DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

STATISTICAL REVIEW AND EVALUATION

BLA (FINAL)

BLA/Supplement Number:	125335/0 /37 and later amendments
Product Name:	Anascorp (Centruroides (Scorpion) Immune F(ab)2 Intravenous (Equine))
Indication(s):	The management of patients with clinically important signs, primarily driven by data on pathological agitation, of scorpion envenomation
Applicant:	Rare Disease Therapeutics, Inc. (RDT)
Date(s):	2/1/2011(DCC Receipt Date)
Review Priority:	Priority (6 month review)
Statistical Branch:	Therapeutics Evaluation Branch
Primary Statistical Reviewer:	Xue Lin, Ph.D.
Concurring Reviewer :	Jessica (Jeongsook) Kim PhD., acting branch chief, Therapeutics Evaluation Branch, (HFM-219)
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Clinical Reviewer(s):	Hon-Sum Ko, MD, Nisha Jain, MD
Project Manager:	Debbie Cordaro

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1. EXECUTIVE SUMMARY

This submission is response to FDA's Complete Response (CR) letter dated July 23, 2009. The product (Anascorp) is indicated for the treatment of clinically important signs of scorpion envenomation. It was granted orphan drug indication by the FDA in June 2000. The submission includes one randomized, placebo-controlled study (AL 02/03), four open-label studies (AL 02/04, 02/05, 02/06 and 03/07), one retrospective study (AL 03/06). This reviewer uses the data from study AL 02/03 as the primary source for efficacy evaluation. Data from the open labels studies and the retrospective study only provides supportive evidence. The primary efficacy endpoint of AL 02/03 is the resolution of clinically important signs of scorpion envenomation within 4 hours. The study enrolled 15 subjects, 8 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 limit of the 95% confidence interval 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 was not clearly justified in the protocol. The sponsor admits that the trial was not designed as a confirmatory trial (Response to AI letter Question #79). The sponsor provided the investigator's letter, as supporting evidence that, due to ethical concerns, it is inappropriate to conduct a large scale, randomized, placebo controlled study on the targeted disease population (Page 31 of the original submission, section 14 of Physician's Insert).

In summary, the randomized, placebo controlled study AL 02/03 meets the efficacy success criterion by a substantial margin. However, the criterion along with the sample size was not clearly justified in the protocol. This reviewer defers to the clinical reviewer the adequacy of the trial as it is the only randomized trial in this submission. This reviewer does not identify adverse safety signal from the updated Integrated Summary of Safety (ISS). Conditioning on the clinical reviewer's assessment on the acceptability of the study AL 02/03, this reviewer does not object to the approval of the product.

2. INTRODUCTION

2.1 Overview

This submission is response to FDA's Complete Response (CR) letter dated July 23, 2009. The product (Anascorp) is for the treatment of clinically important signs of scorpion envenomation. The submission includes one randomized, placebo-controlled study (AL 02/03), 4 open-label studies (AL 02/04, 02/05, 02/06 and 03/07), one retrospective study (AL 03/06). The primary efficacy endpoint for AL 02/03 is the resolution of clinically important signs of scorpion envenomation within 4 hours. The study enrolled 15 subjects, 8 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 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.

2.2 Data Sources

- SAS xpt files in Amendment #39, 40 and 41.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Study Design and Endpoints

The submission includes one randomized, placebo-controlled study (AL 02/03), four open-label studies (AL 02/04, 02/05, 02/06 and 03/07), one retrospective study (AL 03/06). This reviewer used the data from study AL 02/03 as the primary source for efficacy evaluation. Data from the open labels studies and the retrospective study only provided supportive evidence.

In study AL 02/03, patients were randomized to receive either placebo (saline) or Anascorp. If pathological agitation was severe, midazolam sedation (standard of care) was initiated when the treating physician deems it necessary. The primary efficacy endpoint is the resolution of clinically important signs of scorpion envenomation within 4 hours. 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.

Results and conclusions

The study enrolled 15 subjects, 8 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 limit of the 95% confidence interval 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 was not clearly justified in the protocol.

This reviewer raised the following question in the CR letter:
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 remains the same. The trial ends up with 15 patients with an almost 1:1 ratio (8 vs. 7). You did not justify the new allocation ratio together with the sample size. Please comment.

The sponsor's RESPONSE is the following:
Yes, this is correct; we did not justify the new allocation ratio together with the sample size. The protocol stated that treatment proportions would be calculated and clinically interpreted. The study was not designed to achieve the usual levels of statistical significance but only to achieve the necessary information for a descriptive examination of the antivenom effect of Anascorp.

The sponsor admits that the trial was not designed as a confirmatory trial but instead an exploratory study. The sponsor claims that, due to ethical concerns, it is inappropriate to conduct a large scale, randomized, placebo controlled study. This reviewer defers to the clinical reviewer the adequacy of the trial as the only randomized trial in this submission.

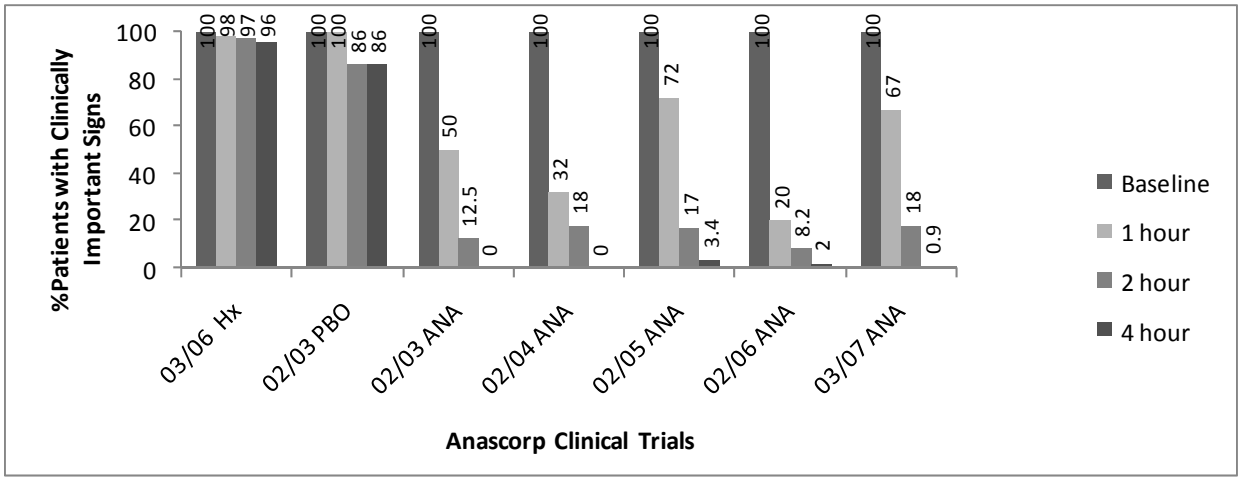
For both arms of the AL 02/03 study, midazolam sedation was initiated when the treating physician deems it necessary. To evaluate the effect of midazolam as a potential confounding factor, this reviewer analyzed the midazolam dosage as well as the time on midazolam, comparing Anascorp to the placebo group. The results are summarized in Table 1. It appears that midazolam dosage given prior to the study drug were comparable between the two arms, though placebo group received slightly higher dosage. After study drug was administrated, the Anascorp arm received considerably less midazolam, and spent less time on midzaolam. These analyses 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 the time from treatment to resolution of envenomation. The figure suggests that Anacorp treated patients tend to have quicker resolution of important signs of envenomation, compared with historical control and placebo patients.

Figure 1. Time from Initiation of Treatment to Resolution of Envenomation



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

3.2 Evaluation of Safety

At FDA's request in the CR letter, the sponsor submitted an updated integrated summary of safety (ISS). The ISS included 1534 subjects exposed to Anarscorp and the majority came from the treatment protocol (AL 03/07) in which 1425 subjects were exposed to Anascorp. The following table summarizes the ISS population:

Table 2 ISS population

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

In addition, a retrospective study AL 03/06 was used in the safety evaluation. It is a

retrospective hospital chart review compiling historical data of patients treated for systemic symptoms following scorpion envenomation. The number of patients in AL 03/06 was 97. The following table summarizes the AEs, comparing Anascorp treated patients with historical controls and placebo treated patients:

Table 2 Summary of Adverse Events (AEs)

Parameter	Anascorp (N=1534)	Historical Control (N=97)	Placebo (N=7)
Patients with ≥ 1 AE	421 (27%)	38 (39%)	1 (14%)
Patients who withdrew due to an AE	0	NA	0
Patients with SAEs	34 (2.2%)	0*	0
Patients Deaths	0	0	0
Patients with ≥ 1 AE by intensity Mild Moderate Severe Unknown	 329 (78.1) 136 (32.3) 28 (6.7) 3 (0.7)	NA	1 (14%) 0 0 0
Patients with ≥ 1 AE by relationship to study drug Definitely related Possibly related Not related Not accessible	 4 (1.0) 103 (24.5) 315 (74.8) 47 (11.2)	NA	 0 1 (14%) 1 (14%) 1 (14%)
Reports (i.e. AEs) Number of AE reports Number of SAEs Number of AEs considered definitely related to study drug	 755 39 4	 75 0* NA	 3 0 0

*AE severity was not recorded in AL 03/06.

This reviewer noticed discrepancy between the sponsor's findings (Table 5.3.1.a of the updated Integrated Summary of Safety (ISS), Page 19 of 124) and Table 2 for patients by intensity and patients by relationship to study drug for the Anascorp treated subjects. Apparently, when patients had multiple adverse events, the sponsor only counts one event (maybe the highest intensity or most closely relationship to the drug).

The sponsor reported the following AEs summary by preferred term (as in amendment 42):

Table 5.3.2. All Adverse Events Reported in >1% Patients, by Frequency

	Anascorp N (%)	**Historical Control N (%)**	**Placebo N (%)**
N	1534	97	7
Patients reporting ≥1 adverse event	421 (28)	38 (39)	1
Preferred Term			
Vomiting	72 (4.7)	7 (7.2)	0

Table 5.3.2. All Adverse Events Reported in >1% Patients, by Frequency

	Anascorp N (%)	Historical Control N (%)	Placebo N (%)
Pyrexia	63 (4.1)	6 (6.2)	1 (14)
Rash	41 (2.7)	1 (1.0)	1 (14)
Nausea	32 (2.1)	0	0
Pruritus	31 (2.0)	0	0
Headache	29 (1.9)	0	0
Rhinorrhoea	28 (1.8)	0	0
Myalgia	25 (1.6)	0	0
Fatigue	24 (1.6)	0	0
Cough	22 (1.4)	0	0
Diarrhoea	20 (1.3)	0	0
Lethargy	17 (1.1)	0	0
Intubation/Endotracheal intubation	6 (0.4)	5 (5.2)	0
Hypoxia	1 (0.1)	4 (4.1)	0
Phemonia aspiration	7 (0.5)	4 (4.1)	0
Stridor	2 (0.2)	3 (3.1)	0
Hospitalisation	14(0.9)	2 (2.1)	0
Hallcuination	0	2 (2.1)	0
Blood potassium decreased	0	2 (2.1)	0
Lumbar puncture	0	2 (2.1)	0
Accident	0	2 (2.1)	0
Respiratory acidosis	1 (0,2)	0	1 (14)

The numbers in the table have been confirmed by this reviewer.

4. SUMMARY AND CONCLUSIONS

4.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

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4.2 Conclusions and Recommendations

In summary, the randomized, placebo controlled study AL 02/03 meets the efficacy success criterion by a substantial margin. However, the criterion along with the sample size was not clearly justified in the protocol. This reviewer defers to the clinical reviewer the adequacy of the trial as it is the only randomized trial in this submission. This reviewer does not identify adverse safety signal from the updated Integrated Summary of Safety (ISS). Conditioning on the clinical reviewer's assessment on the acceptability of the study AL 02/03, this reviewer does not object to the approval of the product.

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