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Applicant	Instituto Bioclon, S.A. de C.V.
Established Name	Crotalidae Immune Fab2 Equine Injection
(Proposed) Trade Name	Anavip
Pharmacologic Class	Antivenom
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	Lyophilized powder, reconstitute each vial with 10 ml of sterile normal saline. Combine and further dilute to a total of 250 ml with sterile normal saline, infuse intravenously over 60 minutes.
Dosing Regimen	10 vials for initial dose, administer an additional 10 vials at a time if the initial dose fails to halt the progression of envenomation. Subject should be observed in a health care setting at least 18 hours

	following initial control of signs and symptoms. Re-emerging symptoms may be suppressed with additional 4 vial doses as needed.
Indication(s) and Intended Population(s)	Management of coagulopathy in patients with North American crotalid envenomation

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GLOSSARY

Abbreviation	Definition
AE	Adverse Event
BLA	Biologics License Application
BOCF	baseline observation carried forward
CSR	Clinical Study Report
ITT	intent-to-treat
IVRS	Interactive Voice Response System
LOCF	last observation carried forward
MCAR	missing completely at random
MI	multiple imputation
OR	odds ratio
SAE	Serious Adverse Event
SSS	snakebite severity score
WOCF	worst observation carried forward

1. EXECUTIVE SUMMARY

Anavip [Crotalidae (pit-viper) Immune F(ab')₂ (Equine) Injection] is an equine-derived antivenom. This Biologics Licensure Application (BLA) seeks licensure of Anavip for the management of coagulopathy in patients with North American crotalid envenomation.

The primary source of evidence to support the BLA is a Phase III, randomized, double blind, active controlled, multicenter study. One hundred and twenty-one (121) subjects were randomized and treated in a 1:1:1 ratio to three treatment groups:

Group 1 (Anavip/Anavip): Anavip with Anavip maintenance therapy;

Group 2 (Anavip/Placebo): Anavip with Placebo (normal saline) maintenance therapy;

Group 3 (CroFab/CroFab): CroFab with CroFab maintenance therapy.

The sponsor reported that the primary comparison between Anavip/Anavip and CroFab/ CroFab is not statistically significant (two-sided p-value=0.06, odds ratio (OR) =0.275 and 95% CI: 0.058, 1.048). Though the comparison between Anavip/Placebo and CroFab/ CroFab is nominally statistically significant (OR=0.135, p-value=0.01), a pre-specified hierarchical testing strategy prevents formally performing this test since the primary comparison between Anavip/Anavip and CroFab/ CroFab is not statistically significant.

Though the sponsor pre-specified the primary analysis to be on the intent-to-treat (ITT) population, the sponsor's actual primary efficacy analysis is a complete case analysis which excludes from the ITT population seven subjects who do not have any primary efficacy data. Although it would be preferable for the primary analysis to be on the ITT population, the sponsor did not pre-specify a primary missing data imputation method, the seven subjects excluded did not have any follow-up data beyond baseline, as a result, the complete case analysis is regarded as the primary analysis in this review and the ITT analyses with various imputation methods are treated as supportive evidence.

Post-hoc ITT analyses using baseline observation carried forward (BOCF) and multiple imputation (MI) for the missing cases show that the primary comparison between Anavip/Anavip and CroFab/ CroFab is statistically significant. However, when imputing the missing cases as all coagulopathy or as all non-coagulopathy, the primary comparison between Anavip/Anavip and CroFab/ CroFab is not statistically significant.

Post-hoc analysis with no imputation for missing data identifies baseline coagulopathy as a highly significant prognostic factor (OR=7.397, p-value=0.006) and when the primary efficacy analysis is adjusted for this factor, the primary comparison between Anavip/Anavip and CroFab/ CroFab is statistically significant (OR=0.184; 95% CI: 0.033, 0.794; p-value=0.02).

In summary, though the study results do not seem to provide evidence strong enough to support a superiority claim of Anavip over CroFab on management of coagulopathy in patients with North American crotalid envenomation, Anavip does show some evidence of effect on management of coagulopathy in patients with North American crotalid envenomation compared to CroFab.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Crotaline snakebite is the most commonly reported venomous snakebites in the US. A person bitten by a Crotaline snake may need to be treated with antivenom. Antivenoms contain venom-specific antibody derivatives of hyperimmune plasma. These fragments bind to venom, thereby preventing or reversing the local and systemic effects of envenomation.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Crotaline viper envenomation in the US is treated with one of two licensed products: Wyeth Antivenin (Crotalidae) Polyvalent (Polyvalent) or CroFab, with CroFab considered standard of care.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The pivotal study for this BLA was conducted under IND 11275. On March 13, 2012, this reviewer suggested that the sponsor include all randomized subjects in the ITT analysis and conduct sensitivity analyses on the missing assessments, and questioned about the sample size increase during the trial. The sponsor responded in amendment 40, agreeing to the two suggestions. As to the sample size increase, the sponsor claimed that the increase was to compensate for pharmacy errors and drop-outs, and since the data were kept blinded with no statistical analysis carried out, there was no Type I error inflation.

The Pre-BLA meeting was held on May 8, 2012 and the sponsor submitted the BLA on March 18, 2013.

On June 10, 2013, an information request was sent to the sponsor asking them to conduct an analysis including subjects who were randomized and treated but had no primary efficacy data, using the multiple imputation (MI) method, and also to conduct several other sensitivity analyses. In addition, the sponsor was asked to investigate why the Anavip/Anavip and CroFab/CroFab groups had a much higher rate of missing primary efficacy assessment than the Anavip/Placebo group. The sponsor responded on June 22, 2013 (amendment STN125488/0.12) and a telecon was held on June 24, 2013. The sponsor then sent in the corrected MI analysis on July 16, 2013 (amendment STN125488/0.15).

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

There are three clinical studies in this BLA submission. One is a pharmacokinetic study and the other two are comparative clinical trials of Anavip with CroFab, one of which is Phase II and the other Phase III. The Phase III study is the primary source of evidence to

support the application. The Phase II study provides supportive evidence and hence is only briefly reviewed.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The documents reviewed are the following:

1. The original submission STN125488/0.0 Section 5.3.5.1, Clinical Study Report (CSR) and tabulation data.
2. Amendment STN125488/0.12 Section 5, multiple imputation analysis and sensitivity analyses report
3. Amendment STN125488/0.15 Section 5, Supplemental table, multiple imputation exact logistic regression and sensitivity analyses.

5.3 Table of Studies/Clinical Trials

Table 1 summarizes the clinical studies in this BLA submission.

Table 1. Summary of Clinical Studies

Protocol Name	Study Type	Number of subjects	Phase
YA 06/07	Healthy volunteer, PK study, safety, in Mexico	14	I
AN 03/02	Randomized, controlled, open-label, multicenter study, in the U.S.	12	II
YA 07/02	Randomized, controlled, blinded, multicenter study, in the U.S.	121	III

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

The sponsor conducted one pharmacokinetic study which enrolled 14 healthy volunteers. For the review of this study, this reviewer defers to the pharmacological reviewer.

The sponsor conducted two comparative clinical trials (AN 03/02 and YA 07/02) of Anavip with CroFab in subjects who suffered from crotalid envenomation.

The YA 07/02 study is the primary source of evidence to support the application. Study AN 03/02 provides supportive evidence and hence is only reviewed briefly in this memo.

6.1 Trial #1

YA 07/02 is a randomized, controlled, double-blind, multicenter Phase III study comparing two Anavip regimens with CroFab in subjects with pit viper envenomation.

6.1.1 Objectives

The study objectives are:

- To confirm the effectiveness of Anavip in preventing the occurrence of delayed coagulopathies and to establish its safety for treatment of crotalinae envenomation;
- To confirm the effectiveness of Anavip to prevent the occurrence of venonemia during the subacute period following a snakebite, and the associated decreases in absolute platelet counts and proportion of subjects experiencing platelet counts below an established safety threshold.

6.1.2 Design Overview

This is a randomized, double blind, active controlled, multicenter, Phase III study. Approximately 120 subjects were planned to be enrolled and randomized to one of three treatment groups in a 1:1:1 ratio:

Group 1 (Anavip/Anavip): Anavip with Anavip maintenance therapy;

Group 2 (Anavip/Placebo): Anavip with Placebo (normal saline) maintenance therapy;

Group 3 (CroFab/CroFab): CroFab with CroFab maintenance therapy.

The study had an in-hospital Acute Treatment Phase that included screening and baseline assessments, initial and maintenance dosing (Day 0), and an out-patient Follow-up (Subacute) Phase that included four follow-up visits. On Days 5, 8 and 15, subjects returned to the site for the follow-up visits and on Day 22, subjects were contacted by phone.

6.1.3 Population

The study population is subjects 2 to 80 years of age, presenting for emergency treatment of pit viper bite without current use of any antivenom, or use within the last month.

6.1.4 Study Treatments or Agents Mandated by the Protocol

During the Acute Treatment Phase, sequential doses (10 vials of Anavip or 5 vials of CroFab per dose) were infused until initial control was achieved. Subjects received as many doses as necessary to achieve initial control at the discretion of the treating physician. Subsequently, subjects received maintenance doses (consisting of 4 vials of Anavip for Anavip/Anavip Group, 250 mL of normal saline for Anavip/Placebo Group, or 2 vials of CroFab for CroFab/CroFab Group) every 6 hours for 3 doses.

The Follow-up (Subacute) Phase of the study began immediately after the third maintenance dose. Subjects returned to the site on Days 5, 8, and 15 for scheduled follow-up visits. Subjects whose clinical signs (symptomatic coagulopathy) or coagulation parameters (platelet count < 50,000 platelets/mm³) indicated the need for additional antivenom during the Subacute Phase received additional doses (2 vials of CroFab or 4 vials of Anavip), and an "Extra Visit" was documented. Dosing was provided as needed until the subject was stabilized.

6.1.6 Sites and Centers

Subjects were enrolled at 16 sites in the southern US. Subjects were stratified according to geographic region based on snake species distribution (coagulopathic vs. non-coagulopathic sites). One site was in the non-coagulopathic region and the remaining 15 sites were in the coagulopathic region.

6.1.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint was the proportion of subjects experiencing coagulopathy during the Follow-up (Subacute) Phase of the study. Subjects were assessed as experiencing coagulopathy if they had any one of the following:

- Absolute platelet levels $< 150,000/\text{mm}^3$ as measured on either Day 5 (± 1 day) or Day 8 (± 1 day)
- Absolute fibrinogen levels < 150 mg/dL as measured on either Day 5 (± 1 day) or Day 8 (± 1 day)
- Clinical coagulopathy between end of maintenance dosing and Day 5 requiring additional antivenom

Secondary efficacy endpoints were the following:

- Percentage of subjects who experience venonemia as measured on Day 5 (± 1 day) or Day 8 (± 1 day);
- Absolute platelet level measured on Day 5 (± 1 day) and Day 8 (± 1 day);
- Lowest absolute platelet level measured on Day 5 (± 1 day) or Day 8 (± 1 day);
- Absolute fibrinogen level measured on Day 5 (± 1 day) and Day 8 (± 1 day);
- Lowest absolute fibrinogen level measured on Day 5 (± 1 day) or Day 8 (± 1 day).

For the study to be successful, the proportion of coagulopathy in Group1 (Anavip/Anavip) needs to be lower than that in Group 3 (CroFab/CroFab) at a two-sided 0.05 alpha level. And only if the comparison between Anavip/Anavip and CroFab/CroFab is statistically significant, the comparison between Anavip/Placebo and CroFab/CroFab can be made, also at the two-sided 0.05 alpha level. See Section 6.1.9 for details.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Study hypothesis

The null hypothesis tested is that the coagulopathy rates for the Anavip and CroFab treatment groups are equal:

$$H_{01}: p_1=p_3, H_{02}: p_2=p_3$$

where p_1 , p_2 and p_3 represent the proportion of subjects with coagulopathy in the Anavip/Anavip Group, Anavip/Placebo Group and CroFab/CroFab Group, respectively. The alternative hypothesis is that the coagulopathy rates are different between the treatment groups:

$$H_{11}: p_1 \neq p_3, H_{12}: p_2 \neq p_3$$

Multiplicity

The sponsor pre-specified a hierarchical testing procedure. The Anavip/Anavip Group is compared to the CroFab/CroFab Group first, at a two-sided 0.05 alpha level, and if successful, the Anavip/ Placebo Group is compared to the CroFab/CroFab Group, also at a two-sided 0.05 alpha level.

Statistical methods

The number and percent of subjects who experience coagulopathy are summarized by treatment group. The comparison of coagulopathy rates between treatment groups adjusted for region (coagulopathic and non-coagulopathic) is tested using an exact logistic regression model with terms for treatment and region. Summaries for models include parameter estimates of the odds ratios, the 95% confidence intervals of the odds ratios and associated p-values.

Sample size

In the original protocol submitted in 2008, the sponsor proposed a sample size of 93 subjects. The sample size calculation was based on the assumptions that the coagulopathy rate in the Anavip treated group was 5% and 50% in the CroFab treated group. They also assumed a 10% withdrawal rate.

The sponsor amended the protocol on December 3, 2010 (amendment #2) to increase the planned sample size from 93 to 120 subjects, without adequate justification. Based on the enrollment data, 85 subjects had been randomized and treated by the time they amended the protocol. This reviewer made an inquiry about the sample size increase on March 13, 2012. The sponsor stated that the study remained blinded and thus the sample size increase would not inflate Type I error. The sponsor also stated that the sample size increase was due to reported pharmacy errors and potential for drop-outs. The 27 subjects increase is 29% of the original sample size, which seems to be an over-compensation for 3 cases of pharmacy errors and 5 cases of drop-out at the time of the sample size increase. The sample size increase boosted the study power.

Definitions of analysis populations

In the sponsor's original protocol, the Intent-to-Treat (ITT) Population included all enrolled subjects who were randomized for treatment, received at least one dose of treatment and had at least one assessment of the primary efficacy endpoint during the follow-up phase of the study. For analysis purposes, subjects were assigned to the treatment to which they were randomized. At this reviewer's suggestion, the sponsor changed the ITT population definition to include all randomized subjects in the primary efficacy analysis, regardless of number of assessments done (IND 11275, amendment 40).

The Per Protocol Population consists of ITT subjects who had at least one assessment of the primary efficacy endpoint during the follow-up phase and did not have any major protocol deviations (e.g. treatment given different than what the subject was assigned).

The Safety Population includes all subjects who received at least one dose of Anavip or CroFab. For analysis purposes, subjects were assigned to the treatment they first received.

Missing data

According to the SAP, "If at least one assessment of the primary efficacy endpoint (but not necessarily all three assessments) was recorded for a visit and none of the assessments were indicative of coagulopathy, the result of 'coagulopathy not experienced' will be assigned. If

at least one assessment of the primary efficacy endpoint was indicative of coagulation and the other assessments were missing, the result of ‘coagulopathy experienced’ will be assigned.” The sponsor also stated that “No other imputation of missing endpoints will be made”.

At this reviewer’s request, the sponsor agreed to conduct sensitivity analyses on the partially missing assessments (IND 11275, amendment 40) and these analyses were in the original BLA submission. However, the “ITT analysis” in the original BLA submission on the primary efficacy endpoint excludes from the ITT population seven subjects who received study treatment but did not have any primary efficacy data. At this reviewer’s request, the sponsor submitted an analysis using the multiple imputation (MI) method and also several other sensitivity analyses (BLA 125488/0.14, /0.15, submitted July 14, 2013).

Randomization and blinding

The sponsor used blocked randomization of size 6, and randomization was stratified by region (coagulopathic and non-coagulopathic). An Interactive Voice Response System (IVRS) was used and the pharmacists who prepared the study drug knew the subjects’ treatment assignment. The study subjects, the investigators and other study personnel were to be blinded to the treatment assignment. The sponsor reported in their CSR one case of emergency unblinding and three cases of unblinding by mistake (Section 9.4.6 and 10.2, CSR).

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Table 2 summarizes the study population reported by the sponsor.

Table 2. Summary of Study Populations

	Group 1 Anavip/Anavip	Group 2 Anavip/Placebo	Group 3 CroFab/CroFab	Total sample size
Randomized	41	41	41	123
ITT population	41	40	40	121
Per Protocol population	38	35	36	109
Safety population	43	37	41	121

(Source: Adapted from Table 3, Section 11.1, CSR)

Two subjects were randomized but did not receive any study drug. The first subject (#20-005) was randomized to the Anavip/Placebo Group. This subject met the exclusion criterion of current use or use within the last month of any antivenom. This subject did not sign the informed consent form and was discontinued due to not meeting all entry criteria. The other subject (#16-001) was randomized to the CroFab/CroFab Group and clinical evaluation after enrollment indicated that the subject had either mild envenomation or dry bite and the subject was determined to be not eligible to receive study drug. The sponsor excluded these two subjects from the ITT population and this reviewer does not object to the exclusion.

The sponsor reported that major protocol deviations relating to dosing occurred in five subjects (one subject in the Anavip/Anavip Group, three subjects in the Anavip/Placebo Group and one subject in the CroFab/CroFab Group). In four subjects, the deviation was due to pharmacy error (subjects were given the wrong study drug either at initial dosing or maintenance dosing). One subject received commercial CroFab and the Wyeth product to treat worsening clinical symptoms. These five subjects were not in the Per Protocol population. Additionally, seven subjects (two subjects in the Anavip/Anavip Group, two subjects in the Anavip/Placebo Group and three subjects in the CroFab/CroFab Group) without any primary efficacy data were also excluded from the Per Protocol population.

The sponsor reported that due to pharmacy error, two subjects in the Anavip/Placebo Group received Anavip for maintenance and thus were analyzed in the Anavip/Anavip Group in the Safety population (yielding n=43). Additionally, one subject in the Anavip/Placebo Group received CroFab for the initial treatment and thus was analyzed in the CroFab/CroFab Group in the Safety population (yielding n=41).

6.1.10.1.1 Demographics

Table 3 summarizes the demographics for the ITT population reported by the sponsor.

Table 3. Demographics of the ITT Population

	Group 1 (N=41) Anavip/Anavip	Group 2 (N=40) Anavip/Placebo	Group 3 (N=40) Crofab/Crofab
Age (years)			
N	41	40	40
Mean (SD)	32.9 (22.26)	40.3 (21.02)	45.6 (16.52)
Median	36	43	48
Min, Max	2, 80	7, 77	5, 80
Age < 10 (years)	12 (29.3%)	5 (12.5%)	1 (2.5%)
Age ≥ 10 (years)	29 (70.7%)	35 (87.5%)	39 (97.5%)
Sex			
Male	30 (73.2%)	30 (75.0%)	28 (70.0%)
Female	11 (26.8%)	10 (25.0%)	12 (30.0%)
Race/Ethnicity			
American Indian or Alaska Native	1 (2.4%)	0 (0.0%)	1 (2.5%)
Asian	1 (2.4%)	2 (5.0%)	0 (0.0%)
Black or African American	2 (4.9%)	1 (2.5%)	2 (5.0%)
Hispanic or Latino	8 (19.5%)	7 (17.5%)	10 (25.0%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	1 (2.5%)	1 (2.5%)
White	28 (68.3%)	29 (72.5%)	26 (65.0%)
Multiple Race/Ethnicities	1 (2.4%)	0 (0.0%)	0 (0.0%)
Region			
Coagulopathic	39 (95.1%)	38 (95.0%)	38 (95.0%)
Non-coagulopathic	2 (4.9%)	2 (5.0%)	2 (5.0%)

(Source: Table 2.2, original data with p-values removed, Section 14.1, CSR)

It appears that the demographics are balanced among the three groups except for age. The Anavip/Anavip Group had more subjects who were less than 10 years old, and the CroFab/CroFab Group had more subjects who were at least 10 years old.

6.1.10.1.3 Subject Disposition

Table 4 summarizes subject disposition reported by the sponsor.

Table 4. Summary of Subject Disposition

	Group 1 Anavip/Anavip	Group 2 Anavip/Placebo	Group 3 CroFab/CroFab
Randomized Patients, n	41	41	41
Completed Study			
Yes	37 (90.2%)	35 (85.4%)	37 (90.2%)
No	4 (9.8%)	6 (14.6%)	4 (9.8%)
Primary Reason did not Complete Study			
Did not Meet Entry Criteria	0 (0.0%)	1 (2.4%)	0 (0.0%)
Consent is withdrawn	1 (2.4%)	0 (0.0%)	1 (2.4%)
Investigator Judgment	0 (0.0%)	0 (0.0%)	1 (2.4%)
Lost to Follow-up	2 (4.9%)	5 (12.2%)	2 (4.9%)
Death	1 (2.4%)	0 (0.0%)	0 (0.0%)

(Source: Original Table 2, Section 10.1, CSR)

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

Table 5 summarizes the primary efficacy results on the ITT population reported by the sponsor.

Table 5. Summary of Primary Efficacy Results (ITT Population*)

	Group 1 (n = 41) Anavip/Anavip	Group 2 (n = 40) Anavip/Placebo	Group 3 (n = 40) CroFab/CroFab
Experienced Coagulopathy on Either Day 5 or Day 8, n	39	38	37
Yes	4 (10.3%)	2 (5.3%)	11 (29.7%)
No	35 (89.7%)	36 (94.7%)	26 (70.3%)
Treatment Group (vs. Group 3)			
Odds Ratio (95% CI) ¹	0.275 (0.058, 1.048)	0.135 (0.014, 0.686)	
P-Value ¹	0.0605	0.0099	
P-Value ²	0.0448	0.0060	
Region (vs. Group 3)			
Odds Ratio (95% CI) [1]	0.365 (0.015, 25.842)	0.236 (0.007, 21.050)	
P-Value ¹	0.8715	0.7405	

Source: Section 14.2, Table 6.1

CI = confidence interval

¹ Exact parameter estimates and likelihood ratio tests from a logistic model compared coagulopathy rates between Anavip (Group 1, 2) and CroFab (Group 3).

² Exact conditional scores tests from a logistic model compared coagulopathy rates between Anavip (Group 1, 2) and CroFab (Group 3).

* Excluding seven subjects with no follow-up data.

(Source: Original Table 5 Section 11.4.1.1, CSR)

In the original submission, the sponsor reported an OR of 0.275 (95%CI: 0.058, 1.048) and a two-sided p-value of 0.06 for the comparison of Anavip/Anavip with

CroFab/CroFab. The Anavip/Placebo did show a significantly lower coagulopathy rate compared to CroFab/CroFab (OR=0.135, p-value=0.01), however by the pre-specified hierarchical testing scheme, this comparison should not be made, given that the p-value for the comparison of Anavip/Anavip with CroFab/CroFab failed to reach statistical significance (p-value is greater than 0.05).

This reviewer observed that the sponsor’s “ITT analysis” was actually a complete case analysis, which excluded seven subjects from the ITT population. These seven subjects were randomized and treated but did not have any of the three assessments on either Day 5 or Day 8. These subjects should have been included in the ITT analysis, but the sponsor did not pre-specify a primary missing data imputation method and the seven subjects only had baseline data (see Section 6.1.11.4 for sensitivity analyses using different imputation methods).

The Per Protocol analysis of the primary endpoint reported by the sponsor is in Table 6. The Per Protocol analysis excludes subjects with major protocol deviations and subjects without any follow-up data. The Per Protocol analysis results show that both the Anavip/Anavip Group and Anavip/Placebo Group have significantly lower coagulopathy rates than the CroFab/CroFab Group.

Table 6. Summary of Primary Efficacy Results (Per Protocol Population)

	Group 1 (N=38) Anavip/Anavip	Group 2 (N=35) Anavip/Placebo	Group 3 (N=36) Anavip/Placebo
Experienced Coagulopathy on Either Day 5 or Day 8	38	35	36
Yes	3 (7.9%)	2 (5.7%)	10 (27.8%)
No	35 (92.1%)	33 (94.3%)	26 (72.2%)
Treatment Group (vs. CroFab)			
Odds ratio (95% CI) ¹	0.227 (0.037, 0.983)	0.167 (0.017, 0.870)	
p-value	0.0468	0.029	
Region (coagulopathic vs. non-coagulopathic)			
Odds ratio (95% CI) ¹	0.293 (0.011, 22.012)	0.153 (0.001, 17.416)	
p-value	0.7775	0.6381	

1. Exact parameter estimate and likelihood ratio test from an exact logistic model
(Source: Adapted from Table 6, section 11.4.1.2, CSR)

6.1.11.2 Analyses of Secondary Endpoints

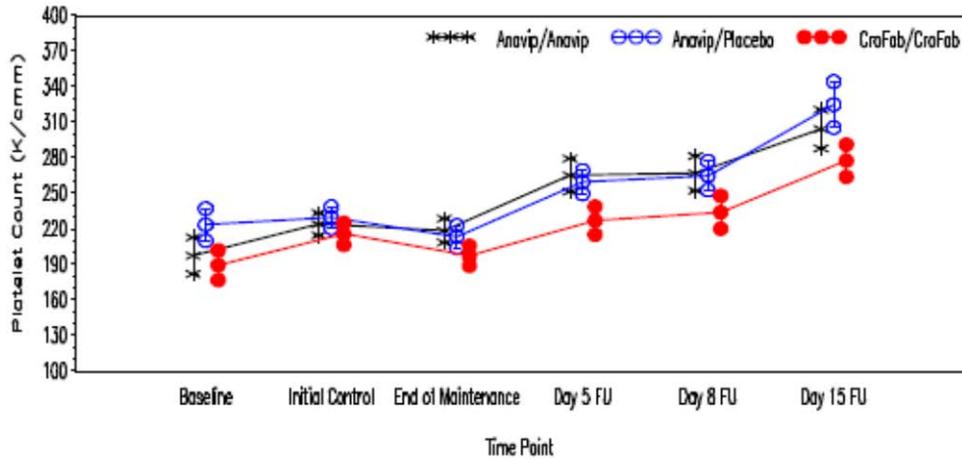
Venom and Antivenom Levels and Venonemia Rates

The sponsor reported that the laboratory analysis on venom and antivenom levels could not be interpreted, because the analysis was performed after more than 90 days of storage and the majority of the CroFab samples had degraded by then.

Platelet Count

Figure 1 shows platelet count over time for the three treatment groups reported by the sponsor for the ITT population (platelet counts were missing for some subjects at time points post baseline).

Figure 1. Platelet Count Over Time for the Three Treatment Groups



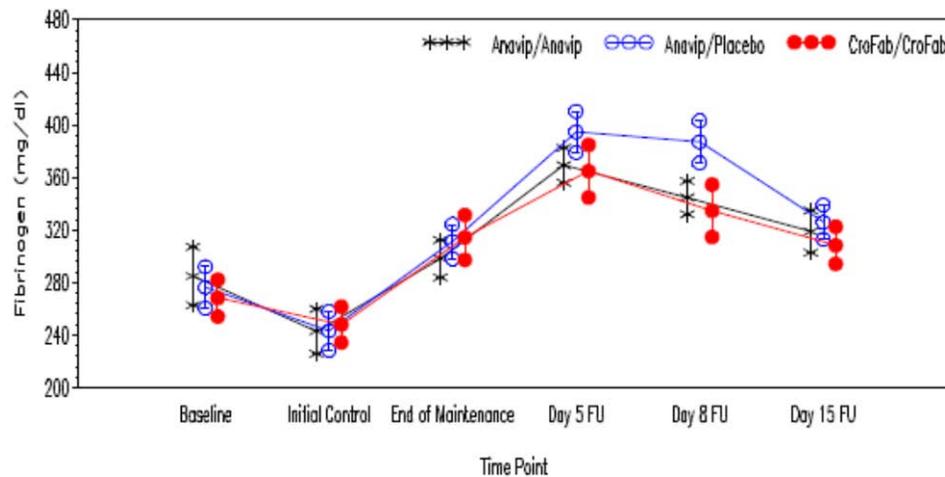
(Source: Original Figure 2, Section 11.4.1.2, CSR)

In each treatment group, the platelet count increases slightly from baseline at the initial control and then decreases a little bit from that at the end of maintenance, and then increases steadily at Day 5, 8 and reaches the highest at Day 15. Between the treatment groups, mean platelet count in both the Anavip/Anavip Group and the Anavip/Placebo Group was higher than that in the CroFab/CroFab Group on Day 5 and Day 8.

Fibrinogen

Figure 2 shows fibrinogen levels over time for the three treatment groups reported by the sponsor for the ITT population (Fibrinogen levels were missing for some subjects at time points post baseline).

Figure 2. Fibrinogen Levels Over Time for the Three Treatment Groups



(Source: Original Figure 3, Section 11.4.1.2, CSR)

In each treatment group, baseline mean fibrinogen decreased during the initial control period, increased at end of maintenance and continued to increase to maximum levels at Day 5, and then gradually decreased during the follow-up period to Day 15. At baseline, the three treatment groups had similar fibrinogen levels, and at both the initial control and end of maintenance time points, the fibrinogen levels continued to be similar among the three groups. On Day 5 and Day 8, Anavip/Placebo Group tended to have higher mean fibrinogen levels than the other two groups. However, at Day 15 all three groups had similar fibrinogen levels.

6.1.11.3 Subpopulation Analyses

The sponsor did not perform subgroup analysis by gender and race. This reviewer conducted these analyses using the ITT population and the results are in Tables 7 and 8. There do not appear to be systematic gender differences in terms of treatment effect. For the subgroup analysis by race, Hispanic and White subjects account for the vast majority of the enrolled subjects, and this reviewer combined subjects from the other races in the analysis. There does not appear to be any systematic difference between races in terms of treatment effect.

Table 7. Subgroup Analysis by Gender (ITT Population)

Gender	Experienced Coagulopathy on Either Day 5 or Day 8	Anavip/Anavip	Anavip/Placebo	CroFab/CroFab
		F=11 M=30	F=10 M=30	F=12 M=28
Female	Yes	0 (0%)	1 (10%)	4 (33.3%)
	No	11 (100%)	8 (80%)	8 (66.7%)
	Missing	0 (0%)	1 (10%)	0 (0%)
Male	Yes	4 (13.3%)	1 (3.3%)	7 (25%)
	No	24 (80%)	28 (93.3%)	18 (64.3%)
	Missing	2 (6.7%)	1 (3.3%)	3 (10.7%)

Table 8. Subgroup Analysis by Race (ITT Population)

Race	Experienced Coagulopathy on Either Day 5 or Day 8	Anavip/Anavip	Anavip/Placebo	CroFab/CroFab
		H ¹ =8 W ² =28 O ³ =5	H ¹ =7 W ² =29 O ³ =4	H ¹ =10 W ² =26 O ³ =4
Hispanic	Yes	0 (0%)	0 (0%)	3 (30%)
	No	8 (100%)	7 (100%)	6 (60%)
	Missing	0 (0%)	0 (0%)	1 (10%)
White	Yes	3 (10.7%)	2 (6.9%)	6 (23.1%)
	No	23 (82.1%)	26 (89.7%)	18 (69.2%)
	Missing	2 (7.1%)	1 (3.4%)	2 (7.7%)
Others	Yes	1 (20%)	0 (0%)	2 (50%)
	No	4 (80%)	3 (75%)	2 (50%)
	Missing	0 (0%)	1 (25%)	0 (0%)

H: Hispanic W: White O:Other

6.1.11.4 Dropouts and/or Discontinuations

Missing Data Distribution

Though the number of subjects lost to follow-up in the Anavip/Placebo Group is slightly higher than the other two groups (Table 4), this group has the least number of subjects with missing values for the six assessments (three on each of Day 5 and 8) which determine the primary efficacy outcome. In addition to the 7 subjects without any assessment data, 12 subjects had incomplete assessment data, meaning that they had some of the 6 assessments, but not all of them. Table 9 shows the break-down of the missing data by treatment group.

Table 9. Missing Primary Efficacy Assessment by Treatment Group

Treatment group	ITT population	Subjects with all six assessments missing	Subjects with some of the six assessments missing	Total subjects with any missing data ¹
Group 1 (Anavip/Anavip)	41	2 (4.9%)	6 (14.6%)	8 (19.5%)
Group 2 (Anavip/Placebo)	40	2 (5%)	1 (2.5%)	3 (7.5%)
Group 3 (CroFab/CroFab)	40	3 (7.5%)	5 (12.5%)	8 (20%)
Three groups combined	121	7 (5.8%)	12 (9.9%)	19 (15.7%)

1: Column 5 = Column 3 + Column 4

Missing Data Causes

At this reviewer's request, the sponsor investigated the causes of the missing data. The sponsor reviewed missing data and provided a table detailing the reasons for missing (BLA 125488/0.12). In the majority of cases, the study coordinator could not reach the subject (invalid phone number, did not return the call, or homeless), or the subject didn't have transportation to get back to the study site for the follow-up visit. The sponsor concluded that it is due to random chance that the Anavip/Anavip and CroFab/CroFab groups had high occurrences of missing assessments.

In particular, this reviewer looked into the seven subjects who did not have any follow-up data beyond baseline. Two subjects withdrew consent, one subject is homeless, one subject provided an invalid phone number and could not be reached, one subject was not able to be contacted, one subject was called several times and no response was received, and, for one subject, no explanation was provided. There seems to be no substantial evidence of informative missingness and missing completely at random (MCAR) may be plausible.

This reviewer examined the missing data, including the missing primary efficacy assessment and the other follow-up data, and did not find any specific pattern. In particular, it does not appear that subjects with low baseline platelet count or fibrinogen level were more likely to be lost for follow-up. And it does not appear that subjects who had a low platelet count or fibrinogen level on Day 5 were more likely to have a missing

assessment on Day 8. In addition, it does not appear that any site had a substantially higher proportion of missing data than others.

Sensitivity Analyses

Separate sensitivity analyses were conducted for the seven subjects with all six assessments missing (column 3 of Table 9) and for the 12 subjects with incomplete assessments (column 4 of Table 9).

At the request of this reviewer, the sponsor conducted post hoc analyses with different missing data imputation methods to assess the impact of the missing data for the seven subjects with only baseline data. Table 10 summarizes those analysis results.

Table 10. Summary of Primary Efficacy Endpoint Sensitivity Analyses for Subjects with no Follow-up Data (ITT Population)

	Imputation method		Anavip/Anavip (n=41) vs. CroFab/CroFab (n=40)	Anavip/Placebo (n=40) vs. CroFab/CroFab (n=40)
1	Missing primary endpoint assigned as having coagulopathy	Odds Ratio (95% CI)	0.326 (0.090, 1.047)	0.212 (0.046, 0.772)
		p-value	0.06	0.01
2	Missing primary endpoint assigned as not having coagulopathy	Odds Ratio (95% CI)	0.295 (0.063, 1.116)	0.146 (0.015, 0.737)
		p-value	0.08	0.01
3	Baseline observation carried forward [#]	Odds Ratio (95% CI)	0.262 (0.056, 0.974)	0.129 (0.013, 0.644)
		p-value	0.05	0.007
4	Missing assigned to favor CroFab treatment	Odds Ratio (95% CI)	0.462 (0.125, 1.547)	0.303 (0.064, 1.148)
		p-value	0.26	0.09
5.	Missing Assigned to Favor Anavip Treatment	Odds Ratio (95% CI)	0.206 (0.045, 0.752)	0.101 (0.010, 0.492)
		p-value	0.01	0.002
5	Multiple imputation*	Odds Ratio (95% CI)	0.262 (0.076, 0.906)	0.130 (0.027, 0.631)
		p-value	0.03	0.01

[#] BOCF coincides with LOCF and WOCF in this case.

*In this MI analysis, variables included in the model were fibrinogen (Baseline, Day 5, Day 8), platelet count (Baseline, Day 5, Day 8) and region. Imputation was carried out separately by treatment. One hundred imputed datasets were created.

(Source: Adapted from Supplemental table, Section 5, tsupt06-1-exact-itt-sens.pdf, BLA 125488/0.12, Supplemental table, Section 5.4, suppt-exactlog-mi-10jul2013, BLA 125488/0.15)

For those subjects who had incomplete assessment data, the sponsor assumed that the missing data met the criteria of not experiencing coagulopathy (Section 6.1.8 Missing

data). As a result, 11 out of 12 subjects with incomplete data were assigned “coagulopathy not experienced” by this algorithm (6 in the Anavip/Anavip Group, 1 in the Anavip/Placebo Group and 4 in the CroFab/CroFab Group). A careful examination of the coagulopathy cases shows that this assumption is overly optimistic. Out of the 16 coagulopathy cases with complete primary efficacy assessments, the majority (11 out of 16) had only 1 assessment out of 6 that did not meet the criteria for “coagulopathy not experienced”. Since the Anavip/Anavip Group has the largest proportion of incomplete data, this assumption clearly favors this group. The sponsor conducted sensitivity analyses to evaluate the impact of the incomplete assessment data (Table 11). All imputation methods, except the one which favors the Anavip/Anavip groups (row 3 in Table 11), yield a p-value larger than 0.06, the result the sponsor reported for the primary comparison between Anavip/Anavip and CroFab/CroFab.

Table 11. Summary of Primary Efficacy Endpoint Sensitivity Analyses for Subjects with Incomplete Data (ITT Population*)

	Imputation method		Anavip/Anavip (n=39) vs. CroFab/CroFab (n=37)	Anavip/Placebo (n=38) vs. CroFab/CroFab (n=37)
1	Any missing components assigned as coagulopathy	Odds ratio (95% CI)	0.344 (0.094, 1.124)	0.107 (0.011, 0.530)
		p-value	0.08	0.002
2	Missing component assigned to favor CroFab treatment	Odds ratio (95% CI)	0.434 (0.117, 1.467)	0.135 (0.014, 0.686)
		p-value	0.21	0.01
3	Missing component assigned to favor Anavip treatment	Odds ratio (95% CI)	0.218 (0.047, 0.805)	0.107 (0.011, 0.530)
		p-value	0.02	0.002

*Excluding the seven subjects with no follow-up data.
(Source: Adapted from Table 13, Section 11.4.1.3 of the CSR)

6.1.11.5 Exploratory and Post Hoc Analyses

The sponsor noticed that all the coagulopathy cases in the Anavip/Anavip (4 cases) and Anavip/Placebo (2 cases) groups were at Site 10. This site had about 25% of all enrollments. The FDA inspection did not identify any issue with this site. The sponsor states that Site 10 is home to the Southern Pacific Rattlesnake (SPR) which has wide variability in coagulopathic activity and may be responsible for these coagulopathy cases. This reviewer checked the snake bite type for Site 10 and found that the SPR was not over-represented in the coagulopathy cases. One out of four coagulopathy cases in the Anavip/Anavip Group was from a SPR bite, one case (out of two) for the Anavip/Placebo Group and one (out of two) for the CroFab/CroFab Group. Snake type does not appear to explain why Site 10 had all the cases of coagulopathy for the Anavip/Anavip Group and the Anavip/Placebo Group.

This reviewer analyzed baseline platelet count and fibrinogen level and found that the Anavip/Anavip Group had the highest percentage of baseline coagulopathic subjects (defined as platelet levels < 150,000/mm³ or fibrinogen levels < 150 mg/dL at baseline) among the three groups (41.5% compared with 17.5% and 32.5% for the Anavip/Placebo and CroFab/CroFab groups, respectively). Furthermore, baseline coagulopathic subjects were more likely to experience coagulopathy after treatment. Thirty-three percent (33%) of baseline coagulopathic subjects continued to experience coagulopathy on either Day 5 or 8, compared to only 6% for baseline non-coagulopathic subjects. Table 12 shows the coagulopathy rate for the three groups, when controlling for baseline coagulopathy.

Table 12. Coagulopathy Rate by Treatment Group and Baseline Coagulopathy*

Baseline coagulopathy	Experienced coagulopathy on either Day 5 or 8	Anavip/Anavip	Anavip/Placebo	CroFab/CroFab	Total
Yes	Number of subjects	N=17	N=7	N=12	N=36
	Yes	3 (17.65%)	2 (28.57%)	7 (58.33%)	12 (33.3%)
	No	14 (82.35%)	5 (71.43%)	5 (41.67%)	24(66.7%)
No	Number of subjects	N=22	N=31	N=25	N=78
	Yes	1 (4.55%)	0 (0)	4 (16%)	5 (6.4%)
	No	21 (95.45%)	31 (100%)	21 (84%)	73(93.6%)

*This analysis is for the ITT population excluding the seven subjects without any follow-up data.

This reviewer also performed an exact logistic regression analysis adjusting for both region and baseline coagulopathy; the results are in Table 13. This analysis indicates that when additionally adjusting for baseline coagulopathy, the treatment effect for both Anavip/Anavip and Anavip/Placebo is statistically significant. Furthermore, the effect of baseline coagulopathy is highly statistically significant, showing that if the subject was coagulopathic at baseline, the odds of experiencing coagulopathy after treatment is significantly higher than for a subject who was not coagulopathic at baseline, when controlling for treatment and region. However, this analysis is post-hoc and can only be viewed as supportive evidence.

Table 13. Primary Efficacy Analysis Results Adjusting for Region and Baseline Coagulopathy*

	Group 1 (N=39) Anavip/Anavip	Group 2 (N=38) Anavip/Placebo
Treatment Group (vs. CroFab)		
Odds ratio (95% CI)	0.184 (0.033, 0.794)	0.121 (0.010, 0.764)
p-value	0.02	0.02
Baseline coagulopathy (vs. non-coagulopathy)		
Odds ratio (95% CI)	7.397 (1.642, 42.334)	10.328 (2.197, 61.360)
p-value	0.006	0.002
Region (coagulopathic vs. non-coagulopathic)		
Odds ratio (95% CI)	0.121 (0.003, 11.016)	0.225 (0.007, 16.429)
p-value	0.46	0.64

*This analysis is for the ITT population excluding the seven subjects without any follow-up data.

6.1.12 Safety Analyses

The Safety population includes all subjects who received at least one dose of Anavip or CroFab; subjects were assigned to the first treatment received. Due to pharmacy errors, two subjects randomized to Anavip/Placebo Group received Anavip as the first maintenance dose and thus were included in the Anavip/Anavip Group for the safety analysis, and one subject randomized to Anavip/Placebo Group received CroFab for the initial treatment and thus was included in CroFab/CroFab Group for the safety analysis. Consequently, the Safety population has 43 subjects in Anavip/Anavip Group, 37 subjects in Anavip/Placebo Group and 41 subjects in CroFab/CroFab Group.

6.1.12.3 Deaths

One subject (Anavip/Anavip Group) died from multiple injuries sustained during a motor vehicle accident; the death was reported to be unrelated to study drug.

6.1.12.4 Nonfatal Serious Adverse Events

The sponsor reported that a total of nine subjects, including six (14.0%) subjects in Anavip/Anavip Group, one (2.7%) subject in Anavip/Placebo Group, and two (4.9%) subjects in CroFab/CroFab Group experienced at least one SAE (Table 14). Most SAEs were classified as severe and not related to study drug. The only treatment-related SAE was severe swelling (Anavip/Anavip Group) that was considered possibly related to study drug.

Table 14. Summary of AEs and SAEs

	Group 1 (n = 43) Anavip/Anavip	Group 2 (n = 37) Anavip/Placebo	Group 3 (n = 41) CroFab/CroFab
Patients Reporting at Least 1 AE ¹	35 (81.4%)	24 (64.9%)	33 (80.5%)
Number of AEs ¹	130	72	137
Patients Reporting at Least 1 Related AE ²	15 (34.9%)	8 (21.6%)	15 (36.6%)
Patients Reporting at Least 1 AE by Severity			
Mild	23 (53.5%)	15 (40.5%)	16 (39.0%)
Moderate	7 (16.3%)	7 (18.9%)	13 (31.7%)
Severe	5 (11.6%)	2 (5.4%)	4 (9.8%)
Patients Reporting at Least 1 AE during Follow-up Period ³	28 (65.1%)	22 (59.5%)	30 (73.2%)
Patients Reporting at Least 1 SAE ¹	6 (14.0%)	1 (2.7%)	2 (4.9%)
Number of SAEs ¹	6	1	4
Deaths	1 (2.3%)	0	0

¹ Only those AEs reported on AE CRF page were considered for analysis (Not counting Follow-up AEs).

² Included all events reported as "Definite", "Possible", or "Not assessable" relationship to study drug.

³ Only AEs reported on the Follow-up Evaluation CRF page were counted.

(Source: Original Table 20, Section 12.2.1, CSR).

6.2 Trial #2

Study AN 03/02 is a randomized, open-label, phase II study. Twelve subjects aged 18 to 70 years with signs of pit viper envenomation received CroFab or Anavip dosing until initial control was achieved, followed by maintenance dosing.

All patients in both treatment groups achieved initial control of local injury and coagulopathy following early antivenom treatment. In the CroFab group, at the end of maintenance dosing, 5 of 6 subjects had platelet counts above 150,000/mm³, one subject's platelet counts were 146,000/mm³, and all 6 had fibrinogen levels above 150 mg/dL. During the follow-up phase all 6 exhibited platelet counts below 150,000/mm³ and 2 also exhibited fibrinogen below 150 mg/dL. Two of 6 in the control group had inpatient management with administration of additional doses.

In the Anavip arm, at the end of maintenance dosing, 5 of 6 subjects had platelet counts above 150,000/mm³, and one subject's platelet counts were 114,000/mm³ and were trending upward. All 6 had fibrinogen levels above 150 mg/dL. During the follow-up phase, 5 of 6 subjects had platelet counts above 150,000/mm³, with no downward trend; one subject's platelet counts was 127,000/mm³ on follow-up Day 1, reached 160,000/mm³ on Day 4 and continued trending upward. All 6 subjects in Anavip group had fibrinogen levels above 150 mg/dL during the follow-up phase. None in the Anavip group required rehospitalization or retreatment with Anavip.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The primary source of evidence to support the BLA is a Phase III, randomized, double blind, active controlled, multicenter study. One hundred and twenty-one (121) subjects were randomized and treated in a 1:1:1 ratio to three treatment groups:

Group 1 (Anavip/Anavip): Anavip with Anavip maintenance therapy;

Group 2 (Anavip/Placebo): Anavip with Placebo (normal saline) maintenance therapy;

Group 3 (CroFab/CroFab): CroFab with CroFab maintenance therapy.

The sponsor reported that the primary comparison between Anavip/Anavip and CroFab/ CroFab is not statistically significant (two-sided p-value =0.06, OR =0.275 and 95% CI: 0.058, 1.048). Though the comparison between Anavip/Placebo and CroFab/ CroFab is nominally statistically significant (OR=0.135, p-value=0.01), the pre-specified hierarchical testing strategy prevents formally performing this test since the primary comparison between Anavip/Anavip and CroFab/ CroFab is not statistically significant.

Though the sponsor pre-specified the primary analysis to be on the ITT population, the sponsor's actual primary efficacy analysis is a complete case analysis which excludes from the ITT population seven subjects who do not have any primary efficacy data. Although it would be preferable for the primary analysis to be on the ITT population, the sponsor did not pre-specify a primary missing data imputation method, the seven subjects excluded did not have any follow-up data beyond baseline, and the investigation into the reasons for subjects lost to follow-up seems to suggest the MCAR assumption is plausible. As a result, the complete case analysis is regarded as the primary analysis in this review and the ITT analyses with various imputation methods are treated as supportive evidence. Post-hoc ITT analyses using BOCF and multiple imputation (MI) for the missing data show that the primary comparison between Anavip/Anavip and CroFab/ CroFab is statistically significant. However, when imputing the missing cases as all coagulopathy or as all non-coagulopathy, the primary comparison between Anavip/Anavip and CroFab/ CroFab is not statistically significant.

Post-hoc analysis identifies baseline coagulopathy as a highly significant prognostic factor (OR=7.397, p-value=0.006) and when the primary efficacy analysis is adjusted for this factor, the primary comparison between Anavip/Anavip and CroFab/ CroFab is statistically significant (OR=0.184; 95% CI: 0.033, 0.794; p-value=0.02).

There do not appear to be systematic gender or race differences in terms of treatment effect.

10.2 Conclusions and Recommendations

In summary, though the study results do not seem to provide evidence strong enough to support a superiority claim of Anavip over CroFab on the management of coagulopathy in patients with North American crotalid envenomation, Anavip does show some evidence

of effect on the management of coagulopathy in patients with North American crotalid envenomation compared to CroFab.