



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

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)

Statistical Branch: Therapeutics Evaluation Branch

Primary Statistical Reviewer: Xue Lin, Ph.D.

Concurring Reviewer (1): Jessica (Jeongsook) Kim PhD., team leader, Therapeutics Evaluation Branch, (HFM-219)

Concurring Reviewer (2): Ghanshyam Gupta, PhD., Chief, Therapeutics Evaluation Branch, (HFM-219)

Medical Office/Division: OBRR /DH

Clinical Reviewer(s): Hon-Sum Ko, MD

Project Manager: Debbie Cordaro

Table of Contents

1. EXECUTIVE SUMMARY	3
1.1 BRIEF OVERVIEW OF CLINICAL STUDIES	3
1.2 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. CONCLUSIONS AND RECOMMENDATIONS.....	7
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. The submission includes one Phase 3, 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 randomized to the treatment group and 7 to the placebo group. Based on the results of the study, Anascorp is significantly superior to the placebo. 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 95% confidence limit for the difference is 35.71% which is greater than the 20% superiority margin the sponsor proposed. However, the 20% superiority margin along with the study size of 15 is not clearly justified in the protocol.

1.1 Brief Overview of Clinical Studies

There is only one Phase 3 study in this submission. This 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. Clinically important signs of the scorpion envenomation were divided into pathological agitation and respiratory compromise. Clinically important pathological agitation includes abnormal eye movements, thrashing of limbs, loss of ability to ambulate. Clinically important respiratory compromise includes incoordinate ventilatory effort, upper airway compromise, hypoxemia and other respiratory compromise. 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.

1.2 Major Statistical Issues and Findings

Based on the results of the study, Anascorp is significantly superior to the placebo. 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 95% lower confidence limit for the difference is 35.71% which is greater than the 20% superiority margin the sponsor proposed. However, the 20% superiority margin along with the study size of 15 is not clearly justified in the protocol.

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 (AL 02/03) 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 four data sets are in FDA's Electronic Document Room (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 to 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 due to the rounding errors.

** 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)(4)) and 2 Anascorp – treated patients (patient #(b)(4), and #(b)(4)). 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)(4)-----) and 1 Anascorp – treated patients (patient #(b)(4)). 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 Wilcox 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 the 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: (35.71%, 99.64%) using StatXact with exact method.

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. CONCLUSIONS AND RECOMMENDATIONS

Based on the results of the study, Anascorp is significantly superior to the placebo. 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

95% confidence limit for the difference is 35.71%, which is greater than the 20% superiority margin the sponsor proposed. However, the 20% superiority margin along with the study size of 15 is not clearly justified.

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

I recommend the following comments in the CR letter:

1. No clear study hypothesis is pre-specified in the final protocol of pivotal study AL02/03.
2. The 20% superiority margin has never been clinically justified.
3. In the original protocol of study AL 02/03(IND (b)(4)), you determined the sample size of 12 with a 2:1 ratio by assuming 85% success rates in the Anascorp-treated group and 10% in the placebo group. However, in the final protocol the allocation ratio becomes 1:1 and the sample size keeps the same. The trial ends up with 15 patients with an almost 1:1 ratio (8 vs. 7). You have never justified the new allocation ratio together with the sample size.

DISTRIBUTION LIST

cc:

Original/HFM-380/Debbie Cordaro

DCC/HFM-99

HFM- 215 /Chron

HFM-392/Hon-Sum Ko

HFM-219/Xue (Mary) Lin

HFM-219/ Jessica (Jeongsook) Kim

HFM-219/ Ghanshyam Gupta

HFM-215/Henry Hsu