



Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

STATISTICAL REVIEW AND EVALUATION BLA

BLA/Supplement Number: 125335/0 (MID-Cycle Review Memo)

Product Name: Anascorp

Indication(s): For the treatment of clinically important signs of scorpion envenomation

Applicant: Instituto Bioclon SA de CV

Date(s): 1/22/2009(DCC Receipt Date)

Review Priority: Accelerated (6 month review)

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Table of Contents

1. EXECUTIVE SUMMARY	3
1.1 CONCLUSIONS AND RECOMMENDATIONS	3
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES	3
1.3 MAJOR STATISTICAL ISSUES AND FINDINGS	3
2. INTRODUCTION	4
2.1 OVERVIEW	4
2.2 DATA SOURCES	4
3. STATISTICAL EVALUATION	4
3.1 EVALUATION OF EFFICACY	4
3.2 EVALUATION OF SAFETY	7
3.3 GENDER, RACE, AGE AND OTHER SPECIAL/SUBGROUP POPULATIONS	7
4. SUMMARY AND CONCLUSIONS	7
4.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE	7
4.2 CONCLUSIONS AND RECOMMENDATIONS	8
DISTRIBUTION LIST.....	8

1. EXECUTIVE SUMMARY

This is an original BLA submission of Anascorp for the treatment of clinically important signs of scorpion envenomation. Anascorp is a sterile preparation of scorpion venom-specific binding fragments, presented as a lyophilized powder in a 10ml vial. There is only one Phase 3 study in this submission, which is a prospective, randomized, double-blind, and placebo-controlled study. The objective of this study is to demonstrate the efficacy and safety of Anascorp. The primary efficacy endpoint is the resolution of clinically important signs of scorpion envenomation within 4 hours for patients treated with Anascorp. Anascorp will be declared clinically superior to placebo if the symptom resolution success rate in the Anascorp group is at least 20% greater than the percentage in the placebo group.

The study enrolled 15 subjects; 8 were randomized to the treatment group and 7 to the placebo group. The symptom resolution success rate is 100% for the Anascorp-treated group and 14.3% for the placebo-treated group. The difference of the two success rates are 85.7% and the lower confidence limit for the difference is 40.7%.

The 20% superiority margin along with the study size of 15 are not clearly justified. Further investigation is necessary. Statistical review is still on-going and this review memo should be considered as the mid-cycle review memo.

1.1 Conclusions and Recommendations

Statistical review is still on-going and this review memo should be considered as the mid-cycle review memo. There are no specific safety analyses that are crucial for product approval and labeling.

1.2 Brief Overview of Clinical Studies

There is only one Phase 3 study in this submission. This study is a prospective, randomized, double-blind, and placebo-controlled study. The objective of this study is to demonstrate the efficacy and safety of Anascorp. Patients 6 months to 18 years of age presenting for emergency treatment with severe systemic signs of scorpion sting envenomation are included in the study. The primary efficacy endpoint is the resolution of clinically important signs of scorpion envenomation within 4 hours for patients treated with Anascorp. The primary endpoint was assessed at baseline, 1, 2 and 4 hours after treatment and at hospital discharge. Follow-up was conducted by phone interview seven days and 14 days after discharge. The study enrolled 15 pediatric subjects; 8 were randomized to the treatment group and 7 to the placebo group. The study was conducted at three sites in Tucson, Arizona.

1.3 Major Statistical Issues and Findings

The symptom resolution success rate is 100% for the Anascorp-treated group and 14.3% for the placebo-treated group. The difference of the two success rates are 85.7% and the

95% lower confidence limit for the difference is 40.7%. The 20% superiority margin along with the study size of 15 are not clearly justified. Further investigation is necessary and statistical review comments on that issue will be made at the final stage of this review.

2. INTRODUCTION

2.1 Overview

Anascorp is a sterile preparation of scorpion venom-specific binding fragments, presented as a lyophilized powder in a 10ml vial. Its intended indication is for the treatment of clinically important signs of scorpion envenomation.

There is only one Phase 3 study (AL 02/03) in this submission. Besides this pivotal trial, there are 4 open-label studies (AL 02/04, 02/05, 02/06 and 03/07) and one retrospective study (AL 03/06).

The pivotal study is a prospective, randomized, double-blind, and placebo-controlled trial. The objective of this study is to demonstrate the efficacy and safety of Anascorp in the treatment of systemic manifestations of scorpion sting. The primary endpoint is percentage of patients whose clinically systemic signs of scorpion envenomation have been resolved successfully within 4 hours after treatment. Anascorp will be declared clinically superior to placebo if the Anascorp symptom resolution success percentage is at least 20% greater than the placebo success percentage.

2.2 Data Sources

The electronic data sets analyzed include R53SEVER, r42sting, r32base, r52physi; all three data sets are in EDR DATS Log Number 459248. The venom data set on page 352 of Volume 8 of the paper submission was also analyzed.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Study Design and Endpoints

The pivotal study (AL 02/03) is a prospective, randomized, double-blind, and placebo-controlled study. This is the only Phase 3 trial in this application. The study planned to enroll at least 12 evaluable patients in a 1:1 ratio and actually enrolled 15, 8 randomized to the treatment group and 7 to the placebo group. The objective of this study is to demonstrate the efficacy and safety of Anascorp in the treatment of systemic manifestations of scorpion sting. The primary efficacy endpoint is the resolution of clinically important signs of scorpion envenomation within 4 hours for patients treated with Anascorp. The primary endpoint is defined as binary variable (syndrome present or

syndrome absent) based on the presence or absence of key respiratory and neuromotor components as determined by the study physician and nurse. Secondary efficacy endpoints include venom levels, the quantity of midazolam required for sedation in both groups of patients, physical and symptom assessments and severity evaluation of scorpion envenomation.

Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

Fifteen patients were randomized (8 to Anascorp and 7 to placebo). Overall, 93% of patients completed the study. One patient in the placebo group discontinued the study due to inability reach her parents for 7 and 14 day follow-up evaluations. All 15 patients were included in the intent-to-treat (ITT) population.

Demographic Characteristics

The following table shows the demographic characteristics of ITT.

Disposition Parameters	Overall N =15	Treatment Groups	
		Anascorp N=8	Placebo N=7
Age*			
Mean(SD)	3.1(2.65)	2.06(1.72)	4.20(3.18)
Min, Max	0.64, 10.3	0.96, 5.93	0.64, 10.31
Sex, n (%)			
Male	7(46.7)	4 (50.0)	3(42.9)
Female	8(53.3)	4 (50.0)	4(57.1)
Race, n (%)			
African American/Hispanic	1(6.7)	1(12.5)	0(0.0)
Black	1(6.7)	0(0.0)	1(14.3)
American Indian	1(6.7)	1(12.5)	0(0.0)
Caucasian	7(46.7)	3(37.5)	4(57.1)
Hispanic	4(26.7)	3(37.5)	1(14.3)
Native American	1(6.7)	0(0.0)	1(14.3)
Weight(kg)			
Mean(SD)	15.1(8.9)	11.9(4.0)	18.8(11.7)
Min, Max	7.7, 42	7.7, 20	8.2, 42
Height(cm) **			
Mean(SD)	99.1(32.1)	80.7(4.67)	136.0(0.0)
Min, Max	77.4,136	77.4, 84	136,136

*The results for age are slightly different from sponsor's results, maybe because the reviewer didn't calculate age as an integer.

** Only 2 subjects in Anascorp group and 1 subject in placebo group have height data.

Baseline Characteristics

1. *serum venom level*

The following table shows the descriptive statistics of the baseline serum venom level for the two treatment groups:

Characteristics	Treatment Groups	
	Anascorp Total=8	Placebo Total=7
Baseline Serum Venom Level (ng/mL)		
N	6	6
Mean(SD)	7.1(4.6)	6.6(10.1)
Min, Max	0, 12.9,	0, 26.8

This reviewer investigated baseline serum venom level to find out if patients in the placebo-treated group have a higher level of baseline serum venom level than those in the Anascorp-treated group. In the sponsor's data set, information for the baseline venom serum level is missing for 1 placebo-treated patient (patient #-(b)(6)-) and 2 Anascorp – treated patients (patient #(b)(6), and #(b)(6)). A worst case analysis was conducted in which the missing values in the placebo-treated group were replaced with maximum value in this group, and for the Anascorp-treated group, the missing value was replaced by the smallest value in this group. Both t-test and Wilcoxon rank sum test failed to reject the null hypothesis that the baseline serum venom level for the placebo-treated group is no higher than that of Anascorp-treated group at the 0.05 significance level. This may be due to the small sample size and large SD.

2. *time between sting and hospitalization*

The reviewer calculated the time elapsed between Scorpion sting and arrival at hospital. The following table shows the descriptive statistics of the time elapsed for the two treatment groups:

Characteristics	Treatment Groups	
	Anascorp Total=8	Placebo Total=7
Time elapsed from time of sting to hospitalization (minutes)		
N	7	4
Mean(SD)	134.9(81.9)	149(24.7)
Min, Max	45, 285	131, 185

This reviewer investigated time elapsed from time of sting to hospitalization to find out if patients in the placebo-treated group waited longer before they got treatment than those in the Anascorp-treated group. In the sponsor's data set, information for the time elapsed from time of sting to hospitalization is missing for 3 placebo-treated patients (patient #------(b)(6)-----) and 1 Anascorp – treated patients (patient #-(b)(6)-). A worst case analysis was conducted in which the missing values in the placebo-treated group were

replaced with maximum value in this group, and for the Anascorp-treated group, the missing value was replaced by the smallest value in this group. And both t-test and Wilcoxon rank sum test fail to reject the null hypothesis that the time elapsed for the Anascorp-treated group is no shorter than that of placebo-treated group at the 0.05 significance level. This may be due to the small sample size and large SD.

Statistical Methodologies

In their protocol, the sponsor proposed to present the systemic sign response using frequencies and percentages. According to the sponsor, Anascorp is to be declared clinically superior to placebo if the Anascorp success percentage is $\geq 20\%$ than the placebo success percentage.

Results and Conclusions

Sponsor's results

The symptom resolution success rate at 4 hours after the treatment is 100% (8 out of 8) for the Anascorp-treated group and 14.3% (1 out of 7) for the placebo-treated group. The difference of the two success rates are $100\% - 14.3\% = 85.7\%$.

Statistical reviewer's findings

The efficacy analysis was done on the symptom resolution success rates at 4 hours after the treatment for the two treatment groups. This reviewer found a 95% confidence interval for the difference: (40.7%, 97.6%) using StatXact.

3.2 Evaluation of Safety

There are no specific safety analyses that are crucial for product approval and labeling.

3.3 Gender, Race, Age and Other Special/Subgroup Populations

Due to the limited sample size (8 for the treatment group and 7 for the placebo group), no subgroup analysis is conducted.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

The symptom resolution success rate is 100% for the Anascorp-treated group and 14.3% for the placebo-treated group. The difference of the two success rates is 85.7% and the lower confidence limit for the difference is 40.7%.

The 20% superiority margin along with the study size of 15 is not clearly justified. Further investigation is necessary and statistical review comments on that issue will be made at the final stage of this review.

4.2 Conclusions and Recommendations

Statistical review is still on-going and this review memo should be considered as the mid-cycle review memo. There are no specific safety analyses that are crucial for product approval and labeling.

DISTRIBUTION LIST

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