum at baseline. This child had been stung on the heel of the foot. Tha applicant suggests that venom absorption through this relatively calloused entry site followed uptake kinetics significantly different from those of other sting sites, explaining the lack of venom detection.
- One Placebo recipient had no venom measurable in serum at baseline. This child was, at 10.3 years old and 42 kg, by far the largest subject enrolled in either arm of the study. In addition, blood was collected for venom assay 5.3 hours after the onset of symptoms, later than for any other child enrolled. This child was the only Placebo recipient to experience a spontaneous recovery within the 4-hour study period. These factors, combined, suggest

Among the 5 Anascorp recipients with detectable serum venom at baseline, all had a drop in serum free venom levels to below lower limit of quantitation by 1 hour after baseline. Venom levels among the 5 Placebo recipients with detectable serum venom at baseline dropped through the course of the study, but became below quantitation limits in only 1 of 5 cases with measurable venom at baseline.

Serum Venom Levels

	Venom (ng/mL)		
	Baseline	After Baseline	
		1 Hour	4 Hours
Anascorp (N=8)	(N=6) [1]	(N=6) [1]	(N=5) [1]
Mean (SD)	7.13 (4.56)	0.00 (0.00)	0.00 (0.00)
Median	8.66	0.00	0.00
Range	0.00-12.91	0.00 – 0.00	0.00 – 0.00
Placebo (N=7)	(N=6) [2]	(N=7)	(N=6) [2]
Mean (SD)	6.60 (10.14)	2.65 (3.03)	1.79 (1.93)
Median	3.39	1.31	1.54
Range	0.00 – 26.79	0.00 – 8.57	0.00 – 4.98

[1]N=6 for baseline and 1 hour (samples for #(b)(6) and #(b)(6) missing at all time points) and N=5 for 4 hour time point (additionally sample for #(b)(6) missing)
[2]N=6 for baseline (sample for #(b)(6) missing) and for 4 hour time point (sample for #(b)(6) missing)

The difference in kinetics for venom levels in the study arms supports the hypothesis that Anascorp efficacy is a consequence of venom binding by antivenom. The report suggests that this difference iindicates that the dose of Anascorp administered (3 vials) was sufficient for the prompt and sustained neutralization of the quantity of venom injected.

Comment The applicant has not provided documentation that the serum venom assay is not interfered with by the presence of antivenom. In the absence of demonstrating assay validity to detect active venom when antivenom is present, the venom levels in Anascorp-treated subjects cannot be interpreted.

Other Variables
Resolution of the signs of cranial nerve and somatic skeletal nerve dysfunction (see above for baseline percentages) occurred in 100.0% of Anascorp recipients 4 hours after study drug infusion, whereas these signs were present in 4 Placebo recipients (57.1%) at the same time-point.

Drug-Drug and Drug-Disease Interactions
Drug-drug and drug-disease interactions were not evaluated in this study.

Efficacy Conclusions
1. The study report claims success because:
(a) The primary endpoint demonstrated resolution of the clinical syndrome, less than 4 hours after study drug infusion, in all 8 Anascorp cases but in only 1 out of 7 Placebo-treated patients.
(b) Anascorp recipients received (i) a mean dose of 0.1 mg/kg midazolam during the first hour after initiation of study drug infusion, but ceased to require sedation within one hour after treatment began, whereas Placebo recipients received a mean of 0.3 mg/kg midazolam during the first hour and continued to receive for a mean total of 4.6 mg/kg between study enrollment and hospital discharge, and (ii) midazolam sedation for a mean of 22.5 minutes after treatment began compared with 534 minutes (8.9 hours) for Placebo recipients.
(c) Where sampling was available, blood venom levels dropped to undetectable levels by one hour after baseline among Anascorp recipients, but in only one Placebo recipient.
2. The design of this study with a small sample size, as previously indicated to the applicant, limits the reliability of the conclusions drawn from it.

3. This study did not demonstrate any effect on mortality or major morbidities after scorpion envenomation. Specifically, the success is driven primarily by data on “pathological agitation”, which is entirely dependent on the Investigators’ interpretation of child behavior. No efficacy has been demonstrated on “respiratory compromise” or any life-threatening manifestations of scorpion envenomation. Essentially, despite an attempt to study the most severe forms of envenomation, this study does not seem to have enrolled subjects having a sufficiently serious or life-threatening condition to demonstrate success of Anascorp in the treatment of such cases of envenomation. A study on patients with more serious manifestations would be needed.
4. This study also has confounding factors which complicate interpretation of the data, including (a) use of midazolam as concomitant medication, as reaction to midazolam could also manifest as agitation, involuntary movement, hyperactivity, combativeness, and respiratory compromise, (b) undefined nature of placebo, (c) imbalance between arms in the subjects’ age (and hence maturity and body weight/height), (d) disparity among treatment arms in the time between scorpion sting and administration of test product, and (e) uncertainty of envenomation in some patients whose serum did not have measurable levels of venom.

SAFETY EVALUATION
Evaluation of safety parameters was performed in the Safety analysis set.

EXTENT OF EXPOSURE
All 8 patients randomized to the treatment arm of the study received 3 vials of Anascorp, as specified in the protocol, diluted in 50 mL normal saline. The 7 patients randomized to Placebo received the “inactive excipient” without antivenom, diluted in 50 mL normal saline and administered IV over a range of 10 to 35 minutes.

Comment It is unclear what the placebo is. If it is the inactive excipient, the placebo is simply the product vehicle, and not proteinaceous material.

Antivenom Levels

	Antivenom (μg/mL)		
	Baseline	After Baseline	
		1 Hour	4 Hours
Anascorp (N=8)	(N=6) [1]	(N=6) [1]	(N=5) [1]
Mean (SD)	0.00 (0.00)	73.85 (25.45)	69.05 (23.26)
Median	0.00	74.40	68.77
Range	0.00 – 0.00	29.53 – 108.20	35.75 – 98.64
Placebo (N=7)	(N=6) [2]	(N=7)	(N=6) [2]
Mean (SD)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Median	0.00	0.00	0.00
Range	0.00 – 0.00	0.00 – 0.00	0.00 – 0.00

[1]N=6 for baseline and 1 hour (samples for #(b)(6) and #(b)(6) missing at all time points) and N=5 for 4 hour time point (additionally sample for #(b)(6) missing)
[2]N=6 for baseline (sample for #(b)(6) missing) and for 4 hour time point (sample for #(b)(6) missing)

ADVERSE EVENTS
Brief Summary of Adverse Events
No serum reactions to study drug occurred in the study population, which included 12 patients who received no H1-, H2- blockers or corticosteroids and 3 patients (2 Anascorp recipients and 1 Placebo recipient) who received diphenhydramine prior to hospital admission. It is possible that diphenhydramine could have obscured AEs of allergic nature. A total of 6 AEs were reported during the conduct of the study, with 3 occurring in each treatment group.

Summary of Adverse Events

Parameter	Treatment Groups, n (%)	
	Anascorp N=8	Placebo N=7

Patients with ≥ 1 AE	2 (25.0)	1 (14.3)
Patients who withdrew due to an AE	0 (0.0)	0 (0.0)
Patients with reaction to product	0 (0.0)	0 (0.0)
Patients with SAEs	0 (0.0)	0 (0.0)
Patient deaths	0 (0.0)	0 (0.0)
Patients with ≥ 1 AE by intensity		
Mild	2 (25.0)	1 (14.3)
Moderate	0 (0.0)	0 (0.0)
Severe	0 (0.0)	0 (0.0)
Patients with ≥ 1 AE by relationship to study drug		
Definitely related	0 (0.0)	0 (0.0)
Possibly related	0 (0.0)	1 (14.3)
Not related	2 (25.0)	1 (14.3)
Not assessable	0 (0.0)	1 (14.3)

Analysis of Adverse Events

- Patient (b)(6) in the Anascorp group experienced vomiting and diarrhea several days after treatment that resolved within 2 days of its onset.
- Patient #(b)(6) in the Anascorp groupexperienced one episode of vomiting 6 days after treatment.

The above 3 events were considered unrelated to treatment, and in neither patient were these findings associated with signs of serum sickness.

- One Placebo patient (Patient #(b)(6)) developed mild respiratory acidosis, fever, and a rash on the stomach and diaper area shortly after treatment. The respiratory acidosis was considered possibly related to treatment, but after the blind break was believed to be from a reaction to midazolam. The fever was considered unrelated to treatment and the relationship of the patient's rash to study drug was not assessable. All 3 events resolved on the day of onset.

Summary of Adverse Events in Patients Reporting ≥ 1 AE

Parameter		Treatment Groups, n (%)	
		Anascorp (N=8)	Placebo (N=7)
Gastrointestinal	Diarrhea	1 (12.5)	0 (0.0)
	Vomiting	2 (25.0)	0 (0.0)
General	Pyrexia	0 (0.0)	1 (14.3)
Metabolic	Respiratory acidosis	0 (0.0)	1 (14.3)
Skin	Rash	0 (0.0)	1 (14.3)

No patient experienced an acute serum reaction. However, 3 patients (2 Anascorp recipients and 1 Placebo recipient) received diphenhydramine prior to hospital admission, and this could have obscured the ability to fully detect and evaluate an acute serum reaction had it occurred.

Follow-up calls seeking signs of delayed reactions were completed for 8/8 patients randomized to Anascorp and to 6/7 in the Placebo group; no patient had symptoms suggestive of serum sickness during this time. Two patients in the Anascorp group experienced an episode of vomiting during the 7 days post-hospitalization, and one Anascorp recipient received acetaminophen for a bruised ear. No symptoms were reported for either Anascorp or Placebo recipients at the 14-day follow-up evaluation.

DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

No deaths or SAEs occurred during the conduct of this study.

CLINICAL LABORATORY EVALUATION

Hematology, chemistry, and urine dipstick test findings were unremarkable.

SAFETY CONCLUSIONS

1. Anascorp appears to have been well tolerated in Study AL-02/03, and no allergic reactions were reported. No patient experienced serum sickness during the treatment period or during the 14-day follow-up period.

2. Since patients were discharged 4 hours after Anascorp administration (none of the Anascorp recipients had “clinically important signs” of envenomation at the end of 4 hours), and the follow-up was by phone without actual observation by the Investigator or laboratory tests, reliability of the limited safety data must be interpreted with caution.
3. Some patients received antihistamines and/or corticosteroids which could have masked reactions to the product, further complicating the interpretation of the safety data.

Other Clinical Data

This BLA submission includes 5 other open-label studies (AL-99/02, AL-02/04, AL-02/05, AL-02/06, and AL-03/07) in which Anascorp was used in scorpion envenomation, and one study of chart review for patients not treated with antivenin in order to establish the natural history of scorpion envenomation in Arizona (AL-03/06).

Although the applicant considers three of the open-label studies (AL-02/04, AL-02/05, and AL-02/06) as “controlled”, using the natural history study as historic control, this cannot be considered as appropriate, because (a) AL-03/06 was completed (July 2007) after completion of the three “controlled” trials, AL-02/04, AL-02/05 and AL-02/06 (October, 2006), and (b) the protocols for these “controlled” studies were finalized before AL-03/06 was initiated. In an information request dated 3/5/09, the applicant was asked to address:

a) the validity of the methodology for historic data collection in AL-03/06, and
b) the appropriateness of using these historic data for comparison with the data in the “controlled” studies AL-02/04, AL-02/05, and AL-02/06. Your justification should address, but not be limited to, the fact that there is no pre-specified hypotheses-testing in these “controlled” studies utilizing the historic data from AL-03/06.

In response, the applicant provided previous interactions with the Agency regarding their attempt to justify using historic control rather than a rationale to conduct the open-label studies ***prior to*** having the “historic control” data to support their design. In the absence of appropriately supported pre-specified hypothesis testing, it is not acceptable to use the natural history study for comparison with the data in AL-02/04, AL-02/05 and AL-02/06. Their utility is essentially to support safety of Anascorp in scorpion envenomation. These studies share a common study report.

AL-03/06 does not involve the use of the product proposed for marketing, and so will not support safety or efficacy of the product in scorpion envenomation. Therefore it will not be discussed in this review.

AL-99/02 is a controlled study conducted in Mexico to compare Anascorp with a product licensed in Mexico but not in the U.S. Thus, no conclusions can be made on efficacy in scorpion envenomation, and its utility is also for supporting safety of Anascorp in scorpion envenomation.

AL-03/07 is an ongoing, open-label study for treatment use of Anascorp in scorpion envenomation. Its primary utility is in support of safety. The applicant has not provided an up-to-date report for this study. Instead, this submission has included an interim report covering the period 5/23/05 to 9/23/06, a span of 16 months, together with a Statistical Report covering the period up to June 2008, an additional 21 months. FDA sent an Information Request to the applicant on 3/12/09 for a study report covering the

entire period up to June 2008, so that the information and dataset in the Statistical Report can be reconciled with the submitted study report data. In response, the applicant states that there is no up-to-date study report. The response refers to the Statistical Report for the most recent data.

Comment This Reviewer will include information from the "Statistical Report" in this review instead of the data from the interim study report. However, this is an irregular practice, and the applicant should still submit an up-to-date study report that contains all the appropriate documentation together with a complete dataset to support their application. A "Statistical Report" will not normally fulfill regulatory requirements.

Although Study AL-03/06 contributes support for neither efficacy nor safety of Anascorp, it may be important to have background information on scorpion envenomation in the Tuscon area, from which the pivotal study, AL-02/03 was conducted. The following is a summary account of the chart review study, AL-03/06.

AL-03/06: Establishment of Natural History of Scorpion Envenomation in the Absence of Antivenom Treatment in Pediatric Patients

Investigator(s): Leslie Boyer, MD; Andreas A. Theodorou, MD

Study center(s): The University of Arizona Health Sciences Center, Arizona Poison and Drug Information Center, Tucson, Arizona; Tucson Medical Center, Tucson, Arizona

Study period: August 2004 to July 2005 Phase of development:

Objectives:

- Primary objective - to demonstrate duration of clinically important systemic signs resulting from scorpion sting envenomation in the absence of antivenom treatment in pediatric patients.
- Secondary objective - to establish via historical controls the time from sting to resolution of signs of envenomation for comparison with Anascorp-treated patients in prospective studies for which a control population could not otherwise be established.

Methodology:

- Retrospective, multicenter study designed to establish the natural history of scorpion envenomation in the absence of antivenom treatment in pediatric patients.
- Hospital records at the two participating sites in Tucson, Arizona were reviewed for pediatric patients admitted for management of scorpion envenomation from 1990 to 2003. A research nurse reviewed discharge diagnoses for all pediatric charts coded for "scorpion sting," "spider bite," "insect bite," or "unspecified bite or sting." Those diagnoses that were most likely related to scorpion sting were identified. For these cases, demographic, diagnostic, and therapeutic data were entered on the case report form (CRF) as well as data necessary to assess compliance with study inclusion and exclusion criteria.
- Eligibility Criteria

  Inclusion
  - Males and females 6 months to 18 years of age
  - Presenting for emergency treatment with clinically important systemic signs of scorpion sting envenomation

  Exclusion
  - Use of any antivenom within the last month or concomitantly
  - Signs and symptoms confined to local sting site
  - Concurrent medical condition involving a baseline neurologic status mimicking envenomation (chorea, tardive dyskinesia, uncontrolled epilepsy)
  - Incomplete or unavailable medical record

- A physician sub-investigator reviewed the research nurse's findings for the key outcome indicators, which consisted of clinically important systemic signs of scorpion envenomation and adjunctive sedation treatment (dose and timing of dose) when medical judgment was required. If the conclusions of the research nurse and sub-investigator differed, the principal investigator reviewed the charts. The outcome variables were then coded.
- Data collection involved the following.
  Baseline data: demographic information, medical history, physical examination, vital signs, laboratory tests (hematology, chemistry, urinalysis), physical assessment, symptoms assessment, scorpion sting information, concomitant medications, and adverse events. Severity evaluation was based on signs of respiratory compromise (pulmonary edema, incoordinate ventilatory efforts, upper airway compromise due to excessive secretion, pulse oximeter < 90%, other respiratory compromise) and pathological agitation (abnormal eye movements, thrashing of limbs, loss of ability to ambulate, fasciculation). Pulmonary edema and fasciculation were considered supporting criteria only and not considered clinically important unless other signs were present.
  Data at 1 hour and 2 hours after hospital admission: vital signs, severity evaluation, physical and symptom assessments, midazolam sedation (or any other primary sedation), concomitant medications, and adverse events. Data collected at 4 hours after hospital admission included vital signs, severity evaluation, physical and symptom assessments, midazolam sedation (or any other primary sedation), concomitant medications, and adverse events. If hospitalization continued after the 4-hour observation time point, these same data were collected at the time of discharge or at 24 hours, if hospitalization continued. The last available laboratory test prior to hospital discharge was collected.
- Number of Patients planned: ~150 patient charts were retrieved from two participating sites
- Criteria for Evaluation:
  Primary Efficacy Variable: investigator assessment of overall duration of clinically important signs of scorpion envenomation[1].
  Secondary Efficacy Variables: Patient symptoms (respiratory compromise, pathologic agitation, physical assessments, symptom assessments) were collected at baseline and at each timepoint (1 hour, 2 hours, 4 hours, and discharge—defined as closest to discharge if after 24 hours or closest to 24 hours if hospitalization continued after 24 hours). The duration of symptoms of respiratory compromise and pathologic agitation were calculated.
  Physical assessments of severity of scorpion envenomation included: sialorrhea, abdominal distention, vomiting, priapism, cranial nerve dysfunction, and somatic skeletal nerve dysfunction.
  Symptom assessments of severity of envenomation included: pain at sting site, pain remote from sting site, paresthesias remote from sting site, nasopharyngeal pruritis, pharyngeal foreign body sensation, transient blindness, retrosternal pain, and dyspnea.
  The cumulative doses of midazolam or other primary sedative and patient scorpion sting information were also collected.
  Safety: Safety was assessed using treatment- and/or venom-related adverse events, clinical laboratory tests (hematology, chemistry, urinalysis), vital signs, and medical history and physical examination abnormalities.

Summary of Results:

Demographics and Baseline conditions

- Of 119 cases of scorpion "envenomation", 22 were eliminated for failing to meet study inclusion/exclusion criteria, leaving 97 cases for analysis. The mean age (SD) of the study patients was 3.9 (3.3) years, and the mean (SD) weight was 17.4 (11.0) kg. There were more males than females in the study population (53.6% vs. 46.4%, respectively). The majority of patients were of unknown race (54%), then came Caucasians (33%) or Hispanics (9.3%).
- Overall, clinically important systemic signs of envenomation were present in all patients at baseline, with at least one indicator of pathological agitation documented in 95 children (97.9%), despite prior use of benzodiazepine sedation in most cases. In contrast, at least one documented indicator of respiratory compromise in 29 children (29.9%).
- Among the 72 cases for which sting time was available, time to baseline averaged 283.1 minutes. Time to baseline was slightly longer (336.6 minutes, with greatly overlapping range) among the 18 patients for whom symptom onset was available but sting time was not. For the 6 cases with neither sting time nor symptom onset time available, the time from initial medical contact to baseline

[1] Because not every chart included full documentation of sting time, surrogate indicators of envenomation onset (time of first reported symptom, time of first contact with medical care) were also used to calculate duration. Clinically important signs of envenomation were divided into those indicative of respiratory distress and those compromising pathological agitation.

averaged 181.3 minutes. Among the 33 patients for whom data were available, the mean onset of clinically important systemic signs from sting time was 52.5 minutes.

- Eighty-eight (91%) of the patients had received midazolam or other primary sedation prior to hospital admission (N = 46 for midazolam, N=11 for diazepam, N=19 for lorazepam, N = 5 for succinylcholine chloride, N = 3 for vecuronium bromide, N = 2 for phenobarbital, N=1 for pancuronium, bromide, N = 1 for propofol). Other commonly used (≥ 10%) concomitant medications included diphenhydramine (22.7%), acetaminophen (11.3%), and ibuprofen (10.3%). For the 73 patients receiving known amounts of midazolam prior to baseline, the average total dose was 0.41 mg/kg (± 0.56), with a range of 0.00 – 2.47 mg/kg.

Baseline Severity for Envenomation

Characteristic	Patients (N=97)	Postulated Cause of Manifestations		
		Venom	Treatment	Unknown
Clinically important systemic signs of scorpion envenomation	97 (100.0)			
Respiratory Compromise, N (%)				
Pulmonary edema	2 (2.1)	2 (2.1)	0 (0.0)	0 (0.0)
Incoordinate ventilatory efforts	2 (2.1)	2 (2.1)	0 (0.0)	0 (0.0)
Upper airway compromise	8 (8.2)	8 (8.2)	0 (0.0)	0 (0.0)
Pulse oximeter < 90%	4 (4.1)	2 (2.1)	0 (0.0)	2 (2.1)
Other respiratory compromise	21 (21.6)	19 (19.6)	1 (1.0)	1 (1.0)
Any respiratory compromise (except edema)	29 (29.9)			
Pathological Agitation, N (%)				
Abnormal eye movement	72 (74.2)	72 (74.2)	0 (0.0)	0 (0.0)
Thrashing of limbs	92 (94.8)	92 (94.8)	0 (0.0)	0 (0.0)
Loss of ability to ambulate	9 (9.3)	8 (8.2)	1 (1.0)	0 (0.0)
Fasciculation	7 (7.2)	7 (7.2)	0 (0.0)	0 (0.0)
Any agitation (except fasciculation)	95 (97.9)			

Comment The chart review shows that approximately 30% of "envenomated" subjects showed some form of respiratory compromise, with the majority of them having "other respiratory compromise" (21 out of 29 cases). In contrast, in the pivotal study, only 3 subjects (2 in the Anascorp arm and 1 in placebo arm) developed "respiratory compromise"- two with oximeter reading of <90%, and one "upper airway compromise." It is not clear if the "respiratory compromise" observed in the Anascorp clinical development program is of sufficient severity or frequency to support such an indication.

Primary Efficacy Variable (Total duration of the clinical syndrome)
The duration of the clinical syndrome was calculated for 96 of the 97 patients in the study. Mean time to last documentation of any clinically important sign was 763.8 minutes for the 72 cases with documented sting time, 1122 minutes for 18 cases using symptom onset as start time, and 734.7 minutes for the 6 using first medical contact times as start time.

Secondary Efficacy Variables

- Four out of 97 patients had apparent resolution of clinically-important signs during the first 4 hours after admission, leaving 93 (95.9%) still judged affected. The envenomation duration for these 4 patients ranged from 45 minutes to 9.5 hours (sting time to hospital admission).
- Generally, patients continued to receive midazolam during the 4-hour observation period, with an average total of 5.29 mg/kg (± 8.68) and a median of 3.11 mg/kg midazolam between enrollment and hospital discharge. Among the 92 cases in which duration of sedative administration could be calculated, the time from hospital admission (baseline) to midazolam discontinuation averaged 607.4 minutes (± 318.9) and ranged up to 1815 minutes.
- Overall, 96.9% of patients had a severe physical and symptom assessment grade at baseline, which persisted in over half (54.6%) of patients at the 4-hour discharge. Only 2.1% of patients had physical and symptom assessment grades that were considered moderate at baseline, and no patients were rated as mild.

Safety

At least one clinical adverse event occurred in 38 (39.2%) of patients. At least one venom-related and treatment-related clinical AE was reported in 18 (18.6%) and 12 (12.4%) of patients, respectively. No patients experienced an SAE or died during the conduct of the study. The most commonly reported clinical AEs were vomiting (7.2%), pyrexia (6.2%), intubation (5.2%), hypoxia (4.1%), and pneumonia aspiration (4.1%). Generally no clinically significant patterns were noted in summary statistics for changes from baseline to 4-hour discharge values for hematology or chemistry parameters, or for urine dipstick results. Despite receiving large amounts of midazolam sedation, patients did not generally experience substantial depression of vital signs at discharge.

Conclusions by Applicant:

- In this pediatric population of 97 children admitted for intensive care management of scorpion envenomation, without use of antivenom, documented medically important signs of scorpion envenomation persisted for an average of 764 minutes (12.7 hours) after scorpion sting, with just 4% of cases resolved by 4 hours after hospital admission. The duration of envenomation for these 4 patients ranged from 45 minutes to 9.5 hours (sting time to hospital admission).
- In the absence of antivenom treatment, supportive care included midazolam IV infusion to control pathological agitation. Midazolam infusion continued on average until 607 minutes (10 hours) after hospital admission, with a range of up to 1815 minutes (30 hours).
- During hospitalization for intensive supportive care, 39% of children with scorpion envenomation experienced at least one adverse event.

Comment This chart review "study" is enlightening in one respect. It suggests, 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. The role of antivenom in scorpion envenomation is therefore primarily in the shortening of the effects of envenomation rather than providing benefit on mortality or irreversible morbidity.

Study AL-99/02. Randomized, Double-Blind, Variable Dose Comparison of Anascorp vs. Birmex in Patients With Scorpion Sting [Initiated 9/9/99, completed 12/12/00]

Phase of development: Phase 2

Objectives:

- To determine the "intoxication" period in patients with scorpion stings and the time needed to reverse the intoxication with Anascorp
- To quantify the levels of venom in the blood (venonemia) and evaluate the relationship between venom levels in the plasma and the severity of signs and symptoms of scorpion intoxication
- To evaluate the safety and efficacy of Anascorp

Deisgn:

- All study participants were to give informed consent before study entry.
- Upon study entry, the patients would be classified as having mild, moderate, or severe scorpion sting "intoxication" according to their symptoms and physical findings.
- Before the administration of the antivenom, the patient was to be placed on an intravenous drip and a basal blood sample taken.
- Patients were to receive one of the study medications and continue with the assigned antivenom until the signs of "intoxication" resolve.
- Patient response was evaluated every 30 minutes and, if deemed necessary, the patients could receive another dose of antivenom. In that case, a blood sample was taken to determine the serum venom level.
- When signs of systemic envenomation resolved, the patient would be discharged from hospital. Before discharge, a final blood sample was taken.

- The blood samples would be refrigerated and processed within one week.

Summary of Study Procedures

Procedure	**Screen**	**Baseline**	**Treatment Period**	**30 Minutes Post Infusion**	**4 Hours Post Infusion OR at Hospital Discharge**	**Hospitalization (4-24 hours)**
Informed Consent	X					
Inclusion/ Exclusion	X					
Severity Grade		X		X	X	X
Vital Signs BP/HR/T/Resp		X			X	
Concomitant Medications		X	X	X	X	X
Demographics		X				
Medical History		X				
Physical Examination		X			X	X
Study Drug Infusion			X			
Laboratory Test: Antigen Level		X		X	X	X
Adverse Events			X	X	X	X

Evaluations

- Efficacy was to be measured by the:
  - Number of vials needed to reverse scorpion poisoning
  - Minimum and maximum antivenom vial requirement according to grade of poisoning at admittance
  - Difference in serum venom levels between time of hospital admission and discharge via a -----(b)(4)-----, designed by --(b)(4)-- at the ----------(b)(4)----------
  - Serum venom level was to be assayed when a patient received additional dose of scorpion antivenom
  - Time period from antivenom administration to hospital discharge
- Safety was to be evaluated by the:
  - Occurrence of adverse events reported by the attending personnel and deemed to be related to the antivenom use
  - Need to use corticosteroids, antihistamines, NSAIDs, or epinephrine to control an adverse event
  - Hospital stay beyond scorpion "intoxication" to treat any adverse reaction

Comment Since adverse events were defined by relatedness to antivenom use, this study is inadequate to support safety because of lack of a total database of adverse events.

Statistical Methodology

- Univariate analysis was used to determine the central tendency and dispersion measurements for quantitative variables and ratios and proportions for nominal variables.
- Mantel-Haenszel test was used to measure the association between the dependent and independent variables.
- Student's t test was used for means, analysis of variance (ANOVA), Z score, and Poisson distribution.

Eligibility criteria:

- All patients, regardless of age or gender, seeking treatment for mild to severe scorpion intoxication were eligible.
- Patients allergic to horse serum, had more than 24-hours elapse between scorpion sting and hospital admission, or were administered scorpion antivenom or any other drug before hospital admission were excluded.
- Children under 15 years of age who were not accompanied by an adult capable of signing the informed consent were not eligible to participate.

Test product, dose and administration:

- Lyophilized Anascorp [*Centruroides* equine immune F(ab')2] 1 to 3 vials of powder, reconstituted with 5 mL normal saline solution and administered as IV bolus until symptoms of scorpion "intoxication" are resolved
- Reference therapy, as 1 to 3 vials of Birmex (*Centruroides* equine immune $F(ab')_2$ equine prepared by Mexican Social Security Institute (IMSS)), administered as IV bolus.

Comment This study reconstitutes Anascorp in 5 mL normal saline, which is different from the reconstitution 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).

Investigators

Dr Javal Cabral Soto
Dr Celia Escandón Romero
Dr Jorge Humberto Uribe Tellez
Dr Sixto Ferrel Acosta
Dr Anabel Silva Batalla
Dr Beatriz Solano Mejia
Dr Sofia Reyes Nino

Study Centre(s)

Durango District Hospitals

- Hospital Rural de Guadalupe Victoria
- Hospital Rural de Vicente Guerrero

Durango District Medical Clinics

- San Juan de Michis
- La Michilia
- Alejandro
- La Constancia
- Santiago Bayacora
- Troncon del Mezquital
- Zaragoza

Nayarit District Hospitals

- Hospital Rural de San Cayetano

Nayarit Medical Clinics

- San Rafael
- Las Blancas
- Pochotitan
- El Venado
- La Libertad
- Marquesado
- Mojarras
- Colonia Moderna
- Chapalilla

Patients Enrolled:

The number of planned patients was 400; 248 patients completed the study (Birmex and Anascorp); data were complete for 105 patients treated with Anascorp. The Anascorp group included 37 females and 68 males, 29 of whom were aged <18 years of age and 76 over18 years of age.

Results:

Efficacy:

Of the 105 patients treated with Anascorp, 38 patients were admitted with a mild grade of intoxication, 40 with moderate, and 11 with severe. Severity was not reported for 16 patients.

Comment The protocol allows for enrollment of scorpion stings of all severity. As a result, 38/105 (36%) of the patients given Anascorp had "mild" symptomatology, and only 11/105 (10%) had shown evidence of "severe" envenomation.

- For the 89 Anascorp patients with severity reported, the mean dose administered was 1.7 ± 0.94 vials and ranged from 1 to 6 doses.
- The mean time from hospital admission to discharge was 116.1 ± 65.84 minutes for 104 of the 105 patients treated with Anascorp, and ranged from 30 to 405 minutes. Data were missing for one patient.
- For patients treated with Anascorp, venom levels at admission ranged from 0 to 1000 pg/mL for 42 patients, 1001 to 2000 pg/mL for 22 patients, 2001 to 3000 pg/mL for 16 patients, 3001 to >4000 for 20 patients, and was not reported for 5 patients. At discharge, venom levels were 0 for 73 patients and ranged from 1 to 500 pg/mL for 20 patients, 501 to 1000 pg/mL for 2 patients, and 1001 to 2000 for 1 patient. Discharge data were not reported or was missing for 9 patients.

Comment As discussed earlier, venom levels cannot be interpreted without demonstration that the presence of antivenom in serum does not interfere with venom activity. Since the assays for venom are based on binding, such information would likely be lacking.

Safety:
Exposure Each patient treated with Anascorp received between 1 and 6 vials of Anascorp (lyophilized powder) reconstituted with 5 mL normal saline solution and administered as an IV bolus dose. In addition to Anascorp, 6 patients received concurrent steroids or antihistamines, which could have masked adverse events.

Adverse Events Three of 105 patients (ID #-----(b)(6)-----) reported transient adverse events. However, they improved to the extent to meet discharge criteria at 61, 65, and 45 minutes following treatment respectively. There were no reports of deaths, serious adverse events, or other significant adverse events. Vital signs were recorded upon admission.

Comment The data listings are unhelpful in identifying the adverse events, as the AE listing has no information other than a "yes" after the patient ID number. The applicant should provide details of the AEs in the study.

Safety Conclusion:
1. The study report concludes that Anascorp is well tolerated in the treatment of envenomation by scorpions.
2. The adverse event reporting suffers from same problems as in AL-02/03, as some subjects used antihistamines or corticosteroids, and there is inadequate follow-up. In fact, the data listing does not even give any information on the three subjects. As such, it is not possible to make any firm conclusions on safety in the use of Anascorp in this study. In addition, the adverse events were defined by relatedness to Anascorp treatment, the database would not be complete because of non-reporting of events deemed "not related".

Study AL-02/04: Open Label, Confirmatory, Controlled Clinical Study of Alacramyn in Adult Patients with Scorpion Sting Envenomation

Study AL-02/05: Open Label, Confirmatory, Controlled Clinical Study of Alacramyn in Pediatric Patients with Scorpion Sting Envenomation

Study AL-02/06: Open Label, Confirmatory, Controlled Clinical Study of Alacramyn in Pediatric Patients with Scorpion Sting Envenomation

Study Initiation and Completion:

	AL-02/04	AL-02/05	AL-02/06
First Patient In	19-Nov-05	1-May-05	29-May-05
Last Patient Out	16-Sep-06	2-Jun-06	27-Oct-06

Investigators and Study Centers:

AL-02/04:

- América Vera Castro, MD, Hospital General de Cuautla, Cuautla, Morelos, Mexico

AL-02/05:

- Neydi Osnaya Romero, MD, Hospital del Nino Morelense, Cuernavaca, Morelos, Mexico

AL-02/06

- Leslie Boyer, MD, University of Arizona Health Sciences Center, Tucson, Arizona, USA
- Karen Heath, MD, USPHS Indian Hospital, San Carlos, Arizona, USA
- Andreas A. Theodorou, MD, University of Arizona Health Sciences Center, Tucson, Arizona, USA
- Anne Michelle Ruha, MD, Good Samaritan Medical Center and Phoenix Children Hospital, Phoenix Arizona, USA

Objectives:

- To assess the resolution of clinically important systemic signs of scorpion envenomation within four hours after Anascorp treatment;
- To demonstrate that venom blood levels will decrease within one hour following Anascorp treatment.

Design:

Open-label study for patients presenting for emergency treatment of systemic signs of scorpion envenomation within 5 hours of scorpion sting, with the following Study Flow Chart:

Study Flow Chart

Procedure	Screen	Baseline	Treatment Period	1, 2, 3, & 4 Hours after Start of Anascorp	At Discharge	7 Days Follow-up	14 Days Follow-up
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Medical History Physical Exam Demographics Scorpion Sting Information		X					
Severity Evaluation[1]		X		X	X		
Vital Signs Physical and Symptom Assessments[2]		X		X	X		
Pulse Oximetry[3]		X	X	X	X		
Study Drug Infusion[4]			X				
Laboratory Tests: Hematology Chemistry Urinalysis[5]		X		X			
Laboratory Tests: Venom / Anti-venom blood levels[6]		X		X			
Follow-up Questionnaire[7]						X	X
Concomitant Medications		X	X	X	X	X	X
Adverse Events			X	X	X	X	X

1. Refer to Appendix 1 in protocols (Appendix 16.1.1) for Severity Evaluation (respiratory compromise and pathological agitation) of scorpion envenomation.
2. Vital signs, physical assessment and symptom assessment were performed at baseline, and hourly after initiating Anascorp infusion up to the 4-hour discharge. If patients remained hospitalized after the 4-hour observation, assessments were performed at hospital discharge or at 24 hours if hospitalization continued.
3. Pulse oximetry was initiated prior to start of study drug infusion and continued until discharge.
4. Study Drug Infusion Procedures: Upon enrollment, 02/04 patients received 2 vials of Anascorp whereas 02/05 and 02/06 patients received 3 vials of Anascorp. Patients were evaluated 1 hour after start of study drug infusion. If symptom-free, patients remained in clinic for 2, 3 and 4 hour observations. If patients were not symptom free, they received a 2nd dose (one vial) of Anascorp and were evaluated 2 hours after start of initial infusion. If patients were symptom-free, they remained in clinic for 3 and 4 hour observations. If not symptom free, patients received a 3rd dose (one vial) of Anascorp, and were evaluated 3 hours after start of initial infusion. If patients were symptom free, they remained in clinic for 4-hour discharge procedures. If patients were not symptom free, they received adjunctive treatment as necessary.
5. Laboratory tests were initially scheduled to be performed 1 hour after study drug infusion and at 4-hour discharge; if patients remained hospitalized after the 4-hour observation, laboratory tests were to be done prior to hospital discharge or at 24 hours if hospitalization continued. The protocols were amended to discontinue laboratory testing after the 1-hour specimen.
6. Venom and anti-venom levels were initially to be collected 1 hour after study drug infusion and at 4-hour discharge; if patients remained hospitalized after the 4-hour observation, they were to be collected prior to hospital discharge or at 24 hours if hospitalization continued. The protocols were amended to discontinue the 4-hour specimen, keeping only the 1-hour specimen.
7. Patients were contacted 7 days and 14 days after Anascorp treatment for follow-up interviews.

Anascorp was to be diluted in 50 mL normal saline and was administered IV over 10 minutes or as permitted by the IV access. The initial dose was 2 vials in study AL-02/04 and 3 vials in studies AL-02/05 and AL-02/06. In all studies, subsequent single vial doses of Anascorp, up to a maximum of four vials in AL-02/04 and five vials in 02/05 and 02/06, were administered at one hour intervals until resolution of symptoms (see footnote #4 under Study Flow Chart). The lot numbers used for the study drug were from lots B-5F-11, B-2M-01, and B-6B-01.

If clinically significant signs were absent at 4 hours after the initial dose of Anascorp, a final assessment was performed and the patient was discharged; patients who remained symptomatic received adjunctive treatment as necessary and a final assessment was performed at discharge or at 24 hours post-treatment.

Selection and Number of subjects (planned and analyzed):
It was intended that 26 to 53 patients were to be enrolled in each study. Twenty-two patients were enrolled in study AL-02/04, 29 in AL-02/05, and 50 in AL-02/06 for a combined total of 23 adult patients and 78 pediatric patients treated with Anascorp.

Inclusion Criteria
- Males and females presenting for emergency treatment within 5 hours with clinically important systemic signs of scorpion sting envenomation
    - Study AL-02/04 enrolled adults 18 years to 80 years of age
    - Study AL-02/05 enrolled pediatric patients 6 months to 18 years of age
    - Study AL-02/06 initially enrolled pediatric patients 6 months to 18 years of age, but after Amendment 4 was approved, the age range increased from 6 months to 80 years
- Signed written informed Consent and written Authorization for use of Personal Health Information by patient or guardian
- No participation in a clinical drug trial within the last month or concomitantly

Exclusion Criteria
- Allergy to horse serum
- Use of any antivenom within the last month or concomitantly
- Underlying medical conditions that significantly alter immune response: bone marrow suppression, congenital or acquired immuno-deficiency state, chemotherapy, and chronic corticosteroid use
- Concurrent medical condition involving a baseline neurologic status mimicking envenomation (chorea, tardive dyskinesia, uncontrolled epilepsy)
- Pregnant and nursing women

- Use within the past 24 hours of drugs expected to alter immune response: H1 or H2 blockers or corticosteroids

Exclusion criteria were altered as described by Amendments 4, 3, and 3 to Protocols AL-02/04, 02/05, and 02/06, respectively. After approval of these amendments, H1, H2 blockers and corticosteroids were allowed to be given within 24 hours of hospital admission.

Duration of treatment:
For the individual patient, the study started at hospital admission and ended at time of hospital discharge, or at 24 hours after start of study drug infusion, if hospitalization continued. Patients no longer manifesting clinically important systemic signs of envenomation were discharged at 4 hours after receiving study drug. The outcomes at 7 days and 14 days after discharge were assessed by telephone interview for symptoms suggestive of ongoing venom effect, delayed serum sickness or any other adverse events; as necessary, patients with ongoing symptoms or events were referred for appropriate care.

Criteria for evaluation:
Efficacy: The primary efficacy variable was the resolution of systemic scorpion sting signs and symptoms within four hours after the initiation of Anascorp treatment. The secondary efficacy variable was detection of *Centruroides* venom levels from plasma samples taken at baseline, 1 hour after initial study drug infusion, and 4 hours after infusion.

Safety: Safety was assessed using adverse events, clinical laboratory tests (hematology, chemistry, and urinalysis), vital signs, and medical history and physical examination abnormalities. The patients were monitored for treatment-emergent adverse events including acute hypersensitivity reactions and delayed serum sickness.

Statistical methods:
Sample Size A total of >26 to 53 subjects enrolled per pediatric and adult age groups was determined to be sufficient to discern a significant difference between Anascorp and historical (untreated) patients assuming success of 0.85 – 0.95 for Anascorp treated patients.

Subject Populations All subjects who received at least one dose of therapy were evaluated.

Efficacy Analysis The primary efficacy variable (patient success) was the resolution of clinically important systemic signs of scorpion envenomation within 4 hours after initiation of Anascorp treatment.

Safety Analysis Safety analysis using descriptive statistics included summaries of incidence rates, severity, and type of adverse events (AEs).

Venom/Antivenom Analysis Blood venom and antivenom levels were measured at baseline prior to administration of Anascorp and post-baseline, one hour and/or four hours after initiation of Anascorp infusion.

Demographic and Efficacy results
A total of 23 adult patients and 78 pediatric patients were enrolled in the 3 studies.

Adults were all Hispanic whereas pediatric patients were primarily Hispanic (44%) or Native American (44%). For adults were, females (64%) predominated, whereas for pediatric patients, the majority were male (59%).

Study drug infusion was initiated within a few hours (median 1.7 hours; mean 2.2 hours) following scorpion sting; however, infusion was initiated in Mexican patients, on average, over an hour before U.S. patients. The envenomation syndrome resolved within 4 hours of initiating treatment in 98% of patients, with 88% resolving within 1-2 hours.

The rapid resolution of systemic symptoms allowed short duration of hospitalization (median 4.0 hours) for the majority of patients; only 12 of 101 patients (12%) were hospitalized for ≥six hours after initiation of infusion. All patients experienced ≥1 significant sign or symptom of envenomation (respiratory compromise or pathological agitation) at baseline; by discharge, all were free of significant signs and symptoms.

Evaluable venom levels were obtained at baseline and at 1 hour in 71 patients. Venom levels were reduced by ≥90% baseline values in 93% (66 of 71) patients within 1 hour of Anascorp infusion.

Comment As discussed earlier, it is critical to have the serum venom assay validated for non-interference in the presence of antivenom in serum.

Safety results

Extent of Exposure Patients enrolled in study AL-02/04 initially received 2 vials of Anascorp whereas patients in studies AL-02/05 and AL-02/06 initially received 3 vials. Subsequent dosing was 1 vial at one-hour intervals for all protocols up to a maximum of 4 vials for AL-02/04 and 5 vials for the other 2 studies. Nearly 60% of the adult patients in study AL-02/04 received only the initial dose of 2 vials. The number of pediatric patients receiving only the initial dose of 3 vials was 92% in study AL-02/06, in contrast to study AL-02/05 where most (59%) of the pediatric patients required treatment beyond the initial dose. The maximum total time over which Anascorp was administered to patients in any of the 3 studies and the maximum number of vials were 260 minutes and 10 vials, respectively (for patient #(b)(6) in AL-02/05).

Comment Since the maximum allowed for Study AL-02/05 was 5 vials, administering 10 vials of antivenom was definitely a protocol violation.

Study Drug Exposure

	AL-02/04 Adult [18 to 80 years] (N=22)	AL-02/05 Pediatric [6 mo to 18 years] (N=29)	AL-02/06 Pediatric [6 mo to 18 years] (N=49) [1]	Overall (N=101) [1]
Total Number of Vials[1]				
2	13 (59%)	0	0	13 (13%)
3	3 (14%)	12 (41%)	45 (94%)	60 (60%)
4	6 (27%)	13 (45%)	3 (6.2%)	23 (23%)
>4	0	4 (14%)	0	4 (4.0%)
Mean (SD)	2.7 (0.9)	3.9 (1.3)	3.1 (0.2)	3.2 (1.0)
Median	2	4	3	3
Range	2 to 4	3 to 10	3 to 4	2 to 10
Total Study Drug Administration (duration minutes)				
Mean (SD)	31.6 (17.7)	24.9 (18.0)	13.5 (6.6)	20.8 (15.3)
Median	20	20	10	16
Range	10 to 60	5 to 95	5 to 38	5 to 95
Period over which drug was administered (duration minutes)				
Mean (SD)	61.1 (59.4)	61.4 (55.2)	19.5 (30.4)	41.6 (50.3)
Median	20	68	10	17
Range	10 to 220	5 to 260	5 to 203	5 to 260

[1]Subject #(b)(6) excluded because total number of vials unknown, as IV access was lost after only approximately one-quarter of study drug volume was infused, so N=48 for AL-02/06 and N=100 for Overall.

Adverse Events

Overall, nearly 20% of patients reported at least one AE, with a lower percentage in study AL-02/05 (10%) compared to study AL-02/04 and AL-02/06 (23% and 22%, respectively).

All Adverse Events by Organ/System

	AL-02/04 Adult [18 to 80 years] (N=22)	AL-02/05 Pediatric [6 mo to 18 years] (N=29)	AL-02/06 Pediatric [6 mo to 18 years] (N=49)	Overall (N=101)
Patients reporting at least one adverse event	5 (23%)	3 (10%)	11 (22%)	20 (20%)
SYSTEM ORGAN CLASS **Preferred Term**				
GASTROINTESTINAL DISORDERS	1 (4.5%)	1 (3.4%)	5 (10%)	7 (6.9%)
Abdominal distension	1 (4.5%)	0	0	1 (1.0%)
Diarrhoea	0	0	2 (4.1%)	2 (2.0%)
Gastrointestinal haemorrhage	0	1 (3.4%)	0	1 (1.0%)
Vomiting	0	0	3 (6.1%)	3 (3.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (9.1%)	2 (6.9%)	2 (4.1%)	6 (5.9%)
Fatigue	1 (4.5%)	0	0	1 (1.0%)
Pain	1 (4.5%)	0	1 (2.0%)	2 (2.0%)
Pyrexia	0	2 (6.9%)	2 (4.1%)	4 (4.0%)
INFECTIONS AND INFESTATIONS	0	1 (3.4%)	2 (4.1%)	3 (3.0%)
Bronchiolitis	0	1 (3.4%)	0	1 (1.0%)
Otitis media acute	0	0	1 (2.0%)	1 (1.0%)
Rhinitis	0	0	1 (2.0%)	1 (1.0%)
METABOLISM AND NUTRITION DISORDERS	0	0	0	1 (1.0%)
Dehydration	0	0	0	1 (1.0%)[1]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (4.5%)	0	1 (2.0%)	2 (2.0%)
Arthralgia	1 (4.5%)	0	0	1 (1.0%)
Myalgia	0	0	1 (2.0%)	1 (1.0%)
NERVOUS SYSTEM DISORDERS	1 (4.5%)	0	3 (6.1%)	4 (4.0%)
Coordination abnormal	0	0	1 (2.0%)	1 (1.0%)
Headache	0	0	1 (2.0%)	1 (1.0%)
Lethargy	0	0	2 (4.1%)	2 (2.0%)
Paraesthesia	1 (4.5%)	0	0	1 (1.0%)
PSYCHIATRIC DISORDERS	0	0	3 (6.1%)	3 (3.0%)
Agitation	0	0	2 (4.1%)	2 (2.0%)
Crying	0	0	1 (2.0%)	1 (1.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	2 (4.1%)	2 (2.0%)
Respiratory distress	0	0	1 (2.0%)	1 (1.0%)
Upper respiratory tract inflammation	0	0	1 (2.0%)	1 (1.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (4.5%)	0	0	1 (1.0%)
Rash	1 (4.5%)	0	0	1 (1.0%)
VASCULAR DISORDERS	2 (9.1%)	0	0	2 (2.0%)
Hypertension	1 (4.5%)	0	0	1 (1.0%)
Hypotension	1 (4.5%)	0	0	1 (1.0%)

[1]Includes patient #(b)(6) in AL-02/06 (protocol violator due to age) who only had one AE (dehydration) which is captured in OVERALL results.

Adverse Events by Total Number of Vials Received

	AL-02/04 Adult [>18 years]			AL-02/05 Pediatric [6 mo to 18 years]			AL-02/06[1] Pediatric [6 mo to 18 years]		
	≤2 vials (N=13)	3 vials (N=3)	≥4 vials (N=6)	≤2 vials NAP	3 vials (N=12)	≥4 vials (N=17)	≤2 vials NAP	3 vials[2] (N=45)	≥4 vials (N=3)
Patients reporting at least one adverse event	2 (15%)	2 (67%)	1 (17%)	NAP	1 (8.3%)	2 (12%)	NAP	9 (20%)	2 (67%)
Pyrexia	0	0	0	NAP	0	2 (12%)	NAP	2 (4.4%)	0
Vomiting	0	0	0	NAP	0	0	NAP	2 (4.4%)	1 (33%)
Agitation	0	0	0	NAP	0	0	NAP	1 (2.2%)	1 (33%)

	AL-02/04 Adult [>18 years]			AL-02/05 Pediatric [6 mo to 18 years]			AL-02/06[1] Pediatric [6 mo to 18 years]		
	≤2 vials (N=13)	3 vials (N=3)	≥4 vials (N=6)	≤2 vials NAP	3 vials (N=12)	≥4 vials (N=17)	≤2 vials NAP	3 vials[2] (N=45)	≥4 vials (N=3)
Diarrhoea	0	0	0	NAP	0	0	NAP	2 (4.4%)	0
Lethargy	0	0	0	NAP	0	0	NAP	2 (4.4%)	0
Pain	1 (7.7%)	0	0	NAP	0	0	NAP	1 (2.2%)	0
Abdominal distension	0	0	1 (17%)	NAP	0	0	NAP	0	0
Arthralgia	0	1 (33%)	0	NAP	0	0	NAP	0	0
Bronchiolitis	0	0	0	NAP	1 (8.3%)	0	NAP	0	0
Coordination abnormal	0	0	0	NAP	0	0	NAP	1 (2.2%)	0
Crying	0	0	0	NAP	0	0	NAP	1 (2.2%)	0
Fatigue	0	1 (33%)	0	NAP	0	0	NAP	0	0
Gastrointestinal haemorrhage	0	0	0	NAP	0	1 (5.9%)	NAP	0	0
Headache	0	0	0	NAP	0	0	NAP	1 (2.2%)	0
Hypertension	1 (7.7%)	0	0	NAP	0	0	NAP	0	0
Hypotension	0	1 (33%)	0	NAP	0	0	NAP	0	0
Myalgia	0	0	0	NAP	0	0	NAP	1 (2.2%)	0
Otitis media acute	0	0	0	NAP	0	0	NAP	1 (2.2%)	0
Paraesthesia	1 (7.7%)	0	0	NAP	0	0	NAP	0	0
Rash	1 (7.7%)	0	0	NAP	0	0	NAP	0	0
Respiratory distress	0	0	0	NAP	0	0	NAP	1 (2.2%)	0
Rhinitis	0	0	0	NAP	0	0	NAP	1 (2.2%)	0
Upper respiratory tract inflammation	0	0	0	NAP	0	0	NAP	1 (2.2%)	0

[1] Excludes patient #(b)(6) in AL-02/06 (protocol violator due to age) who had dehydration and received 4 vials
[2] Excludes patient #(b)(6) in AL-02/06 as total number of vials unknown due to loss of IV access
NAP = Not applicable as initial dose was 3 vials in AL-02/05 and AL-02/06

No adverse events were considered to be 'definitely' related to study drug. Only 3 patients, one in each study, had adverse events that the investigator considered 'possibly' related to study drug. The AEs considered to be possibly related to study drug are: arthralgia when contacted at 7 day follow-up, which resolved without intervention, and fever in 2 pediatric patients shortly after receiving study drug. In both cases, the fever was short-lived (<4 hours) and the patients recovered, one without any treatment, and the other with acetaminophen.

One pediatric patient in AL-02/06 experienced an adverse event considered to be *severe*; it was not considered to be related to study drug. Patient ---(b)(6)--- had **respiratory distress** that required nebulizer and hospitalization for observation of possible aspiration pneumonia.

Six (12%) AL-02/06 pediatric patients, 1 (2.0%) AL-02/06 adult patient, and 2 (9.1%) AL-02/04 adult patients experienced AEs of *moderate* severity.

- Only one AE, pyrexia in an 8 year old female patient (#(b)(6)) in study AL-02/06, was considered to be possibly related to study drug. This patient also had upper airway inflammation attributed to intubation, which was treated with dexamethasone, amoxicillin, and racemic epinephrine.
- Of the remaining 8 patients, AEs resolved without treatment in 4 of them (#----------(b)(6)----------), 2 others required simple therapies for their AEs: one patient with fever (#(b)(6)) was treated with acetaminophen and one patient with rhinitis (#(b)(6)) treated with one dose of diphenhydramine. Two other patients with moderate AEs required hospitalization: patient #(b)(6) was rehospitalized for vomiting and patient #(b)(6) had prolonged hospitalization for persistent agitation. All AEs had resolved by the 14 day follow-up.

All Adverse Events by Severity

	Mild			Moderate			Severe			
	AL-02/04 (N=22)	AL-02/05 (N=29)	AL-02/06 (N=49)	AL-02/04 (N=22)	AL-02/05 (N=29)	AL-02/06 (N=49)	AL-02/04 (N=22)	AL-02/05 (N=29)	AL-02/06 (N=49)	Overall (N=101)

	Mild			Moderate			Severe			
	AL-02/04 (N=22)	**AL-02/05 (N=29)**	**AL-02/06 (N=49)**	**AL-02/04 (N=22)**	**AL-02/05 (N=29)**	**AL-02/06 (N=49)**	**AL-02/04 (N=22)**	**AL-02/05 (N=29)**	**AL-02/06 (N=49)**	**Overall (N=101)**
Patients reporting at least one adverse event	3 (14%)	3 (10%)	8 (16%)	2 (9.1%)	0	6 (12%)	0	0	1 (2.0%)	20 (20%)
Preferred Term										
Abdominal distension	0	0	0	1 (4.5%)	0	0	0	0	0	1 (1.0%)
Agitation	0	0	1 (2.0%)	0	0	1 (2.0%)	0	0	0	2 (2.0%)
Arthralgia	1 (4.5%)	0	0	0	0	0	0	0	0	1 (1.0%)
Bronchiolitis	0	1 (3.4%)	0	0	0	0	0	0	0	1 (1.0%)
Coordination abnormal	0	0	1 (2.0%)	0	0	0	0	0	0	1 (1.0%)
Crying	0	0	1 (2.0%)	0	0	0	0	0	0	1 (1.0%)
Dehydration	0	0	0	0	0	0	0	0	0	1 (1.0%)[1]
Diarrhoea	0	0	2 (4.1%)	0	0	0	0	0	0	2 (2.0%)
Fatigue	1 (4.5%)	0	0	0	0	0	0	0	0	1 (1.0%)
Gastrointestinal haemorrhage	0	1 (3.4%)	0	0	0	0	0	0	0	1 (1.0%)
Headache	0	0	1 (2.0%)	0	0	0	0	0	0	1 (1.0%)
Hypertension	1 (4.5%)	0	0	0	0	0	0	0	0	1 (1.0%)
Hypotension	1 (4.5%)	0	0	0	0	0	0	0	0	1 (1.0%)
Lethargy	0	0	1 (2.0%)	0	0	1 (2.0%)	0	0	0	2 (2.0%)
Myalgia	0	0	1 (2.0%)	0	0	0	0	0	0	1 (1.0%)
Otitis media acute	0	0	1 (2.0%)	0	0	0	0	0	0	1 (1.0%)
Pain	0	0	1 (2.0%)	1 (4.5%)	0	0	0	0	0	2 (2.0%)
Paraesthesia	1 (4.5%)	0	0	0	0	0	0	0	0	1 (1.0%)
Pyrexia	0	2 (6.9%)	0	0	0	2 (4.1%)	0	0	0	4 (4.0%)
Rash	0	0	0	1 (4.5%)	0	0	0	0	0	1 (1.0%)
Respiratory distress	0	0	0	0	0	0	0	0	1 (2.0%)	1 (1.0%)
Rhinitis	0	0	0	0	0	1 (2.0%)	0	0	0	1 (1.0%)
Upper respiratory tract inflammation	0	0	0	0	0	1 (2.0%)	0	0	0	1 (1.0%)
Vomiting	0	0	3 (6.1%)	0	0	1 (2.0%)	0	0	0	3 (3.0%)

Follow-up evaluation of adverse events by time

At the 7 day and 14 day follow-up telephone calls, patients or family members were interviewed to determine if there were ongoing envenomation effects, signs of serum sickness, or other adverse events. Only one patient was re-hospitalized. This pediatric patient was re-admitted the day after discharge because of persistent vomiting and dehydration. No patients were considered to have possible serum sickness in any study at either time point.

Serious and Other Important Adverse Events

There were no deaths reported in this study. No patient discontinued drug infusion due to an adverse event. Three patients, all from study AL-02/06 experienced serious adverse events not considered related to study drug.

Serious Adverse Events

	AL-02/04 Adult [18 to 80 years] (N=22)	AL-02/05 Pediatric [6 mo to 18 years] (N=29)	AL-02/06 Pediatric [6 mo to 18 years] (N=49)	Overall (N=101)
Patients reporting at least one adverse event	0	0	3 (6.1%)	3 (3.0%)
GASTROINTESTINAL DISORDERS	0	0	1 (2.0%)	1 (1.0%)
Vomiting	0	0	1 (2.0%)	1 (1.0%)
PSYCHIATRIC DISORDERS	0	0	1 (2.0%)	1 (1.0%)
Agitation	0	0	1 (2.0%)	1 (1.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	1 (2.0%)	1 (1.0%)
Respiratory distress	0	0	1 (2.0%)	1 (1.0%)

No patient was considered to have a clinically significant hematology or chemistry laboratory abnormality by the investigator.

Safety Conclusions

1. The study report concludes that
- The median number of vials received was 2, 4, and 3 vials in AL-02/04, AL-02/05, and AL-02/06, respectively. Overall, 73% of all patients had resolution with 3 vials or less.
- Anascorp administration was not associated with death or serious adverse events.
- One-fifth of the ITT population (20%; 20/101) reported at least one adverse event (AE); the remainder reported no adverse events.
- The most frequent AEs, pyrexia (4%; 4/101) and vomiting (3%; 3/101), were reported only in pediatric patients. It is noted that they have also been reported with scorpion envenomation.
- No patients had any signs of an acute hypersensitivity reaction or serum sickness.
- There were no clinically significant laboratory abnormalities, and the majority of patients showed improvement in post-baseline chemistry and hematology values compared to baseline values.
- On discharge / after treatment, nearly all patients had marked improvement in their vital signs, with decreases in heart rate, respiratory rate, and blood pressure readings.

2. As with Studies AL-02/03 and AL-99/02, the adverse event reporting suffers from masking effects by antihistamines or corticosteroids in some patients, and there is inadequate follow-up, based almost entirely on phone contact in lieu of actual interview with physical examination and lab tests. With pediatric patients, the information from phone contact would likely be second-hand and this adds to the uncertainty about accuracy of the follow-up safety data.

Study AL-03/07: Open Treatment Protocol for Use of Anascorp™ in Patients with Scorpion Sting Envenomation [Initiated 5/23/05, ongoing; Interim Report cut-off date 9/23/06 and "Statistical Report" cut-off date June 2008]

Phase: 2/3

Principal Investigator: Leslie Boyer, M.D.
Medical Director, Arizona Poison and Drug Information Center
The University of Arizona
Health Sciences Center
1501 N. Campbell Avenue
Tucson, Arizona 85724

Other Investigators and Study Centers:*
Dr. John Barberii / Dr. Linda Miller, Mt. Graham Regional Medical Center, Safford, AZ
Dr. Frederick Fox, Gila Health Resources, Morenci, AZ
Dr. Karen Heath, San Carlos PHS Hospital, San Carlos, AZ

Dr. Alan Roga, Scottsdale Healthcare Shea and Osborn, Scottsdale AZ
Dr. Michelle Ruha, Phoenix Children's Hospital, Phoenix, AZ
Dr. Fawad Tanvir / Dr. John Barberii, Southeast Arizona Medical Center, Douglas, AZ
Dr. Octavio J. Vidal, Casa Grande Regional Hospital, Casa Grande, AZ
Dr. Joshua Zeidler, Chandler Regional Hospital, Chandler, AZ and Mercy Gilbert Medical Center, Safford, AZ
*from Interim Report; additional centers after Interim Report cut-off include –

Dr. Duane Crist of Mesa, AZ
Dr. Trina Bogart of Glendale, AZ
Dr. Tim Johns of Gilbert, AZ
Dr. Carol Hippenmeyer of Nogales, AZ
Dr. Nelson Faux of Phoenix, AZ
Dr. Frank LoVecchio of Phoenix, AZ
Dr. Clayton Hargis of Safford, AZ
Dr. Barbara Vize of Sells, AZ
Dr. Michael MacNeel of Tucson, AZ
Dr. Andreas Theodorou of Tucson, AZ
Dr. Dwight Humphrys of Whiteriver, AZ

Objective:

- To assess the resolution of systemic signs of scorpion envenomation and
- To evaluate the adverse event profile following Anascorp treatment.

Design:

Patients diagnosed with systemic scorpion sting symptoms who met the selection criteria and for whom written informed consent was provided were entered in the study. 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 the resolution of symptoms.

All patients were monitored for treatment emergent AEs including acute hypersensitivity reactions and serum sickness. 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 adverse events; as necessary, patients with ongoing symptoms or events were referred for appropriate care.

Study Flow Chart

Procedure	Screening	Baseline	Treatment Period	Upon Discharge	24 Hours Follow-up	14 Days Follow-up
Informed Consent	X					
Inclusion/exclusion criteria	X					
Medical History Physical Exam Demographics Scorpion sting information		X				
Physical and Symptom Assessments		X		X		
Study Drug Infusion			X			
Follow-up Questionnaire					X	X
Concomitant Medications		X		X	X	X
Adverse Events			X	X	X	X

Selection and Number of subjects:

Approximately 100-150 patients of any age who required emergency treatment for scorpion sting due to clinically important systemic signs of scorpion envenomation were to be enrolled into the study per year until marketing approval of the product by the FDA was achieved or discontinuation of the study was deemed to be appropriate.

Inclusion Criteria

- Males and females of any age presenting for emergency treatment with clinically important systemic signs of scorpion sting envenomation
- Signed written informed consent and written authorization for use of Personal Health Information by patient or guardian

Exclusion Criteria

Patients with known allergy to horse serum

Test product, dose and mode of administration, batch number:

Anascorp used in this study was at least 85% pure $F(ab')_2$ and no more than 7% Fab, with (b)(4) or less low molecular weight components. The maximum protein content was (b)(4), less than 5% IgG and less than ------(b)(4)-----. Anascorp was diluted in 20 to 50 mL normal saline and was intravenously administered over ten 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.

Comment As in AL-02/03, the study report states that the maximum protein content of the Anascorp used was (b)(4). This differs from the specifications for release, and it is necessary to confirm that the same formulation has been used for AL-02/03 and AL-03/07 as the one proposed for marketing.

Patients treated through 9/23/06, whose data are included in the Interim Report, received Anascorp from clinical lots B-2M-01, B-6B-01 or B-5M-02.

Duration of treatment:

Up to 2.5 hours

Criteria for evaluation:

Resolution of systemic scorpion sting signs and symptoms

Statistical methods:

Sample Size The total number of subjects enrolled was determined by the number of systemic scorpion stings anticipated at the treating centers per year.

Subject Populations All subjects who received at least one dose of therapy were evaluated.

Efficacy Analysis The primary clinical efficacy variable (patient success) was the resolution of clinically important systemic signs of scorpion envenomation after Anascorp treatment.

Safety Analysis Safety analysis using descriptive statistics included summaries of incidence rates, severity, and type of AEs.

Safety Results:

Because the Interim Report is Outdated, the following results are based primarily on the "Statistical Report" with cut-off date of June 2008.

Depending on the time the patient enrolled into AL-03/07, the "Statistical Report" divides the time frame between 5/23/05 to June 2008 into 3 parts: Part 1 being from August 2005 to September 2006, Part 2 between October 2006 and June 2007, and Part 3 between July 2007 and June 2008. As of June, 2008, 554 patients (Part 1 with 122 patients, Part 2 with 268, Part 3 with 164) have been treated under Study AL-03/07. The overall completion rate by the patients was >90% (Part 1 - 96.6%, Part 2 - 93.5%, and Part 3 - 93.6%).

The average age for each part of the study was between 10.3 and 16.4 years of age. The smallest percentage of adults for a study part was “Part 2” (12.2%). The percentage of adults in Part 2 was approximately half the percentage of adults in Part 1 (28.8%), meaning a greater percent of the “Part 1” population was made up of patients >18 years of age.

Adverse Events

Among the 554 patients treated by June 2008, 204 (36.8%) had reported an adverse event (95% C.I. 32.8% to 41.0%), with a total of 372 AEs. The most common reported AEs were vomiting (7.4%), pyrexia (4.9%) and rash (4.5%).

The number of patients reporting “related” AEs was 70, with a rate of 12.6% (based on total of 554 subjects; 95% C.I. 10.0% to 15.7%). The only “related” AEs with a rate >2% was rash (2.5%) and vomiting (2.5%).

Seven patients (1.3%) reported at least one SAE, one with “related” SAEs – eye swelling and stridor (#--(b)(6)--). The narratives are given below:

- Patient -----(b)(6)----- was a 3.8 year old black male with significant medical history of chronic bronchitis and allergies to peanuts, amoxicillin, and cats, who was stung 2.4 hours prior to receiving Anascorp infusion. Vital signs on admission included HR of 140 bpm, RR of 26 breaths per minute, and BP of 152/98 mmHg. The patient received a total of 3 vials of Anascorp over 20 minutes. Five minutes after the infusion ended, the patient developed hives on both eyelids, vomited once and developed labored breathing. He was treated with IV diphenhydramine, subcutaneous epinephrine, nebulized racemic epinephrine, and IV solumedrol. His symptoms resolved in 34 minutes, and he was admitted to the pediatric ICU for overnight observation. The patient was discharged the next morning without further problems on follow-up. Incidentally, the nurse involved in his acute care had eaten a peanut butter sandwich between the time she set up the intravenous line and the time she stopped the infusion, and the mother stated that the patient had a similar reaction when he had ingested peanuts in the past. A formal allergy consultation, with skin prick testing, later demonstrated that the child reacted both to peanuts and to horse serum. The investigator considered these AEs to be a Type I hypersensitivity reaction (anaphylaxis), but whether to antivenom or to peanut antigen could not be determined.
- Patient -----(b)(6)----- was a one year old white female who presented to the emergency department (ED) unresponsive and flaccid. She had been ill for several days prior to admission. The mother found the patient frothing at the mouth and nose, with clenched teeth and rigid movements. Because a scorpion was found next to the child, a decision was made to treat with Anascorp. Vital signs on admission included heart rate (HR) of 180 beats per minute (bpm), respiratory rate (RR) of 36 breaths per minute, and blood pressure (BP) of 164/111 mmHg. Midway through the second vial of Anascorp, the patient was noted to have respiratory acidosis and hypercapnia. Midway through the third vial of Anascorp, patient experienced severe respiratory distress requiring intubation. The Anascorp infusion was discontinued so the IV could be used to deliver other medication. Two hours and 15 minutes after her initial exam, the patient was transferred to Phoenix Children’s Hospital. Vital signs at transfer were HR of 165 bpm and BP of 112/69 mmHg; (no RR as patient was intubated and mechanically ventilated). The patient was extubated within an hour of arriving at Phoenix Children’s Hospital, but remained hospitalized for observation. Twenty-four hours later, the patient was discharged; follow-up 14 days later found no sequelae.
- Patient -----(b)(6)----- was a five year old white female with significant medical history of Down’s syndrome and post-cardiac surgery who was stung 30 minutes prior to start of Anascorp infusion. On presentation to the ED, the patient had nystagmus, muscle twitching, agitation, severe bronchorrhea, rhinorrhea, and an episode of vomiting, which raised concerns for possible aspiration. Vital signs included HR of 180 bpm and RR of 32 breaths per minute. Oxygen saturation by pulse oximetry was 94%. The patient received a total of 5 vials of Anascorp over 2 hours 10 minutes. After treatment, her envenomation symptoms were resolved, but she had low oxygen saturation readings in the mid-80’s, requiring supplemental oxygen and a chest X-ray showed alveolar infiltrates. The patient received inhaled salbutamol and furosemide for respiratory distress, and was transferred to Phoenix Children’s Hospital for care under her cardiologist. At time of transfer, HR was 126 bpm and RR was 36 breaths per minute. The patient was discharged 4 days later without further sequelae.
- Patient -----(b)(6)----- was a 1.7 year old black male who was stung nearly 4 hours prior to start of Anascorp infusion. On presentation to the ED, he had nystagmus, hypersalivation, and agitation. Vital signs on admission included HR of 147 bpm, RR of 24 breaths per minute, and BP of 124/60 mmHg. The patient received a total of 3 vials of Anascorp over 1 hour 14 minutes with resolution of envenomation symptoms. After 3 hours of observation, the patient was discharged with HR of 114 bpm and RR of 24 breaths per minute. Thirty minutes after discharge, the patient was reported to start vomiting, and was readmitted for observation to rule out aspiration. The patient was discharged the next morning with amoxicillin, which was prescribed for one week. No further problems were recorded.
- Patient -----(b)(6)----- was a 46 year old Hispanic male with PMH of hypertension, prior myocardial infarction, and migraines, who was stung over 5 hours prior to receiving Anascorp infusion. Vital signs on admission included HR of 131 bpm, RR of 22 breaths per minute, and BP of 125/92 mmHg. The patient received a total of 5 vials of Anascorp over 2 hours 8 minutes. Forty-five minutes after completion of the last dose, the patient became extremely agitated and irritable with limb thrashing. Leather restraints were applied, and the patient was transferred to the ICU, where he was treated with lorazepam, diazepam, haloperidol, morphine, and pantoprazole. His agitation resolved 2 days later, and he was discharged. He complained of fatigue for 3 days after discharge that resolved without treatment and mild numbness in the hand that was stung at the 14 day follow-up call.

- Patient -----(b)(6)----- was a 1 year old Asian female who was stung less than one hour prior to receiving Anascorp infusion. Vital signs on admission included HR of 109 bpm, RR of 20 breaths per minute, and BP of 101/54 mmHg. The patient had envenomation symptoms which included abnormal eye movements, increased secretions, respiratory distress, and limb thrashing. She received a total of 5 vials of Anascorp over 70 minutes with resolution of her symptoms. During treatment, a fever of 102.1°F was noted, and despite a negative chest X-ray, she was admitted for observation to rule out possible aspiration pneumonia. She received acetaminophen during her hospitalization, and her fever resolved. She was discharged the next day with no further sequelae.
- Patient -----(b)(6)----- was a 5.6 year old white male who was stung 3.3 hours prior to start of Anascorp infusion. At baseline, he had abnormal eye movements, limb thrashing, diaphoresis, and tachycardia, with HR of 175 bpm on admission. He was treated with 4 vials of Anascorp, and his envenomation symptoms resolved. However, prior to discharge, he vomited twice, and the treating physician decided to admit him for observation. He was discharged approximately 6 hours later.

Follow-up after Discharge

Patients received phone calls at 24 hrs and 14 days for assessment of the following: itchiness, rash, petechiae, arthralgia, myalgia, nausea, vomiting, dehydration, chest pain, hematuria, "other", and serum sickness. There was a total of 5 patients (1.1%) reporting serum sickness at Day 14, none at 24 hrs.

CRFs were reviewed by the principal investigator, Dr. Boyer, for assessment of possible serum sickness. Dr. Boyer determined that 5 patients in study 03/07 with rash (----------(b)(6)----------), and 1 patient with pruritus (---(b)(6)---), might have had serum sickness, although in no case was the full serum sickness syndrome described.

- Patient ----(b)(6)---- was a 4 year old white female, weight 14.5 kg, who was stung approximately 3 hours prior to start of Anascorp infusion. Vital signs on admission included heart rate (HR) of 131 beats per minute (bpm) and respiratory rate (RR) of 24 breaths per minute. The patient received a total of 3 vials of Anascorp over 1 hour 25 minutes, after which envenomation symptoms were resolved. The patient was observed for 1 hour 15 minutes and discharged with HR of 113 bpm and RR of 16 breaths per minute. When contacted at the 14 day follow-up, the family reported that one day after discharge, the patient had 3 episodes of vomiting that resolved without treatment. Twelve days post-discharge, the patient developed a rash on chest and legs and complained of itching of hands and feet. After treatment with one dose of diphenhydramine, both rash and itching resolved. No arthralgias, myalgias, or signs of serum sickness other than this transient rash were noted.
- Patient --(b)(6)-- was a 2 year old white male, weight 15 kg, who was stung 1 hour prior to start of Anascorp infusion. Vital signs on admission included HR of 155 bpm and RR of 28 breaths per minute. The patient received a total of 2 vials of Anascorp over 50 minutes after which envenomation symptoms were resolved. The patient was observed for an additional 40 minutes and discharged with HR of 85 bpm and RR of 20 breaths per minute. When contacted at the 14 day follow-up, the family reported that 7 days after discharge, the patient had developed a "hive-like" rash on the back of his neck that worsened and spread to entire body except the face. The patient was treated with diphenhydramine and hydrocortisone cream every 4 hours for 3 days with resolution. The patient also complained of a headache on days 15 and 16 post-discharge that was treated with acetaminophen with resolution. No arthralgias, myalgias, or signs of serum sickness other than the rash were noted.
- Patient ---(b)(6)--- was an 80 year old white male, weight 79 kg, who was stung 3 hours prior to start of Anascorp infusion. Vital signs on admission included HR of 102 bpm, RR of 18 breaths per minute, and BP of 146/90 mmHg. He received a total of 4 vials of Anascorp, and was discharged with resolution of symptoms only 2 hours from start of infusion. One week after discharge, the patient developed a rash, accompanied by itching. He was treated with diphenhydramine and methylprednisolone, with resolution of the rash one week later. The patient also developed edema around his mouth one day after onset of the rash, which lasted 3 days. Finally, the patient complained of fatigue beginning 13 days post-discharge, which resolved after 5 days without any treatment. No arthralgias, myalgias, or signs of serum sickness other than the cutaneous findings and fatigue were noted.
- Patient --(b)(6)-- was a 6 month old male, weight 7.1 kg, who was stung approximately 1.5 hours prior to start of Anascorp infusion. Vital signs on admission included HR of 220 bpm, RR of 39 breaths per minute, BP of 132/99 mmHg, and temperature of 38.3°C. The patient received a total of 4 vials of Anascorp, and he was discharged 3 hours from start of infusion with resolution of symptoms and improvement of vital signs (HR 150 bpm, RR 30 breaths per minute, BP 118/60 mmHg, and temperature of 37.8°C. Nine days post-discharge, the patient developed a rash in the axilla and diaper area. Dexamethasone was prescribed, and the patient had resolution of the rash 6 days later. No arthralgias, myalgias, or signs of serum sickness other than the rash were noted.
- Patient ---(b)(6)--- was a 2.5 year old white male, weight 15.9 kg, who was stung approximately 2.25 hours prior to start of Anascorp infusion. Vital signs on admission included HR of 138 bpm, RR of 18 breaths per minute, BP of 120/77 mmHg, and temperature of 37.2 °C. He received a total of 3 vials of Anascorp, and he was discharged only 1.5 hours after the start of infusion with resolution of symptoms and improvement of vital signs (HR 84 bpm, RR 25 breaths per minute, BP 96/44 mmHg, and temperature of 36.3 °C). Eight days after discharge, the patient developed a generalised body rash, initially most prominent in the axillary and groin regions, without accompanying pruritus. No treatment was given, and the rash resolved after 9 days. Also, 16 days post-discharge, the patient experienced a short-lived fever lasting only 1 day, which resolved without treatment. No arthralgias, myalgias, or signs of serum sickness other than the rash and fever were noted.
- Patient ---(b)(6)--- was a 4.4 year old white male, weight 24.1 kg, who was stung 4.75 hours prior to receiving 3 vials of Anascorp. Vital signs on admission included HR of 169 bpm, RR of 22 breaths per minute and BP of 120/53 mmHg. Symptoms resolved one hour after infusion, and the patient was discharged 30 minutes later. One week after discharge,

In addition, comments were made by investigators about 4 other patients suggestive of serum sickness. Patient ---(b)(6)--- had diarrhea 9 days post-discharge and fever plus "spots in eyes" beginning 11 days post-discharge. Patient ---(b)(6)--- developed influenza symptoms 10 days after discharge; the investigator felt that serum sickness could mimic influenza. Patient (b)(6) had bilateral leg myalgia 2 days after discharge and generalized body itching 4 days after discharge, lasting 2 days which the investigator considered may have been serum sickness. Patient -(b)(6)- developed hives and itching on his left arm 5 days post-discharge, lasting 48 hours; one week later, he developed hives and itching around his waist, lasting 3 days, which he treated with topical baking soda paste to relieve the itching.

Laboratory Findings Clinical laboratory data were not collected in this study.

Conclusions

1. The "Statistical Report" concludes that based on the results of this study, there appears to be evidence that the use of Anascorp for the treatment of envenomation is safe, effective and well tolerated.
2. This study based on a treatment protocol provides a large database to support the safety of Anascorp in the treatment of scorpion evenomation.
3. Data collection encounters the same deficiencies as in the other open-label clinical trials for Anascorp. The use of antihistamines or corticosteroids is not specifically prohibited in the protocol, and there are often confounding concomitant medications such as benzodiazepams and narcotics. Follow-up does not involve direct patient-Investigator contact, but via phone calls by the clinical site research or study nurses. In addition, this study does not include clinical laboratory testing.
4. Unlike in other studies on Anascorp, an attempt has been made by the Principal Investigator, Dr. Leslie Boyer, to examine the follow-up record in search of occurrence of serum sickness. Due to the limitations discussed above, the 6 cases with rash or pruritus on follow-up can only be regarded as being tentative, but not be conclusively established for the diagnosis of serum sickness.

Overall Conclusion from Open-Label Studies AL-99/02, AL-02/04, AL-02/05, AL-02/06, AL-03/07

- These open-label studies lend support for the safety of Anascorp in the treatment of scorpion envenomation in adult and pediatric patients, but are not adequate and well-controlled clinical trials to provide substantial evidence of effectiveness.
- Despite the limitations of study design, such as allowing the use of confounding concomitant medications and the lack of personal contact or laboratory tests at follow-up, administration of Anascorp, which is an equine F(ab')2 product, has not been associated with serious allergic reactions, and has not been conclusively shown to produce delayed serum sickness syndrome.

Conclusions and Recommendations

1. This submission has provided clinical data to support the safety of Anascorp despite uncertainties regarding the occurrence of serum sickness on follow-up.

2. Effectiveness in the management of patients with "important signs of scorpion envenomation" is primarily driven by sings of "pathological agitation", and there are uncertainties in the objectiveness of the evaluations. At this time, I recommend a CR Letter for the applicant to address these uncertainties before final decision on product licensure.

3. I recommend the following comments in a CR Letter:

Overall Clinical Comments

1. We note that your study reports in the Clinical Section (Item 8) of this BLA do not bear signatures of the responsible parties. For instance, the pages for "Signature of Sponsor's Responsible Medical Officer" have the wording "not applicable." Please submit signed clinical study reports or documentation that "a responsible medical officer" was responsible for eqch clinical study report.

2. 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. There should be a systematic approach to dosing based on pharmacokinetics, body mass, and the use of concomitant medications in the clinical development program for the product.

3. In all of the clinical studies presented, subject follow-up after discharge is based on telephone interview and not actual 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.

4. 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 benzodiazepams and narcotics. Please address how safety can be adequately evaluated in the presence of these mitigating or confounding factors.

5. In several of the clinical studies, including the pivotal trial, AL-02/03, the decline in serum venom levels by a binding assay after Anascorp treatment is used 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 uninterpretable.

6. 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 has been used for your clinical studies as the one proposed for marketing.

Study AL-02/03

7. The primary efficacy endpoint was to demonstrate resolution of clinically important systemic signs of scorpion envenomation within 4 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.

- As indicated in this protocol, judgment of the resolution of the clinical signs was left at the discretion of the Investigator. 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 out 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.
- 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, as 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, none of the "respiratory compromise" signs are verifiable from the information submitted. Please address the fact that since all signs of "respiratory compromise" in the 3 study subjects subsided within 2 hours of treatment, no effectiveness can be inferred for Anascorp

- For the treatment of a serious and life-threatening condition, the product should demonstrate effect on mortality or major morbidities. In AL-02/03, no efficacy has been demonstrated 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 a study on subjects with more serious manifestations would be needed if your product claim includes treatment of a serious and life-threatening condition.

8. In the original submission of this protocol to IND (b)(4), at least 12 subjects were proposed as sample size 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 being studied are not life-threatening, such as agitation in the absence of respiratory or other serious manifestations, then 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 (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 has been estimated to be 0.1.

9. The placebo is said to be lyophilized material to be reconstituted with normal saline, but the finalized protocol dated 11/30/03 states it is normal saline (p.7 of protocol, BLA vol 1.8, p.194). Please provide detailed information on the nature of the placebo.

10. Please address the imbalance between treatment arms in:

- the subjects' age (and hence maturity and body mass),
- the time between scorpion sting and administration of test product, and
- the median dose of midazolam sedation administered prior to study enrollment.

11. 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.

12. 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.

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

13. 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 would appear 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.

14. 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, this cannot be considered as 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.

AL-99/02

15. 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).

16. 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".

17. 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.

AL-03/07

18. In this BLA submission, you have not provided an up-to-date study report of AL-03/07. Although you have included an interim report covering the period 5/23/05 to 9/23/06, 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.

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