STN: 125335/0

PRIORITY DESIGNATION: Yes

ORPHAN DESIGNATION: Yes

APPLICANT: Rare Disease Therapeutics, Inc.

PRODUCT: Centruroides (Scorpion) Immune $F(ab')_2$ (Equine) Injection
Trade name: Anascorp®

INDICATION: For treatment of clinical signs of scorpion envenomation

ROUTE OF ADMINISTRATION: Intravenous use only

DATE SUBMITTED: 22 January 2009

ADD: 03 August 2011

REVIEWER: Nisha Jain, M.D.

SUBJECT: Final Clinical Review Memo

RPM: Debbie Cordaro

CHAIRPERSON: Robert Fisher, PhD

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1 RECOMMENDATION

1.1 Recommendation on Regulatory Action

The licensure of Anascorp is recommended as adequate safety and efficacy have been demonstrated for treatment of patients with clinical signs of scorpion envenomation. The efficacy of Anascorp was established in a prospective, randomized, double-blind, placebo controlled study in patients with signs of scorpion sting envenomation in Arizona, U.S.

2 EXECUTIVE SUMMARY

Instituto Bioclón, S.A. de C.V. submitted BLA STN 125335 in support of its product, Centruroides (Scorpion) Immune F(ab')$_2$ (Equine) Injection (tradename Anascorp®) indicated for the management of patients with clinically important signs of scorpion envenomation; please note that the sponsor of the BLA was changed to Rare Disease Therapeutics, Inc. in January 2011. The clinical data to support this BLA submission consisted 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 of a retrospective study not involving use of Anascorp (AL-03/06).

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. Birmex[4] in patients with Scorpion sting study in Mexico (CSR-XE-C-05)	**105**
Ongoing AL-03/07. Open treatment protocol for use of Anascorp in patients with scorpion sting envenomation in Arizona, U.S.A, (CSR XE-C-01)	**1425**

[1] Alacramyn is the tradename of the product in Mexico. In the U.S., the proprietary name is "Anascorp".
[2] An additional 7 subjects received placebo.
[3] One report for three "studies": CSR-XE-C-04, for AL-02/04, AL-02/05, and AL-02/06
The pivotal study (AL-02/03) was a double-blind, randomized, placebo-controlled, two-center trial in Arizona in pediatric subjects with "pathological agitation" due to scorpion envenomation. The primary endpoint was 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 placebo.
[4] Scorpion antivenom manufactured by the Mexican government

Among the subjects (N=15) enrolled in study AL-02/03, one subject in each treatment cohort did not have detectable serum venom levels at baseline. Of the remaining 13 subjects with scorpion envenomation, a clinically relevant difference (lower bound of 95% confidence level: 50%) in resolution of the signs of envenomation at 4 hours was observed between Anascorp and placebo subjects.

Success Rates at the End of 4 hrs

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

Anascorp was well tolerated in this study.

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 treatment of clinical signs of scorpion envenomation. The sample size in each study is shown in the Table below:

Protocol #	**Design**	**Sample size**
AL 02/03	Double-blind, randomized, placebo-controlled	Anascorp: 8 (Placebo: 7)
AL 02/04	Open-label, single arm	22
AL 02/05	Open-label, single arm	29
AL 02/06	Open-label, single arm	50
AL 03/07	Open-label, single arm	1425

Safety data from 1425 subjects were obtained in Study AL 03/07. This was an open label single arm multi-center study whose primary objective was to evaluate the adverse event (AE) profile of scorpion envenomation subjects immediately after treatment with Anascorp at 24 hours post-treatment, and 14 days post-treatment. The study was conducted from May 2005, to September 2010. The safety assessment of study drug exposure was summarized using descriptive statistics by age and overall for the following endpoints: duration of actual study drug administration, total time of study drug administration, volume administered and the number of vials received. In addition, number of vials received was also summarized with incident counts and percentages using the following categories: less than or equal to 2 vials, 3 vials, 4 vials, 5 or more vials.

The detailed outcomes of study AL 03/07 are presented below:

Subject Enrollment and Disposition:

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

Efficacy Results:

- As this was an open-label study with no hypothesis testing, the data are not adequate to support efficacy. Nevertheless, for the 1396/1425 subjects with available data, mean time from Anascorp infusion to resolution was 1.42 hours and the maximum time was 20.5 hours. This did not appear to be affected by concomitant use of sedatives. The mean time to discharge was 3.67 hours (historic control: 12.6 hours).
- Only 5 subjects were readmitted to the hospital within 14 days after treatment. During the 14-day follow up period, the most common ongoing symptoms were "other" (11.6%), rash (3.6%), itching (2.8%), vomiting (1.8%), and nausea (1.3%); follow-up data were not available for 6.0% of subjects.

Safety Results:

- Exposure: Subjects received a mean total dose of 3.59 vials, with most receiving 3 (48.1%) or 4 (36.0%) vials of Anascorp.
- All Adverse Events:
    - Overall, 399/1425 subjects (28.0%) experienced a total of 717 Treatment Emergent Adverse Events (TEAEs), with similar incidences in adult (31.6%) and pediatric (27.0%) subjects.
    - The most frequently reported TEAEs were vomiting (4.7%), pyrexia (4.1%), rash (2.8%), nausea and pruritus (2.2% each), headache and rhinorrhoea (2.0% each), myalgia (1.7%), fatigue (1.6%), cough (1.5%), diarrhea (1.2%), and lethargy (1.1%). Pyrexia, rash, and rhinorrhoea were reported more frequently in the pediatric group than in the adult group. Nausea, headache, and myalgia were reported more frequently in adults than in pediatric subjects.
    - All other common TEAEs occurred with similar incidences in both study populations.
    - As to severity, subjects reporting TEAEs experienced TEAEs of mild severity most frequently (17.7%); 8.3% and 1.9% of subjects reported moderate or severe TEAEs, respectively. Severe vomiting, fatigue, and diarrhea were each reported by 0.1% of subjects.
- Adverse Events with at least Possible Relationship to Treatment. Overall, 143 subjects (10.0%) reported at least 1 TEAE with a possible or probable relationship to treatment, or one that was not assessable. The most common treatment-related

As to severity, treatment-related moderate or severe TEAEs were reported in 4.4% of subjects, with a slightly higher incidence in adults (6.5%) than in pediatric subjects (3.8%): vomiting, rash, and pyrexia (0.6% each) and pruritus, diarrhea, and headache (0.3% each) were reported most frequently by all subjects; headache was reported by adults only; rash and pyrexia were more common in pediatric subjects; and diarrhea, rash macular, rash pruritic, fatigue, nausea, and anorexia were reported by pediatric subjects only.

- Deaths, Discontinuations, and Serious Adverse Events (SAEs). No deaths or discontinuations due to TEAEs were reported. Overall, 31/1425 subjects (2.2%) experienced a total of 36 treatment-emergent SAEs (adult 1.3% and pediatric 2.4%). The majority of SAEs were moderate or severe and most were not related to treatment. *Moderate or severe SAEs of respiratory distress and sedation (each in a total of 0.4% overall) were observed exclusively in pediatric subjects; all were considered unrelated to treatment*. Five of 1425 subjects (0.4% overall, 1 adult and 4 pediatric) experienced a total of 9 SAEs considered possibly related or of unknown relationship to treatment (stridor, lethargy, endotracheal intubation, eye swelling, vomiting, nausea, mental state changes, lipase increased, and dehydration). All related SAEs resolved during study, except for one (lipase increased), with unknown outcome.
- Specific Monitored AEs – acute hypersensitivity and serum sickness:
  - Three subjects (0.2%) had symptoms consistent with possible acute hypersensitivity.
  - Thirteen subjects (0.9%) had possible serum sickness, including 6 (0.4%) identified by programmatic evaluation of follow-up symptoms and 8 (0.6%) by medical review of CRF data; 1 with both methods.
    - Of these 13 subjects with possible serum sickness, 8 (4 adult, 4 pediatric) were concluded to have a Type III immune response after medical review (all possible cases identified by medical review; one adult also identified programmatically and another adult also identified as having a serum sickness AE).
    - The remaining 5 subjects (all pediatric; possible cases identified programmatically) included 3 with likely viral infections; 1 with a cold and skin irritation unrelated to treatment; and 1 with symptoms related to a broken bone.
    - Although no study subjects had symptoms consistent with full serum sickness syndrome, medical review of the data indicated that Type III immune responses occurred after treatment with Anascorp in a small number of subjects (8/1425, 0.6%).

In conclusion, the submitted clinical data support both safety and efficacy of Anascorp for treatment of clinical signs of scorpion envenomation..

3 REVIEW RESPONSIBILITIES

Biomonitoring Review	Christine Drabick Robert Wesley
Clinical Review	Nisha Jain
Clinical Pharmacology Review	Iftekhar Mahmood
CMC Review:	Joel Beren (consult) Robert Fisher Douglas Frazier Michael Kennedy Pei Zhang
Epidemiology	David Menschik Michael Nguyen Alan Ou Craig Zinderman
Facilities (DMPQ)	Donald Ertel Lori Peters Nancy Waites
Labeling (APLB)	Pete Arambula Michael Brony Lisa Stockbridge
Lot Release/Testing Plan	Karen Campbell Joseph Quander, III
Pharmacology/ Toxicology Review	Evi Struble
RPM	Debbie Cordaro Cherie Ward-Peralta
Statistical Review	Mary Lin Yun-ling Xu

4 INTRODUCTION AND REGULATORY BACKGROUND

4.1 Product Information

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 $\geq$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 *Centruroides sp*. and then cleaved by pepsin to form $F(ab')_2$ fragments. The $F(ab')_2$ content is $\geq$85% and Fab content is $\leq$7%. The product contains $\leq$5% whole IgG and <0.5% albumin.

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)----------.

4.2 Regulatory Background

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 volume 1, pp 174-182 (Item 19), including Form 3455 for Dr. Leslie Boyer.

In volume 1 of this submission, page 184, is Bioclon'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 <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 definitely lead to an improvement over the current management of scorpion envenomation.

4.3 Currently Available Treatments for Proposed Indications

In the U.S., envenomation by neurotoxic scorpions occurs in the southwestern United States, particularly in Arizona. The sting may produce mild envenomation, which is more common in adults, and presents mainly as localized 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 contain analogous ion channel toxins.

4.4 Availability of Proposed Active Ingredient in the United States

An approved therapy for the treatment of scorpion envenomation is currently not available in the US. 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 production in 2000.

5 ETHICS AND GOOD CLINICAL PRACTICES

5.1 Submission Quality and Integrity

The indication in the proposed package insert is "the management of patients with clinically important signs of scorpion envenomation." The indication granted upon review of the data is "treatment of clinical signs of scorpion envenomation.

5.2 Compliance with Good Clinical Practices

The pivotal study protocol (AL-02/03) and all amendments were approved by the Independent Ethics Committee(s) (IECs) / Institutional Review Board(s) (IRBs) of the participating center, The University of Arizona Health Sciences Center, Arizona Poison and Drug Information Center, Tucson, Arizona and Tucson Medical Center, Tucson, Arizona

The studies were carried out in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines, and the Declaration of Helsinki. An Informed Consent Form (ICF) was prepared by the investigator according to the provisions of International Conference on Harmonisation GCP and was approved by an IEC/IRB prior to use.

5.3 Financial Disclosures

Financial certification and disclosure information (Form 3454) have been submitted. The applicant certifies that there have been no arrangements where the amount of the compensation could have affected the outcome of the study.

6 TRADE NAME

The trade name Anascorp is approved by Advertising and Promotional Labeling Branch (APLB) and OBRR.

7 ORPHAN DRUG STATUS

Anascorp was granted orphan drug status.

8 PREA/PeRC

Exempt from PREA because of orphan drug status

9 SOURCES OF CLINICAL DATA

Tables of Studies/Clinical Trials and Sites

The clinical development program for product licensure consisted of Study AL-02/03, a prospective, randomized, double-blind, controlled study of the product vs. placebo in pediatric patients with systemic signs of scorpion sting envenomation in Arizona, U.S. (CSR XE-C-02).

Study Number, Study Title and Study Report Number (in Parentheses)	# Subjects using Alacramyn[1]
AL-02/03. Prospective, randomized, double-blind, controlled study of product 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. Birmex[3] in patients with Scorpion sting study in Mexico (CSR-XE-C-05)	**105**
Ongoing AL-03/07. Open treatment protocol for use of Anascorp in patients with scorpion sting envenomation in Arizona, U.S.A, (CSR XE-C-01)	**1425**

[1] Alacramyn is the tradename of the product in Mexico. In the U.S., the proprietary name is Anascorp.
[2] An additional 7 subjects used placebo.
[3] *Centruroides* equine immune $F(ab')_2$ equine is prepared by Mexican Social Security Institute (IMSS))

This pivotal study was conducted at the University of Arizona Health Sciences Center, Arizona Poison and Drug Information Center, Tucson, Arizona; Tucson Medical Center, Tucson, Arizona. The investigators of this study were Leslie Boyer, MD and Andreas A. Theodorou, MD. This study was initiated on June 18, 2004 and completed on August 26, 2005.

10 DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

Study AL-02/03: Prospective, Randomized, Double-Blind, Controlled Study of Anascorp vs. Placebo in Pediatric Patients with Systemic Signs of Scorpion Sting Envenomation

10.1. Design: Synopsis

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 subjects were to be randomized in a 1:1 treatment ratio of Anascorp to placebo. Male and female subjects 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.

10.2 Objective(s)

Primary Objective: The primary objective was to demonstrate resolution of clinically important systemic signs of scorpion envenomation within 4 hours for subjects treated with Anascorp.

Secondary Objective: The secondary objective of this study was to assess the safety of Anascorp treatment

10.3 Endpoints

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

Secondary endpoints were to demonstrate that -

- subjects treated with Anascorp will require significantly less benzodiazepine sedation for control of agitation than controls; and
- venom blood levels will decrease within one hour after Anascorp treatment, while the placebo group will have elevated blood venom levels for several hours.

10.4 Inclusion/Exclusion 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)

10.5 SAP

The primary efficacy variable was 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.

- Components of respiratory compromise: pulmonary edema, in-coordinate ventilatory effort, upper airway compromise, hypoxemia (pulse oximetry reading < 90% saturation), and other respiratory compromise.

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. 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).

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 was 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 pediatric intensivists at both treatment sites. It was reasoned that successfully-treated children might require far less sedation than placebo treated subjects. 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 treated subjects, but that placebo treated subjects would continue to manifest elevated venom levels for many hours while the clinical syndrome persisted. For all subjects, 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 Instituto de Biotecnologia in Cuernavaca, Morelos, Mexico for venom and antivenom measurements. However, as the antivenom assay is a binding assay for equine $F(ab')_2$, it may not be able to distinguish activity vs. venom in the serum

Analysis Populations

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

Primary Efficacy Analysis

The primary endpoint was resolution of clinical 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. The statistical plan did not include formal hypothesis testing as it was not explained adequately in the protocol what was meant by "clinically superior" if the success percentages differed by ≥20%.

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.
- Subject 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, symptoms were tabulated and summarized.

Safety Analysis

All randomized subjects who received study drug were included in the safety analyses. Reasons for premature discontinuation were listed and categorized.

Follow-Up Evaluations

At 7 days and 14 days post-hospital discharge, telephone contact was made with the subject, parent/guardian, or other person regarding possible re-hospitalization of the subject (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.

Other Clinical Studies

The BLA submission included data from 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 chart review study for patients not treated with antivenin in order to establish the natural history of scorpion envenomation in Arizona (AL-03/06).

The applicant considered three of the open-label studies (AL-02/04, AL-02/05, and AL-02/06) as "controlled." However, the natural history study, AL-03/06 cannot be

considered as historic control 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.

AL-03/06 does not involve 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, Birmex, licensed in Mexico but not in the U.S. Thus, no conclusions can be made on efficacy in scorpion envenomation. Its utility is to support the 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 includes an interim report covering the period May 23, 2005 through September 23, 2006, a span of 16 months, together with a Statistical Report covering the period up to June 2008, an additional 21 months. FDA sent an Information Request to the applicant on March 12, 2009 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 stated there was no up-to-date study report. The response refers to the Statistical Report for the most recent data.

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

Note:
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 where the pivotal study, AL-02/03 was conducted. The following is a summary account of the chart review study, AL-03/06.

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: Phase 2

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).

  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.

Study AL-99/02. Randomized, Double-Blind, Variable Dose Comparison of Anascorp vs. Birmex in Patients With Scorpion Sting

Study period: September 9, 1999 to December 12, 2000]
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

Design:

- All study participants were given informed consent before study entry.
- Upon study entry, subjects were classified as having mild, moderate, or severe scorpion sting "intoxication" according to their symptoms and physical findings.
- Before the administration of the antivenom, the subject was to be placed on an intravenous drip and a baseline blood sample taken.

[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.

- Subjects received one of the study medications and continue with the assigned antivenom until the signs of "intoxication" resolved.
- Subject response was evaluated every 30 minutes and, if deemed necessary, subjects received another dose of antivenom. In that case, a blood sample was taken to determine serum venom level.
- When signs of systemic envenomation resolved, the subject would be discharged from the hospital. Before discharge, a final blood sample was taken.
- The blood samples would be refrigerated and processed within one week.

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)----------
  - Serum venom level was to be assayed when a subject received additional dose of scorpion antivenom
  - Time period from antivenom administration to hospital discharge
- Safety was to be evaluated by
  - 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

Note: 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, 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.

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 of patients presenting for emergency treatment of systemic signs of scorpion envenomation within 5 hours of scorpion sting.

Selection and Number of Subjects (planned and analyzed):
It was intended that 26 to 53 subjects were to be enrolled in each study. Twenty-two subjects 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 subjects and 78 pediatric subjects 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 subjects 6 months to 18 years of age
    - Study AL-02/06 initially enrolled pediatric subjects 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

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Duration of Treatment
For the individual subject, 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. Subjects no longer manifesting clinically important systemic signs of envenomation were discharged at 4 hours after receiving study drug. 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, subjects with ongoing symptoms or events were referred for appropriate care.

Criteria for Evaluation:
Efficacy
The primary efficacy variable was resolution of systemic scorpion sting signs and symptoms within four hours after 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. Subjects 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) subjects, assuming a success rate of 0.85 – 0.95 for Anascorp treated subjects.

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

Efficacy Analysis
The primary efficacy variable (subject success) was 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.

Study AL-03/07: Open Treatment Protocol for Use of Anascorp™ in Patients with Scorpion Sting Envenomation

Investigators/Study Center(s)

- This was a multicenter study with 25 sites.
- The principal investigator was Dr. Leslie Boyer of University Medical Center, Tucson, AZ.

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

"Statistical Report" cut-off date June 2008

Phase: 2/3

Objectives

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

Design

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

Number of Subjects (Planned and Analyzed)

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

Eligibility Criteria

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

- Exclusion: known allergy to horse serum

Criteria for Evaluation

- Efficacy: resolution of systemic scorpion sting signs and symptoms was evaluated. Additional efficacy endpoints analyzed were time from study drug infusion to resolution of envenomation and to discharge, presence of specific symptoms at follow-up, effect of concomitant medications and duration of hospitalization.
- Safety: Adverse events (AEs), vital signs, and concomitant medications were assessed. The intensity of an AE is a relative estimate made by the investigator:
  - Mild: transient and easily tolerated by the subject and requires no special treatment
  - Moderate: causing subject discomfort that may be ameliorated by simple therapeutic measures
  - Severe: incapacitating, simple therapeutic measures cannot ameliorate the event.

Statistical Methods

- Efficacy

  The presence (yes/no) of selected signs and symptoms of envenomation (i.e., abnormal eye movement, increased secretions, respiratory distress, thrashing of limbs, and other) was recorded and subjects were categorized as being a success or not a success. A subject was considered to be a success at a particular time point if that subject exhibited no signs or symptoms at that time point. Otherwise, the subject was not considered a success. Selected intervals of duration (e.g., time from study drug infusion to resolution, time from study drug infusion to discharge) were summarized by Age Group and Overall.

  The presence of each sign and symptom was summarized using incident counts and percentages for Age Group and Overall by time point (Baseline, Discharge). Ninety-five percent (95%) confidence intervals (CIs) for each sign and symptom were generated and displayed based on binomial distributions.
- Safety
  - Exposure. Study drug exposure was summarized using descriptive statistics for Age Group and overall for the following endpoints: duration of actual study drug administration, total time of study drug administration, volume administered and the number of vials received. In addition, number of vials received was also summarized with incident counts and percentages using the following categories: less than or equal to 2 vials, 3 vials, 4 vials, 5 or more vials.
  - Adverse Events. All AE summaries were restricted to TEAEs. *Although the primary objective of the study was to evaluate AEs immediately after, 24 hours after, and 14 days after treatment with Anascorp, these analyses were not performed for all AEs; only acute hypersensitivity was evaluated immediately after the start of infusion and specific AEs were evaluated at the two follow-up time points*. Ninety-five percent (95%) CIs for endpoints of interest from the analyses described above were generated and displayed based on binomial distributions.

    At the 24-Hour and Day 14 follow-up evaluations, all TEAEs were recorded. In addition, existence of specific AEs (i.e. itching, rash, petechia, arthralgia, myalgia, nausea, vomiting, dehydration, chest pain,

hematuria, possible serum sickness, and other) was queried and recorded: for each of these specific AEs, responses of Yes, No, or Missing were summarized.

- Medical review of suspected cases of subjects with acute hypersensitivity reaction was performed to determine actual cases.
- Possible or probable cases of serum sickness, included in an overall summary of AEs, were identified programmatically and by medical review of all relevant data (including investigator comments) collected on the CRFs.
- Summaries of acute hypersensitivity/serum sickness were included in an overall summary.

- Vital Signs. Vital signs were summarized using descriptive statistics at Baseline and Discharge: changes and percent change from Baseline were summarized.

11 REVIEW OF EFFICACY

STUDY: AL-02/03. Prospective, randomized, double-blind, controlled study of product vs. placebo in pediatric patients with systemic signs of scorpion sting envenomation in Arizona, U.S. (CSR XE-C-02)

Efficacy Summary

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 subjects was considered to have clinically significant signs of scorpion envenomation 4 hours after treatment compared with 85.7% of placebo-treated subjects.

11.1 Indication

Anascorp is indicated for treatment of clinical signs of scorpion envenomation.

11.1.1 Demographics

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

Subjects in the Anascorp group were younger (mean age 2.0 vs. 4.3 years) and correspondingly smaller than those in the placebo group.

Baseline Characteristics

- 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 treated subjects vs. 57.1% for placebo treated subjects).
- Distribution of physical examination abnormalities was similar between groups as well, with 100.0% of subjects 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 subjects 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 treated subjects presented to the hospital and for study enrollment (134.9 and 207.9 minutes) slightly sooner than did placebo treated subjects (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, 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)
Incoordinate ventilatory efforts	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	0 (0.0)	0 (0.0)
Any respiratory compromise	2 (25.0)	1 (14.3)
Pathological Agitation		
Abnormal eye movement	8 (100.0)	7 (100.0)
Thrashing of limbs	8 (100.0)	7 (100.0)
Loss of ability to ambulate	2 (25.0)	3 (42.9)
Fasciculation	4 (50.0)	5 (71.4)
Total dose of midazolam before study drug infusion (mg/kg)		
Mean (SD)	0.2 (0.1)	0.5 (0.7)
Median	0.2	0.3
Min, Max	0.1, 0.4	0.1, 2.0

11.1.3 Subject Disposition

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

11.1.4 Sites (US/out of US)

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

Dr. Leslie Boyer (11 subjects)
The University 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, AZ 85712

11.1.5 Randomization

Randomization was balanced in the two arms

11.1.6 Protocol Violations

BIMO inspection findings

----------Redacted Per Privacy Act----------

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11.1.7 Analysis of Primary Endpoint(s)

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 subjects were considered to have clinically significant signs of scorpion envenomation 4 hours after treatment compared with 85.7% of placebo-treated patients.

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)

At the 4-hour time-point, 0 of 8 Anascorp treated subjects and 6 of 7 placebo treated subjects showed "clinically important signs of envenomation" under a 15-minute overall assessment by the physician. In fact, even at the 2-hour time-point, the difference between the Anascorp arm and the placebo arm was 1 in 8 vs. 6 in 7. The applicant

suggests that because placebo-treated subject #(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 compared to 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.

Of the components of pathological agitation, *limb thrashing* and *abnormal eye movements* were present in 100.0% of subjects in both groups at baseline, despite prior use of benzodiazepine sedation in all cases. These findings resolved within 4 hours for all subjects in the Anascorp-treated group, but were still present at 4 hours in 57.1% of placebo-treated subjects. *Loss of ability to ambulate* resolved within 4 hours for all subjects in both groups. Overall, pathological agitation (except fasciculation) was present in all subjects in both groups at baseline, but resolved in 50.0% and 100.0% of Anascorp-treated subjects by 1 hour and 4 hours after study drug infusion, respectively. In contrast, five placebo-treated subjects (71.4%) continued to experience 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 Hour 1 Hour 2 Hour 4 24 Hour Discharge	8 (100.0) 4 (50.0) 1 (12.5) 0 (0.0) 0 (0.0)	7 (100.0) 6 (85.7) 6 (85.7) 5 (71.4%) 0 (0.0)

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

Signs of "respiratory compromise" were observed in only 3 subjects (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 displayed were 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 were verifiable from the information submitted. Since all signs in the 3 subjects 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."

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.

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) 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.

Secondary Efficacy Variables (extrapolated from statistician memo)

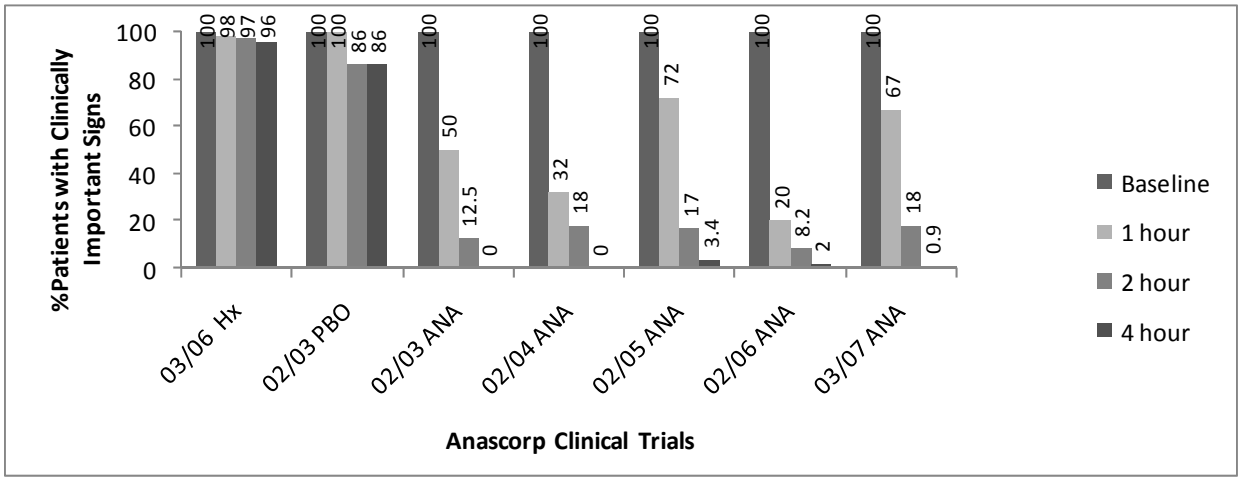
For both arms of the AL 02/03 study, midazolam sedation was initiated when the treating physician deemed it necessary. To evaluate the effect of midazolam as a potential confounding factor, this reviewer analyzed the midazolam dosage as well as the time on midazolam, comparing Anascorp to the placebo group. The results are summarized in Table 1. It appears that midazolam doses given prior to study drug were comparable between the two arms, although the placebo group received a slightly higher dosage. After study drug was administrated, the Anascorp arm received considerably less midazolam, and spent less time on midzaolam. These results are consistent with the sponsor's findings.

Table 1 Midazolam usage

Parameter	Total dose prior to baseline (mg/kg)	Dose from baseline to discharge (mg/kg)	Total dose from prior to baseline through discharge (mg/kg)	Time from Start of Study Treatment to Last Dose of Midazolam (hr)
AL 02/03 Anascorp (N=8)				
Mean (SD), median Min, max	0.2 (0.1), 0.2 0.1-0.4	0.1 (0.1), 0 0.0-0.2	0.3 (0.2), 0.4 0.1-0.5	0.4 (0.5), 0 0.0-1.0
AL 02/03 Placebo (N=7)				
Mean (SD), median Min, max	0.5 (0.7), 0.3 0.1- 2.0	4.6 (5.8), 3.4 0.1- 16.7	5.1 (5.6), 3.9 0.3-16.8	8.6 (4.5), 8.0 3.0-14.1

The sponsor reported the following results (Figure 1.) on time from treatment to resolution of envenomation. The figure suggests Anascorp treated patients tend to have quicker resolution of important signs of envenomation compared with historical control and placebo subjects.

Time from Initiation of Treatment to Resolution of Envenomation



Hx –historical control, PBO – placebo, ANA – Anascorp

Serum Venom Levels

The mean venom levels at baseline were similar in the Anascorp and placebo groups, i.e., 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 treated subjects.
- Mean venom levels among placebo treated subjects 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 treated subject had no quantifiable venom in serum at baseline. This child had been stung on the heel of the foot. The 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 treated subjects 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 treated subject to experience a spontaneous recovery within the 4-hour study period. These factors suggest that this subject sustained an envenomation of lesser severity due to higher volume of distribution, and that this factor plus the later serum

collection time are consistent with a genuinely lower serum venom level than in other cases.

Among the 5 Anascorp treated subjects 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 treated subjects with detectable serum venom at baseline declined 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 indicates that the dose of Anascorp administered (3 vials) was sufficient for the prompt and sustained neutralization of the quantity of venom injected.

The applicant did not provide documentation that presence of antivenom does not interfere with the serum venom assay. In the absence of demonstrating assay validity to detect active venom when antivenom is present, 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 treated subjects 4 hours after study drug infusion, whereas these signs were present in 4 placebo treated subjects (57.1%) at the same time-point.

Efficacy Conclusions

1. The data establish efficacy in the proposed population:
   (a) The primary endpoint demonstrated resolution of the clinical signs of scorpion envenomation, in less than 4 hours after study drug infusion, in all 8 Anascorp cases but in only 1 out of 7 placebo-treated subjects.
   (b) Anascorp treated subjects 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 treated subjects received a mean of 0.3 mg/kg midazolam during the first hour and continued to receive midazolam 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 mean of 534 minutes (8.9 hours) for placebo treated subjects.
   (c) Where sampling was available, blood venom levels dropped to undetectable levels by one hour after baseline among Anascorp treated subjects, but in only one placebo treated subject.

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

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 subjects were of unknown race (54%), followed by Caucasians (33%) and Hispanics (9.3%).
- Overall, clinically important systemic signs of envenomation were present in all subjects 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 was reported 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 subjects for whom symptom onset was available but sting time was not. For the 6 cases with neither sting time nor symptom onset time available, time from initial medical contact to baseline averaged 181.3 minutes. Among the 33 subjects for whom data were available, mean onset of clinically important systemic signs from sting time was 52.5 minutes.
- Eighty-eight (91%) of the subjects 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

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)			

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, AL-02/03, 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 clinical important signs of scorpion envenomation)

The total duration was calculated for 96 of the 97 subjects 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 subjects 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 subjects ranged from 45 minutes to 9.5 hours (sting time to hospital admission).

- Generally, subjects 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, time from hospital admission (baseline) to midazolam discontinuation averaged 607.4 minutes (± 318.9) and ranged up to 1815 minutes.
- Overall, 96.9% of subjects had a severe physical and symptom assessment grade at baseline, which persisted in over half (54.6%) of subjects at the 4-hour discharge. Only 2.1% of subjects had physical and symptom assessment grades that were considered moderate at baseline, and none was rated as mild.

Study AL-99/02. Randomized, Double-Blind, Variable Dose Comparison of Anascorp vs. Birmex in Patients With Scorpion Sting

Efficacy Results

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

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

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

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.

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

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

Adults were all Hispanic whereas pediatric subjects were primarily Hispanic (44%) or Native American (44%). Among adults, females (64%) predominated, whereas for children, 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 subjects, on average, over an hour before U.S. subjects. The envenomation syndrome resolved within 4 hours of initiating treatment in 98% of subjects, 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 subjects; only 12 of 101 subjects (12%) were hospitalized for ≥six hours after initiation of infusion. All subjects 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 subjects. Venom levels were reduced by ≥90% baseline values in 93% (66 of 71) subjects within 1 hour of Anascorp infusion.

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

Study AL-03/07: Open Treatment Protocol for Use of Anascorp™ in Patients with Scorpion Sting Envenomation

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

12 REVIEW OF SAFETY

Study AL-02/03: Prospective, Randomized, Double-Blind, Controlled Study of Anascorp vs. Placebo in Pediatric Patients with Systemic Signs of Scorpion Sting Envenomation

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

Extent of Exposure

All 8 subjects 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 Placebo subjects received the "inactive excipient" without antivenom, diluted in 50 mL normal saline and administered IV over a range of 10 to 35 minutes.

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 subjects who received no H1-, H2- blockers or corticosteroids and 3 patients (2 Anascorp treated subjects and 1 Placebo treated subjects) 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

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

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

- Placebo subject #(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 subject experienced an acute serum reaction. However, 3 subjects (2 Anascorp treated subjects and 1 placebo treated subject) 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 subjects randomized to Anascorp and to 6/7 in the placebo group; no subject had symptoms suggestive of serum sickness during this time. Two subjects in the Anascorp group experienced an episode of vomiting during the 7 days post-hospitalization, and one Anascorp treated subject received acetaminophen for a bruised ear. No symptoms were reported for either Anascorp or placebo treated subjects 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 Conclusion
1. Anascorp appears to have been well tolerated in Study AL-02/03, and no allergic reactions were reported. No subject experienced serum sickness during the treatment period or during the 14-day follow-up period.

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

Safety
At least one clinical adverse event occurred in 38 (39.2%) of subjects. At least one venom-related and treatment-related clinical AE was reported in 18 (18.6%) and 12 (12.4%) of subjects, respectively. No subjects 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, subjects did not generally experience substantial depression of vital signs at discharge.

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 subjects 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.

Study AL-99/02. Randomized, Double-Blind, Variable Dose Comparison of Anascorp vs. Birmex in Patients With Scorpion Sting

Safety Results

Exposure:
Each subject 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 subjects received concurrent steroids or antihistamines, which could have masked adverse events.

Adverse Events
Three of 105 subjects (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.

Safety Conclusion:
1. The study report concludes that Anascorp is well tolerated in the treatment of envenomation by scorpions.

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

Safety results

Extent of Exposure:
Subjects enrolled in study AL-02/04 initially received 2 vials of Anascorp whereas subjects 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 subjects in study AL-02/04 received only the initial dose of 2 vials. The number of pediatric subjects 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 subjects required treatment beyond the initial dose. The maximum total time over which Anascorp was administered to subjects in any of the 3 studies and the maximum number of vials were 260 minutes and 10 vials, respectively (for subject #(b)(6) in AL-02/05).

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 subjects 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%)
Diarrhea	0	0	2 (4.1%)	2 (2.0%)
Gastrointestinal hemorrhage	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%)

	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)
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%)
Diarrhea	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 hemorrhage	0	0	0	NAP	0	1 (5.9%)	NAP	0	0
Headache	0	0	0	NAP	0	0	NAP	1 (2.2%)	0

	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)
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 by the investigator. Only 3 subjects, 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 were: arthralgia (when contacted at 7 day follow-up), which resolved without intervention, and fever in 2 pediatric subjects shortly after receiving study drug. In both cases, the fever was short-lived (<4 hours) and the subjects recovered, one without any treatment, and the other with acetaminophen.

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

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

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

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)**
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]
Diarrhea	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 hemorrhage	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%)

	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)**
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%)
Paresthesia	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 subject was re-hospitalized. This pediatric subject was re-admitted the day after discharge because of persistent vomiting and dehydration. No subjects 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 subject discontinued drug infusion due to an adverse event. Three subjects, 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)
Subjects 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 subject 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 subjects 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 subjects. These events have also been reported with scorpion envenomation.
- No subjects had any signs of an acute hypersensitivity reaction or serum sickness.
- There were no clinically significant laboratory abnormalities, and the majority of subjects showed improvement in post-baseline chemistry and hematology values compared to baseline values.
- On discharge / after treatment, nearly all subjects 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 subjects, 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 subjects, the information obtained

from phone contact would likely be second-hand and this adds to the uncertainty about accuracy of follow-up safety data.

Study AL-03/07: Open Treatment Protocol for Use of Anascorp™ in Patients with Scorpion Sting Envenomation

Safety Results:

Because the Interim Report was 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 May 23, 2005 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 subjects (Part 1 with 122 patients, Part 2 with 268, Part 3 with 164) were treated under Study AL-03/07. The overall completion rate by the subjects 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 subjects >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 commonly reported AEs were vomiting (7.4%), pyrexia (4.9%) and rash (4.5%).

The number of subjects 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 subjects (1.3%) reported at least one SAE, one with "related" SAEs – eye swelling and stridor (--(b)(6)--). The narratives are given below:

- Subject ----(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 heart rate of 140 beats per minute (bpm), respiratory rate of 26 breaths per minute, and blood pressure of 152/98 mmHg. The subject received a total of 3 vials of Anascorp over 20 minutes. Five minutes after the infusion ended, the subject 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

- Subject ----(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 her 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 of 180 (bpm), respiratory rate of 36 breaths per minute, and blood pressure of 164/111 mmHg. Midway through the second vial of Anascorp, the subject was noted to have respiratory acidosis and hypercapnia. Midway through the third vial of Anascorp, she experienced severe respiratory distress requiring intubation. The Anascorp infusion was discontinued so the IV could be used to deliver other medications. Two hours and 15 minutes after her initial exam, she was transferred to Phoenix Childrens Hospital. Vital signs at transfer were heart rate of 165 bpm and blood pressure of 112/69 mmHg; (no respiratory rate as she was intubated and mechanically ventilated). The subject was extubated within an hour of arriving at Phoenix Children's Hospital, but remained hospitalized for observation. Twenty-four hours later, she was discharged; follow-up 14 days later found no sequelae.
- Subject ----(b)(6)---- was a five-year-old white female with significant medical history of Downs Syndrome and post-cardiac surgery who was stung 30 minutes prior to start of Anascorp infusion. On presentation to the ED, she had nystagmus, muscle twitching, agitation, severe bronchorrhea, rhinorrhea, and an episode of vomiting, which raised concerns for possible aspiration. Vital signs included heart rate of 180 bpm and respiratory rate of 32 breaths per minute. Oxygen saturation by pulse oximetry was 94%. She 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 subject received inhaled salbutamol and furosemide for respiratory distress, and was transferred to Phoenix Childrens Hospital for care under her cardiologist. At time of transfer, heart rate was 126 bpm and respiratory rate was 36 breaths per minute. The subject was discharged 4 days later without further sequelae.
- Subject -----(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 heart rate of 147 bpm, respiratory of 24 breaths per minute, and blood pressure of 124/60 mmHg. He received a total of 3 vials of Anascorp over 1 hour 14 minutes with resolution of envenomation symptoms. After 3 hours of observation, he was

- Subject -----(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 heart rate of 131 bpm, respiratory rate of 22 breaths per minute, and blood pressure of 125/92 mmHg. The subject received a total of 5 vials of Anascorp over 2 hours 8 minutes. Forty-five minutes after completion of the last dose, he became extremely agitated and irritable with limb thrashing. Leather restraints were applied, and he was transferred to the intensive care unit, 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.
- Subject ------(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 heart rate of 109 bpm, respiratory rate of 20 breaths per minute, and blood pressure of 101/54 mmHg. She 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.
- Subject ------(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 a heart rate 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:
Subjects received phone calls at 24 hours 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 subjects (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 subjects in study 03/07 with rash (----------(b)(6)----------), and 1 subject with pruritus (-(b)(6)-), might have had serum sickness, although in no case was the full serum sickness syndrome described.

- Subject -(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 of 131 bpm and respiratory rate of 24 breaths per minute. She received a total of 3 vials of Anascorp over 1 hour 25 minutes, after which envenomation symptoms were resolved. The subject was observed for 1 hour 15 minutes and discharged with a heart rate of 113 bpm and respiratory rate of 16 breaths per minute. When contacted at the 14-day follow-up, the family reported that one day after discharge, the subject had 3 episodes of vomiting that resolved without treatment. Twelve days post-discharge, she developed a rash on her chest and legs and complained of itching of hands and feet. After treatment with one dose of diphenhydramine, both the rash and itching resolved. No arthralgias, myalgias, or signs of serum sickness other than this transient rash were noted.
- Subject -(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 a heart rate of 155 bpm and respiratory rate of 28 breaths per minute. He received a total of 2 vials of Anascorp over 50 minutes after which envenomation symptoms were resolved. The subject was observed for an additional 40 minutes and discharged with a heart rate of 85 bpm and respiratory rate of 20 breaths per minute. When contacted at the 14-day follow-up, the family reported that 7 days after discharge, he had developed a "hive-like" rash on the back of his neck that worsened and spread to entire body except the face. He was treated with diphenhydramine and hydrocortisone cream every 4 hours for 3 days with resolution. He also complained of a headache on days 15 and 16 post-discharge, which was treated with acetaminophen with resolution. No arthralgias, myalgias, or signs of serum sickness other than the rash were noted.
- Subject -(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 heart rate of 102 bpm, respiratory rate of 18 breaths per minute, and blood pressure 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, he developed a rash, accompanied by itching. He was treated with diphenhydramine and methylprednisolone, with resolution of the rash one week later. The subject also developed edema around his mouth one day after onset of the rash, which lasted 3 days. Finally, he 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.
- Subject -(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 heart rate of 220 bpm, respiratory rate of 39 breaths per minute, blood pressure of 132/99 mmHg, and temperature of 38.3°C. He received a total of 4 vials of Anascorp and was discharged 3 hours from start of infusion with resolution of symptoms and improvement of vital signs (heart rate 150 bpm, respiratory rate 30 breaths per minute, blood pressure 118/60 mmHg, and temperature of 37.8°C. Nine days post-discharge, he developed a rash in the

- Subject -(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 heart rate of 138 bpm, respiratory rate of 18 breaths per minute, blood pressure of 120/77 mmHg, and temperature of 37.2 °C. He received a total of 3 vials of Anascorp, and was discharged only 1.5 hours after the start of infusion with resolution of symptoms and improvement of vital signs (heart rate 84 bpm, respiratory rate 25 breaths per minute, blood pressure 96/44 mmHg, and temperature of 36.3 °C). Eight days after discharge, he developed a generalized 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 subject 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.
- Subject -(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 heart rate of 169 bpm, respiratory rate of 22 breaths per minute and blood pressure of 120/53 mmHg. Symptoms resolved one hour after infusion, and he was discharged 30 minutes later. One week after discharge, the subject complained of itching without appearance of any rash. The itching resolved after 4 days without any intervention. No arthralgias, myalgias, or signs of serum sickness other than itching were noted.

In addition, comments were made by investigators about 4 other subjects suggestive of serum sickness. Subject -(b)(6)- had diarrhea 9 days post-discharge and fever plus "spots in eyes" beginning 11 days post-discharge. Subject -(b)(6)- developed influenza symptoms 10 days after discharge; the investigator felt that serum sickness could mimic influenza. Subject -(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. Subject -(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.

14 ADVISORY COMMITTEE MEETING

This BLA application was not referred to the Blood Products Advisory Committee because the review of information submitted in the BLA, including the clinical study design and trial results, did not raise concerns or controversial issues.