VENOMVET™

A Polyvalent Antivenin

A SUMMARY OF CLINICAL TRIALS

PRODUCT OVERVIEW.

VENOMVET™ is a polyvalent antivenin that is the first USDA licensed antivenin product for use by veterinarians in the last twenty five years. There are several key components to **VENOMVET™**:

- DEVELOPED EXCLUSIVELY FOR VETERINARY USE AND IS IMPORTED FOR USE UNDER A USDA SALE AND DISTRIBUTION PERMIT (ISSUED APRIL 2014)
- DEVELOPED FOR USE AGAINST ENVENOMATION OF CROTALIDS (RATTLESNAKES, COPPERHEADS AND COTTONMOUTH WATER MOCCASINS)
- STERILE NONPYROGENIC PURIFIED PREPARATION OF POLYVALENT EQUINE IMMUNOGLOBULIN
- LIQUID FORM-NO MIXING OR WAITING-READY TO USE IMMEDIATELY
- **VENOMVET™** ELIMINATES THE Fc FRAGMENT THEREBY REDUCING HYPERSENSITIVITY REACTIONS
- **VENOMVET™** IS A F(ab)2 ANTIVENIN THAT HAS TWO ANTIGEN BINDING SITES PER MOLECULE
- F(ab)2 FRAGMENT CREATED BY PEPSIN DIGESTION OF PURIFIED IgG THAT WORKS BY BINDING AND NEUTRALIZING VENOM TOXINS, FACILITATING THEIR REDISTRIBUTION AWAY FROM TARGET TISSUES AND THEIR ELIMINATION FROM THE BODY
- AMOUNT OF 10ML VIALS USED WILL VARY ON SEVERITY OF EACH PATIENT, BUT USUALLY 1 TO 3 VIALS
- PROPRIETARY FOMULA
- THREE YEAR SHELF LIFE

CLINICAL TRIALS OVERVIEW.

VENOMVET™ is under USDA jurisdiction and not the FDA. **VENOMVET™** is a product licensed by the USDA based on Clinical Trials conducted under Clinical Trial protocols reviewed by the USDA and approved for use in field studies to determine both the safety and efficacy on actual canines that were envenomed by Crotalidae. All of the data used in the Clinical Trials was based on actual cases conducted by numerous veterinarians in THREE REGIONS OF THE UNITED STATES. Based on the data submitted to the USDA from the Clinical Trials, the USDA issued a Sale and Distribution Permit in April 2014 to MT Venom for the sale and distribution of **VENOMVET™** for use by veterinarians only in the treatment of canines envenomed by Crotalidae.

SUMMARY OF CLINICAL TRIAL RESULTS.

TITLE: REPORT FOR THE SAFETY AND EFFICACY OF ANTIVENOM, CROTALIDAE POLYVALENT, EQUINE ORIGIN (CODE 6101.01) FOR THE TREATMENT OF CROTALIDAE ENVENOMATION IN CANINES

CONDUCTED BY: MT VENOM, LLC ("MT"); USDA ESTABLISHMENT NO. 444A

REPORT SUMMARY:

A. This was a prospective observational and confirmatory study using data gathered in questionnaire format to determine both **efficacy** and **safety** in canine patients treated with MT's antivenin, Crotalidae polyvalent, F(ab)2, equine origin (USDA Code 6101.01) ("**VENOMVET™**") against Crotalidae envenomation. The study was designed to measure efficacy by comparison to published mortality rates for other antivenins and by using a Snakebite Severity Score and safety by noting the incidence of hypersensitivity reactions of this equine derived antivenin. Evidence for the safety of **VENOMVET™** was then be determined by comparison, with published (historical) parameters of early and late hypersensitivity reactions of equine derived antivenins.

B. Label claims for this product, and for the product package insert, are:

i) INDICATIONS AND USAGE: **VENOMVET™** is indicated for the management of patients with minimal to severe North American Crotalidae envenomation. The term crotalid is used to describe the Crotalinae subfamily (formerly known as Crotalidae) of venomous snakes which includes rattlesnakes, copperheads and cottonmouths/water moccasins. Early use of **VENOMVET™** (within 6 hours of snakebite) is advised to prevent clinical deterioration and the occurrence of systemic cytotoxicity, neurotoxicity, myotoxicity and hemotoxicity.

ii) DESCRIPTION- **VENOMVET™**: Equine derived Crotalidae Polyvalent Immune F(ab)2 is a sterile, nonpyrogenic, purified preparation of polyvalent equine immunoglobulin obtained from the blood of healthy horses immunized with three of the following snake venoms: *Bothrops alternatus or Bothrops dirorus (previous name: Bothrops neuwiedi) (fer-de-lance), Lachesis muta (lancehead), Crotalus durissus terrificus* or *Crotalus simus (previous name: Crotalus durissus durissus) (South American rattlesnake).*

iii) DOSAGE AND ADMINISTRATION.

Restricted to use by or under the direction of a veterinarian.

It is recommended to mix each vial of antivenin with 100ml – 150mls of a crystalloid fluid and administer IV slowly while taking into consideration the patient's weight and overall fluid load. Completed infusions can be reached at 30 minutes – 1 hour.

As with other equine derived antivenins, monitor the patient closely over the first 10 minutes for signs of hypersensitivity reactions. If one occurs then stop the infusion and when safe to resume, administer at a slower rate.

The number of 10ml vials used on each patient will vary and will be based upon the severity classification of each case, your clinical judgment, the snakebite severity score and coagulation times.

Discontinuation of treatment depends upon the normalization of the state of the patient and resolution of all symptoms, which indicates neutralized venom activity.

The product must not be injected at the site of the bite or perifocal area.

iv) ADVERSE REACTIONS. As with any equine derived antivenin, adverse reactions may occur, including life threatening anaphylactic and anaphylactoid reactions. Medical veterinary care must be available during and after the administration of **VENOMVET™**. Anaphylactic (Type 1 Hypersensitivity) and anaphylactoid reactions may be characterized by hypotension, respiratory distress, vomiting, diarrhea, angioedema, urticaria and wheals, pruritis and fever. Delayed hypersensitivity reactions can also occur requiring patient monitoring post-treatment.

v) CONTRAINDICATIONS/ WARNINGS AND PRECAUTIONS - **VENOMVET™** should not be administered to patients known to be sensitive to equine derived antivenins/equine serum. Only administer **VENOMVET™** if the potential benefits outweigh the risks and medical management is immediately available. Severe, immediate allergic reactions (anaphylaxis and anaphylactoid) may be seen.

KEEP OUT OF THE REACH OF CHILDREN.

vi) CONSIDER ADDITIONAL TREATMENT. Appropriate antibacterial/tetanus prophylaxis is indicated for patients suspected of having puncture wounds.

vii) CLINICAL PHARMACOLOGY / MECHANISM OF ACTION: **VENOMVET™** is a F(ab)2 fragment created by a pepsin digestion of purified IgG that works by binding and neutralizing venom toxins, facilitating their redistribution away from target tissues and their elimination from the body.

viii) COMPOSITION. **VENOMVET™** is a refined, concentrated preparation of serum globulins obtained by fractionating blood from healthy horses that have been immunized with *Bothrops alternatus or Bothrops dirorus (previous name: Bothrops neuwiedi) (fer-de-lance), Lachesis muta (lancehead), Crotalus durissus terrificus* or *Crotalus simus (previous name: Crotalus durissus durissus) (South American rattlesnake)*. Venom. The product contains sodium chloride and phenol.

C. In real-life clinical settings, 40 patients were determined to have worsening envenomation syndrome and enrolled in the clinical trials study. The primary tool to determine efficacy was mortality rate and then stabilization or improvement of Snakebite Severity Scores (SSS). The tools to determine safety of **VENOMVET™** were careful monitoring for, and reporting of, any adverse events and/or hypersensitivity reactions.

The Clinical Trials were conducted in three geographical regions of the United States: (1) Western Region, (2) Southwestern Region, and (3) Southern Region.

D. The Clinical Trials were conducted during the period May 2012 through October 2012. All patient cases were under real life field conditions where canines were brought to a treating veterinarian and the treating veterinarian made a determination that the canine was envenomed by a Crotalidae and was suffering the recognizable effects of envenomation. Data was collected by questionnaire entitled the Snakebite Severity Score and Survey.

E. There were 40 Crotalidae (rattlesnake) envenomed client-owned dogs represented in the Clinical Trials. Dogs ranged in size from 3 to 64 Kg. The canines were housed at the treating veterinarian during treatment for the envenomation and for the administration of **VENOMVET™**. The canines ranged in age from one-half to fourteen years old. There were 22 male patients and 17 female patients (1 was unknown). Each dog had their own questionnaire and I.D. number and data recorded by the treating veterinarian.

F. The clinical trials study concluded that **VENOMVET™** is efficacious at clinical doses and well tolerated in Crotalidae envenomed canine subjects. One unique and distinct advantage of **VENOMVET™** is time to treatment. **Out of 40 patients the mortality rate was 0%. The mean SSS of the 36 patients (with complete records) decreased from 3.417 to 1.597, (P<.05).** Adverse events that could have been related to a hypersensitivity to the MT Antivenin were 7/40 or 17.5 % and all were mild.

G. Each vial of **VENOMVET™** used in the Clinical Trials, and which will be manufactured for use under a USDA Sale and Distribution Permit, undergoes several tests to meet the manufacturing safety, purity and potency standards which are applicable to every lot and vial of **VENOMVET™**. All samples taken during the stages of production are run through the following analysis and tests:

1. Stage One - Immunoglobulin Purification; Enzymatic Digestion Process, Heat Treatment and Salting out Process- pH Specifications;

2. Stage Two – Immunoglobulin Concentrate Analysis – Specifications and Minimum Standards for: Appearance, pH, Identification, Electrophoretic Purity, Total Solids, Protein Content, Phenol Content and Potency Assay;
3. Stage Three – Final Bulk Solution Analysis - Specifications and Minimum Standards for: Appearance, pH, Identification, Potency Assay and Sterility Test;
4. Stage Four – Final Product Control Tests - Specifications and Minimum Standards for: Appearance, Visual Inspection, pH, Electrophoretic Purity, Protein Content, Solid Content, Phenol Content, Extractable Volume, Tightness Control, Sterility.

CLINICAL TRIALS RESULTS AND EVALUATION.

A. SUMMARY.

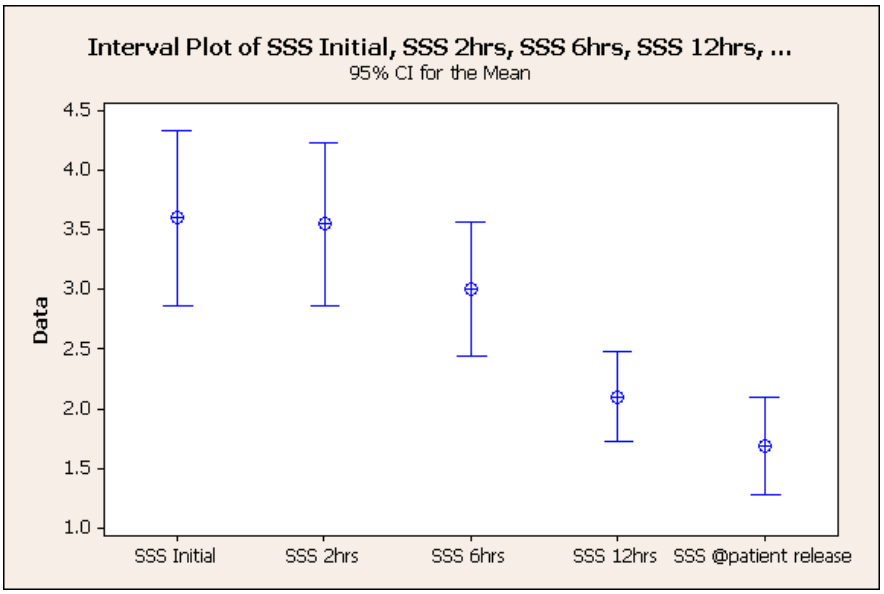
1. Safety. Survivability was 100%. In the Clinical Trial Study, mild hypersensitivity reactions were observed in 14 of the 40 canine patients (35%) at presentation of the patient to the treating veterinarian through release of the patient from the treating veterinarian. However, out of the 14 adverse events, 7 of the adverse events appear unrelated to the administration of **VENOMVET™**, 6 of the adverse events could be caused by either the actual Crotalidae envenomation or the administration of **VENOMVET™** (15%) and only 1 of the adverse events was most likely related to the administration **VENOMVET™** (.025%). Therefore, looking at all of the adverse events, only 7 out of the 14 adverse events in the 40 patients could have been caused by a hypersensitivity reaction to **VENOMVET™** (17.5%). As discussed herein, the hypersensitivity rate of the **VENOMVET™** was well within the published rate of hypersensitivity reactions to equine derived antivenins (<81%). No serum sickness was reported. The results of the Clinical Trial Study established that the **VENOMVET™** is safe for use in canines.

2. Efficacy. All patients treated with **VENOMVET™** survived and therefore a 0% mortality rate. Mean SSS scores stabilized and did not increase after **VENOMVET™** was administered. The mean SSS at the time of patient release was 1.597. The mean SSS of the 36 patients (with complete records) decreased from 3.417 to 1.597, ($P<.05$). At a 1.597 SSS at release the patient was deemed able to be released to the owner and such score is deemed “excellent” under the SSS assessment system. No serum sickness occurred within the 18 cases contacted at the 10 day post-treatment follow-up.

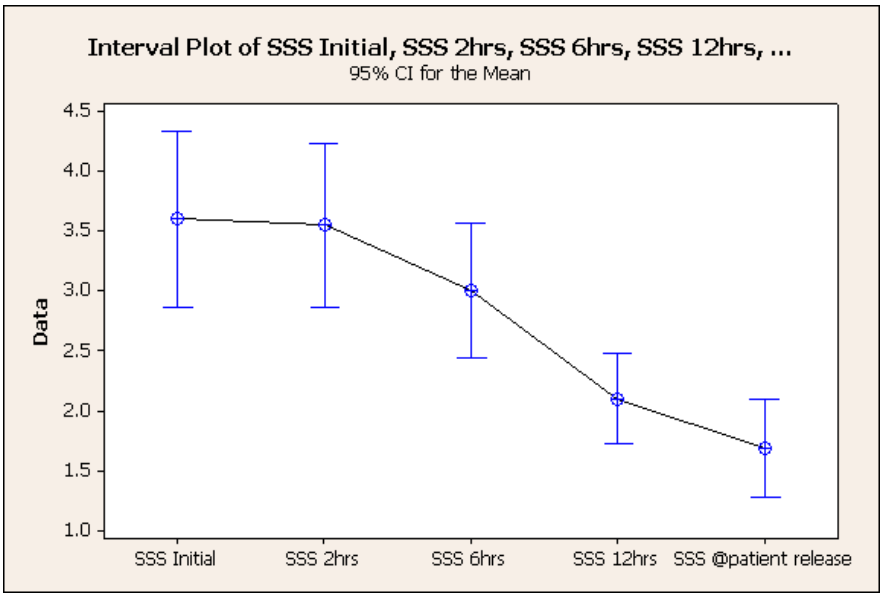
Minitab 16, R i386 2.15.1 and Medcalc 12.3.0.0 were used for statistical analysis.

Below are the relevant Minitab 16 Graphs:

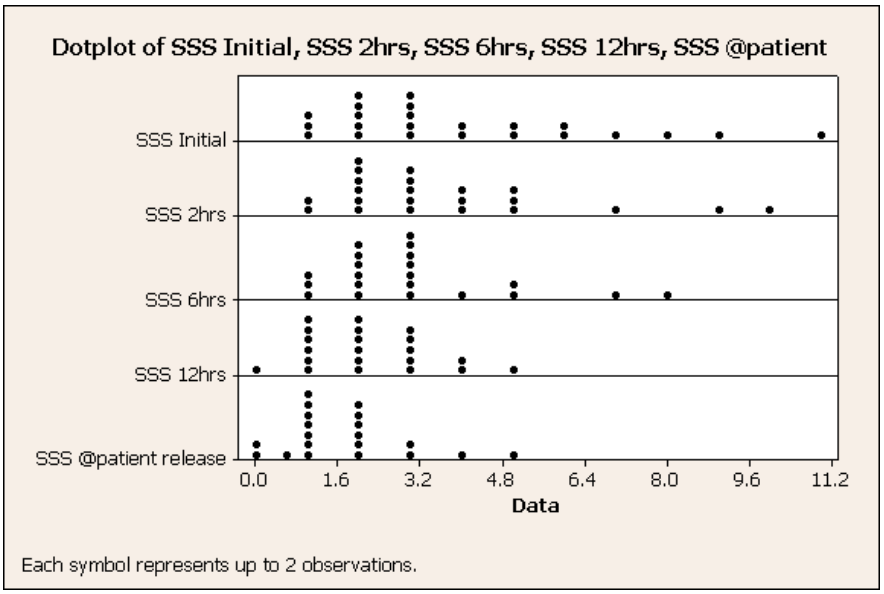
Graph 1:



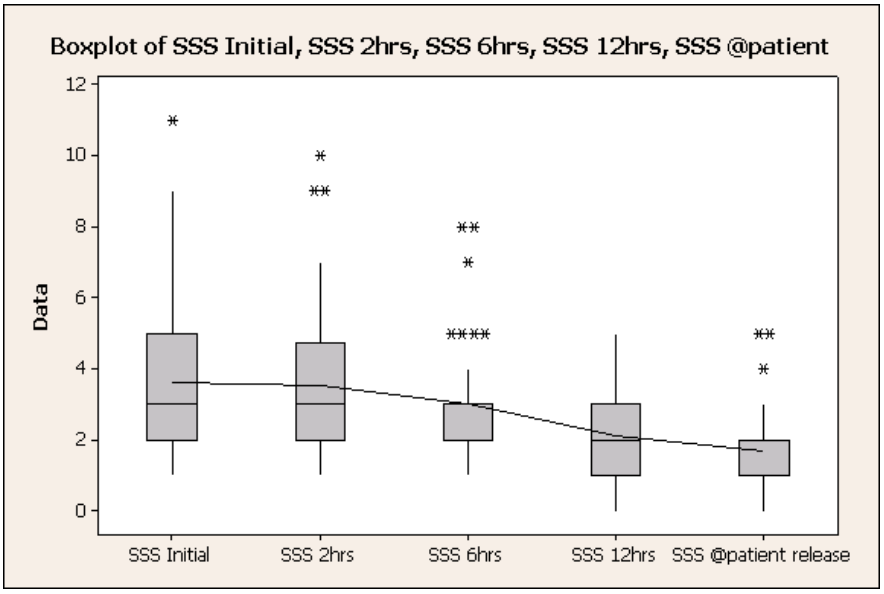
Graph 2:



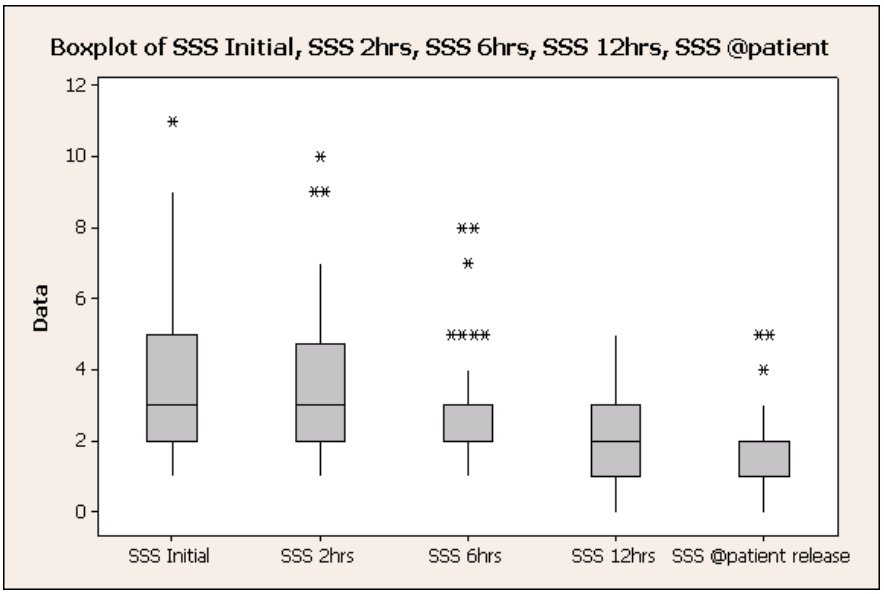
Graph 3:



Graph 4:

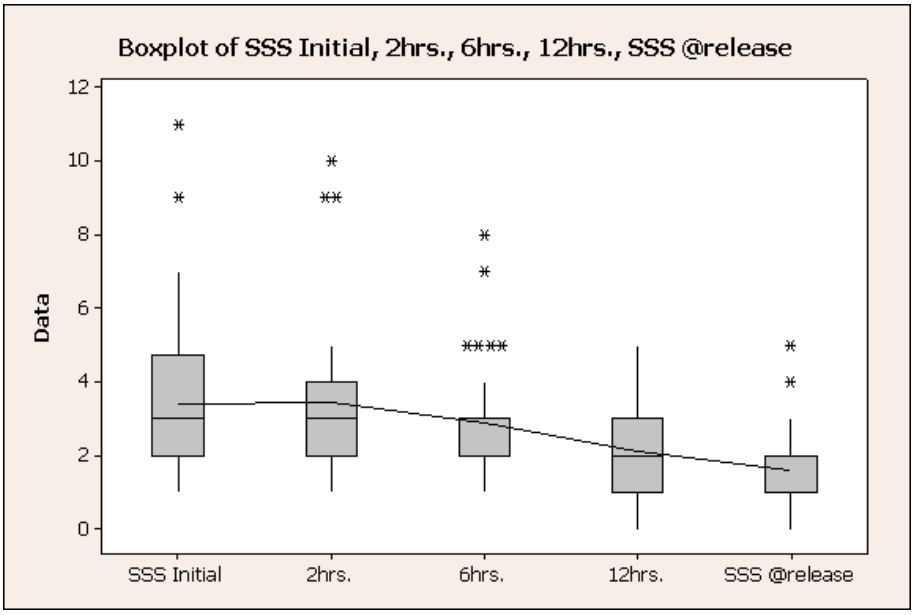


Graph 5:



The nonparametric Friedman Test was also used to compare SSS Initial to SSS 12 hour. The null hypothesis being that SSS Initial = SSS 12 hour, there is no difference between the two. The alternate hypothesis being that the two are significantly different (P<0.05). The null hypothesis was rejected and we can conclude SSS Initial scores are statistically different from SSS 12hr (P<.05). SSS scores dropped significantly between initial readings and the 12 hour point.

Graph 6:



SSS Interquartile Range Box Plots with n=36 and mean connecting line.

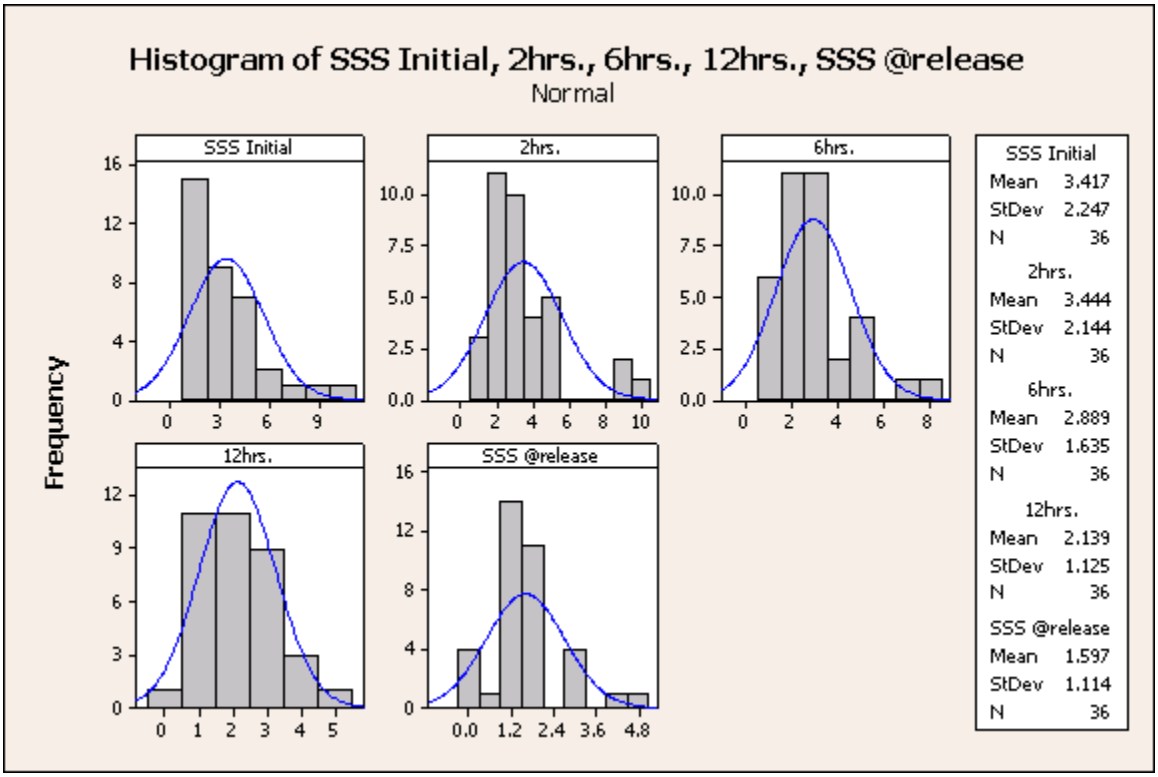
Descriptive Statistics with max N = 36 through patient release.

Variable	N	Mean	StDev	Variance
SSS Initial	36	3.417	2.247	5.050
2hrs.	36	3.444	2.144	4.597
6hrs.	36	2.889	1.635	2.673
12hrs.	36	2.139	1.125	1.266
SSS @release	36	1.597	1.114	1.240

Variable	N	Mean	StDev	Variance	Median
SSS Initial	36	3.417	2.247	5.050	3.000
SSS 2hrs	36	3.444	2.144	4.597	3.000
SSS 6hrs	36	2.889	1.635	2.673	3.000
SSS 12hrs	36	2.139	1.125	1.266	2.000
SSS @release	36	1.597	1.114	1.240	1.000
Initial - release	36	1.819	2.287	5.231	1.750

All the following charts and tables are working with N = 36 through SSS @ release.

Graph 7:



Box plots with a mean connecting line.

H_0 (Null hypothesis): SSS Initial (means) – SSS release = 0 or SSS Initial = SSS release.

H_A(Alternative hypothesis): We're looking for SSS Initial < SSS release.

One-Sample T: Initial - 12, Initial – release.

Variable	N	Mean	StDev	SE Mean	95% CI
Initial–12	36	1.278	2.212	0.369	(0.529, 2.026)
Initial-release	36	1.819	2.287	0.381	(1.046, 2.593)

Table: Minitab Paired T-Test and CI: SSS Initial, SSS 12hrs.

Paired T for SSS Initial - SSS 12hrs

	N	Mean	StDev	SE Mean
SSS Initial	36	3.417	2.247	0.375
SSS 12hrs	36	2.139	1.125	0.188
Difference	36	1.278	2.212	0.369

95% lower bound for mean difference: 0.655

T-Test of mean difference = 0 (vs > 0): T-Value = 3.47 P-Value = 0.001

Table: Paired T-Test and CI: SSS Initial, SSS @patient release.

Paired T for SSS Initial - SSS @patient release

	N	Mean	StDev	SE Mean
SSS Initial	36	3.417	2.247	0.375
SSS @release	36	1.597	1.114	0.186
Difference	36	1.819	2.287	0.381

95% lower bound for mean difference: 1.175

T-Test of mean difference = 0 (vs > 0): T-Value = 4.77 P-Value = 0.000

For the 2 paired t-tests above, the null hypothesis is rejected in favor of the alternative since 0.000 < 0.001 < 0.05, showing p-values are definitely less than α

95% confidence intervals that the difference between the means of SSS initial and release (or 12 hr.) is at least 1.175 (or 0.655). More than 95% confident that the antivenin lowers SSS scores in a statistically significant way.

Power and Sample Size

1-Sample t Test

Testing mean = null (versus > null)

Calculating power for mean = null + difference

= 0.05 Assumed standard deviation = 2.287

Difference	Sample Size	Power
1.175	36	0.915797

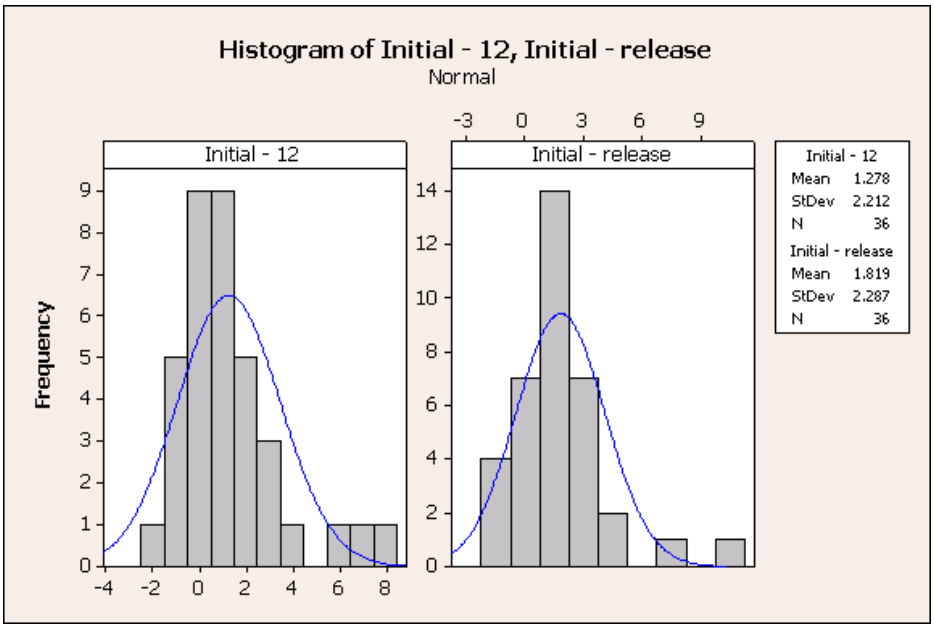
Power 1-β > .80

p = probability value

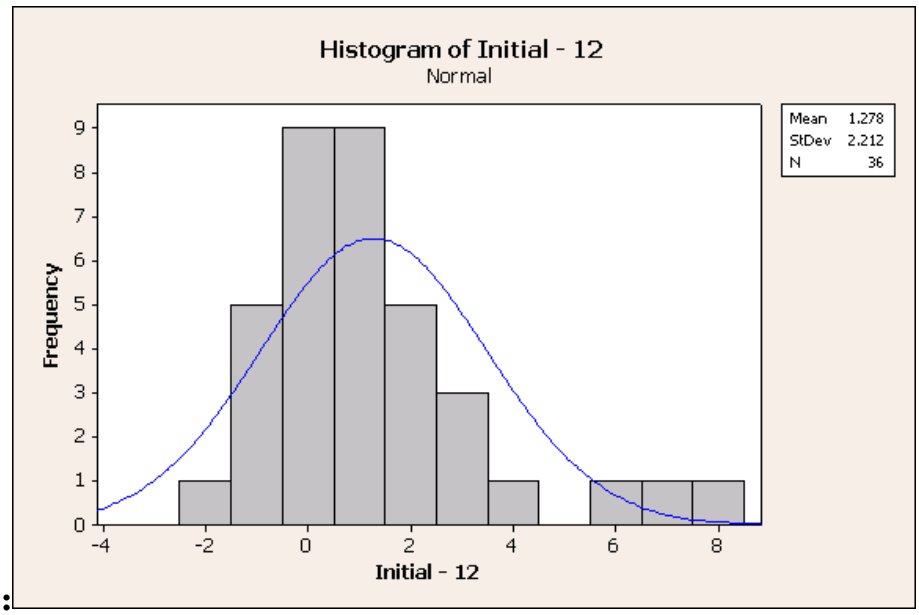
In hypothesis testing, *p* is the calculated p-value, the probability that rejecting the null hypothesis would be a wrong decision.

The following are histograms of the differences in SSS scores between Initial and 12hr and release. They show that the difference in means is normal, which is a requirement for the paired-t test.

Graph 8:

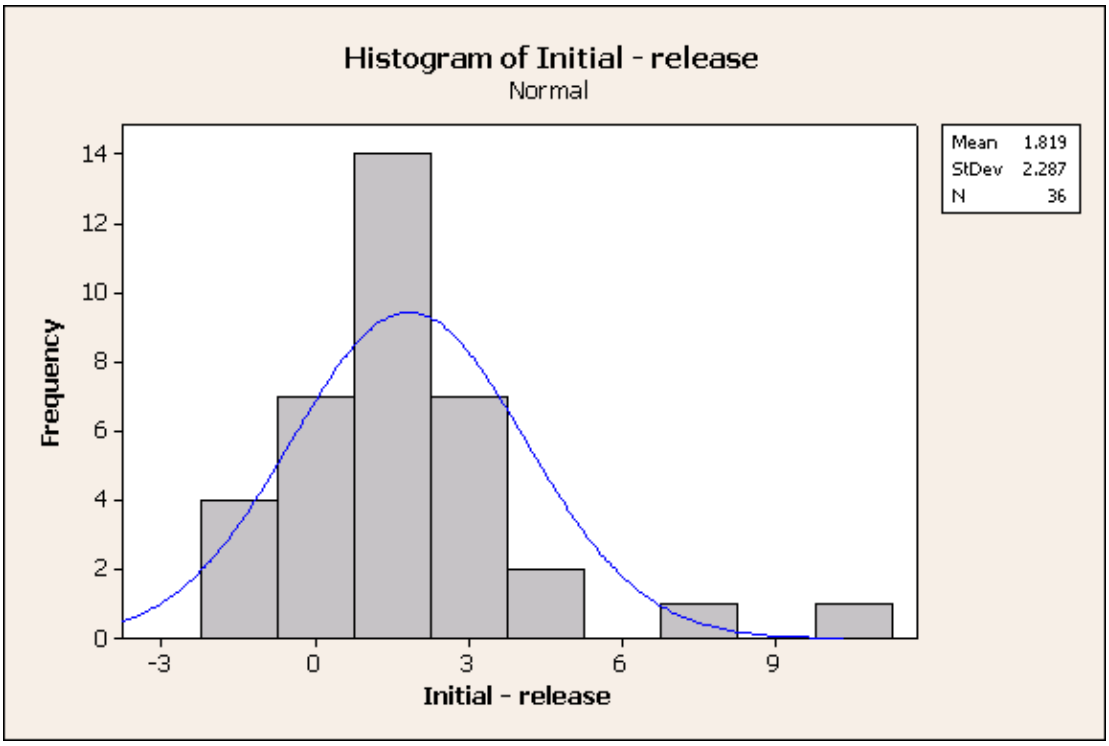


Graph 9:



9:

Graph 10:


Histogram of Initial - release
Normal
Mean 1.819
StDev 2.287
N 36
Frequency
0
2
4
6
8
10
12
14
-3
0
3
6
9
Initial - release

The following are Medcalc outputs.

Table: Medcalc Paired samples t-test:

Sample 1	SSS_Initial SSS Initial
Sample 2	SSS_@release SSS @release

	Sample 1	Sample 2
Sample size	36	36
Arithmetic mean	3.4167	1.5972
95% CI for the mean	2.6563 to 4.1770	1.2204 to 1.9740
Variance	5.0500	1.2403
Standard deviation	2.2472	1.1137
Standard error of the mean	0.3745	0.1856

Paired samples t-test

Mean difference	-1.8194
Standard deviation	2.2871
95% CI	-2.5933 to -1.0456
Test statistic t	-4.773
Degrees of Freedom (DF)	35
Two-tailed probability	P < 0.0001

As a result, MT Venom is 95% confident that the difference in means between SSS Initial and SSS at release is at least 1.175. Administration of the antivenin significantly lowered SSS scores. The power for this test was calculated to be .92

It is noteworthy that SSS scores are generally on the rise at the initial presentation of the patient and then rapidly reverse direction. The statistical data on the snakebite severity scores established the following clinically significant factors regarding the efficacy of **VENOMVET™**:

(1) In the 5 worst patient cases where the initial SSS of the patient was 6 or above, the administration of MT Antivenin dramatically reduced the SSS between SSS initial and SSS at patient release from the treating veterinarian as the table below summarizes:

TABLE: SSS ABOVE 6 AT INITIAL PATIENT EVALUATION.

Patient Id No.	SSS Initial	SSS at Release
01.01.011	6.0	1.0
01.01.024	6.0	3.0
01.01.034	9.0	2.0
03.03.036	7.0	4.0
03.03.039	11.0	1.0

(2) In the 4 patients where the SSS initial was 5, all 4 patients experienced a substantial improvement of the SSS from initial to patient release as the table below summarizes.

TABLE: <u>SSS 5 AT INITIAL EVALUATION.</u>

PATIENT Id No.	SSS Initial	SSS at Release
01.01.006	**5.0**	**2.0**
01.01.007	**5.0**	**5.0**
01.01.019	**5.0**	**0.0**
01.01.020	**5.0**	**2.0**

(3) In the 3 patients where the SSS initial was 4, 2 of the 3 patients' SSS substantially improved from initial to release of the patient to the owner from the treating veterinarian as summarized in the table below and the score for patient 009 was unavailable because the patient was released before the 12 hour mark and so the scores for 12 hour and release assessments are missing although at the 6 hour assessment it had improved to an SSS of 3.

TABLE: <u>SSS 4 AT INTIAL EVALUATION.</u>

Patient Id No.	SSS Initial	SSS at Release
01.01.003	4.0	1.0
01.01.009	4.0	N/A
01.01.017	4.0	1.0

(4) In the 24 patient cases where the SSS initial was between 1 and 3, in all cases but 4, the SSS at release was either stabilized or was reduced which allowed the patient to be released by the treating veterinarian to the owner as the table below summarizes.

TABLE: SSS BETWEEN 1 AND 3 AT INITIAL PATIENT EVALUATION.

Patient Id No.	SSS Initial	SSS at Release
01.01.001	3.0	0.0
01.01.002	1.0	1.0
01.01.004	2.0	2.0
01.01.008	1.0	1.0
01.01.010	1.0	2.0
01.01.012	2.0	1.0
01.01.014	2.0	2.0
01.01.015	2.0	0.0
01.01.016	2.0	0.0
01.01.018	1.0	2.0
04.01.021	3.0	1.0
01.01.022	3.0	2.0
02.02.023	3.0	2.0
01.01.026	2.0	0.5
02.02.027	2.0	3.0
01.01.028	2.0	1.0
01.01.029	2.0	3.0
01.01.030	3.0	3.0

01.01.031	3.0	2.0
01.01.032	3.0	1.0
01.01.034	2.0	1.0
01.01.035	1.0	1.0
03.03.038	3.0	1.0
03.03.040	3.0	1.0

(5) In all of the cases where the SSS initial was 4 or above, in all 12 of those cases the SSS of each patient at release had improved substantially between initial assessment and then release after administration of the **VENOMVET™**. The data shows that that **VENOMVET™** is an effective antivenin treatment to Crotalidae envenomation to canines where the canine is suffering a significant reaction to the snake venom.

(6) In the 28 cases where the SSS initial was between 1 and 3 and therefore a less severe Crotalidae envenomation, MT Antivenin lowered or stabilized the SSS by the time of patient release allowing the release of all patients to their owners with 0% mortality.

CLINICAL TRIAL CONCLUSIONS

The statistical analysis of the data from the Clinical Trial Study for safety of **VENOMVET™** establishes, based on a statistically sufficient number of patients, that **VENOMVET™** is safe for use in canines for the treatment of Crotalidae envenomation.

The approved Clinical Trial protocols provided that the safety endpoint for the Clinical trial Study was: "Analysis of the data to show that the hypersensitivity rate is well within published limits (i.e., <81%)". The statistical data from the Clinical Trial Study found that: (1) adverse reactions were mild; (2) 0% mortality rate of patients, (3) adverse reactions that could be attributable to **VENOMVET™** were 17.5%, which is substantially below the Clinical Trial protocols of <81%, and (4) all patients recovered without sequelae.

The Clinical Trial Protocols provided that the primary endpoints to determine the efficacy of MT Antivenin were: "Analysis of the data (using primary endpoints if possible) should show improvement in survivability and outcome. If there are insufficient primary endpoints to calculate mortality and SSS improvement, then the calculation may be done using secondary endpoints/parameters".

The statistical data from the Clinical Trial Study shows: (1) A 0% mortality rate/ 100% survivability of all patients after the administration of **VENOMVET™**, (2) Improved SSS initial versus SSS at release in 100% of the worst envenomation cases with an initial SSS at 4 or above, (3) A 100% release of patients to owners after treatment of the patients with **VENOMVET™**, (4) No patients were brought back to the treating veterinarians post release from the treating veterinarian for adverse reactions or symptoms related to the administration of **VENOMVET™**, and (5) In the follow up of patients (18 out of 40) 10 days after release, no patients reported any issues, problems or continuing adverse reactions to **VENOMVET™**.

As such, the Clinical Trial Study data establishes that **VENOMVET™** has good efficacy against Crotalidae envenomation.

The Clinical Trial Study supports MT's label claim that **VENOMVET™** is safe and effective as an antivenin therapy against Crotalidae envenomation of canines if administered by a veterinarian (or under veterinary direction) in accordance with label directions.

REFERENCES:

The following veterinarians have used **VENOMVET™** either in the Clinical Trials or as part of their practice or both and are available to discuss their opinions on how **VENOMVET™** has worked based on their use:

Dr. Carsten Bandt, DACVECC

Asst. Professor, Emergency Medicine

University of Florida

bandtc@ufl.edu

352-846-2445

Dr. Bandt also conducted separate clinical trial studies using **VENOMVET™** and will be presenting his findings at the International Veterinary Emergency & Critical Care Society ("IVECCS") in Indianapolis on September 10-14, 2014.

Nada Khalaf, DVM

Kiram Patel ("KP")

VCA McClave Animal Hospital

Reseda, CA

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Angie Volkman, DVM

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PLEASE CALL OR EMAIL MT VENOM WITH ANY QUESTIONS AND YOUR CALL AND EMAIL WILL BE ANSWERED BY QUALIFIED PERSONNEL WHO CAN ADDRESS ANY QUESTION ON **VENOMVET™.**