Approval Date: July 11, 1997

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 141-087

B. Sponsor

Fort Dodge Animal Health
PO Box 400
Princeton, NJ 08543-0400

C. Proprietary Name

Quest™ moxidectin 2% Equine Oral Gel

D. Established Name

Moxidectin

E. Dosage Form

Oral gel

F. Dispensing Status

OTC

G. Route of Administration

Oral

H. Indication

QUEST™ moxidectin 2% Equine Oral Gel, when administered at the recommended dose level of 0.4 mg moxidectin/kg (2.2 lb) body weight, has been demonstrated to be effective in the treatment and control of the following stages of gastrointestinal parasites of horses and ponies:

Large strongyles

- *Strongylus vulgaris* - (adults and L_4/L_5 arterial stages)
- *Strongylus edentatus* - (adults and tissue stages)
- *Triodontophorus brevicauda* - (adults)
- *Triodontophorus serratus* - (adults)

Small strongyles (adults and larvae)

- *Cyathostomum* spp. - (adults)
- *Cylicocyclus* spp. - (adults)
- *Cylicostephanus* spp. - (adults)
- *Gyalocephalus capitatus* - (adults)

- Undifferentiated lumenal larvae

Encysted cyathostomes

- Late L_3 and L_4 mucosal cyathostome larvae

Ascarids

- *Parascaris equorum* - (adults and L4 larval stages)

Pin worms

- *Oxyuris equi* - (adults and L_4 larval stages)

Hair worms

- *Trichostrongylus axei* - (adults)

Large-mouth stomach worms

- *Habronema muscae* - (adults)

Horse stomach bots

- *Gasterophilus intestinalis* - (2^{nd} & 3^{rd} instars)

One administration of the recommended dose rate of QUEST™ 2% Equine Oral Gel also suppresses strongyle egg production for 84 days.

I. Effect of Supplement

This supplement provides for <changes being approved> (Delete this section for Original approvals)

II. EFFECTIVENESS

A series of dose determination studies was conducted at various geographic locations in the US and Canada, which established 0.4 mg moxidectin/kg body weight as the effective dose level of QUEST™ moxidectin 2% Equine Oral Gel for the treatment and control of the equine gastrointestinal parasites included on the product label. The efficacy of this established dose level was confirmed in a series of dose confirmation and field efficacy trials which demonstrated the appropriateness of the of 0.4 mg moxidectin/kg body weight dose level against the broad spectrum of equine endoparasites listed on the label under a number of different field conditions.

A. Dose Determination Studies:

Cyanamid Experiments EQ-91-4, EQ-90-1 and EQ-90-2 were conducted to determine the effective dose level of the moxidectin 2% equine gel formulation necessary to provide control of major equine endoparasites. In these studies, horses and ponies with naturally-acquired gastrointestinal parasite infections were treated with either 0.3, 0.4 or 0.5 mg moxidectin/kg body weight and were necropsied 14 days

posttreatment for parasite recovery and identification. The recovered parasite counts from these test animals were compared with those obtained from control animals receiving a placebo treatment consisting of only the excipient components of the gel formulation. Efficacy against encysted mucosal stages of cyathostome larvae were evaluated with the mural transillumination technique. As described in the 1986 article by Drs. C. R. Reinemeyer and R. P. Herd, "Comparison of two techniques for quantification of encysted cyathostome larvae in the horse" (*Am. J. Vet. Res.* 47:507-509), the mural transillumination procedure involves obtaining uniform sections of mucosal tissue from the cecum and ventral colon, illuminating them from the serosal side with a strong light source and then examining them with a dissecting microscope at 15X magnification. Two additional Cyanamid Experiments, EQ-91-5 and EQ-91-6, were conducted in ponies with experimental infections of *Strongylus vulgaris* (EQ-91-5) or *Strongylus vulgaris* and *Parascaris equorum* (EQ-91-6), respectively, using the same general treatment and evaluation scheme. Efficacy was calculated using geometric means as percent reduction in comparison to control animals. A linear plateau model analysis was used to determine the effective dose level. Based on the dose levels tested in this series of five experiments, the 0.4 mg moxidectin/kg body weight dose rate was determined to provide adequate control against the range of equine endoparasites observed in this series of experiments.

1. **Five Dose Determination Studies**

(i) Study Designation: EQ-91-4

Clinical Investigator:

Thomas R. Bello, DVM., Ph.D.
The Sandhill Equine Center
Southern Pines, NC 28388

Test Animals/Source of Infection: Naturally-infected, mixed-breed ponies

Treatment Design:

Treatment Groups	**Number Treated**
Control (received placebo treatment)	10
Moxidectin Equine Gel, 0.3 mg/kg body weight	10
Moxidectin Equine Gel, 0.4 mg/kg body weight	10
Moxidectin Equine Gel, 0.5 mg/kg body weight	10

Test Duration: Necropsy on Day 14 posttreatment Observations: No adverse reactions to treatment were observed.

(ii) Study Designation: EQ-90-1

Clinical Investigator:

Thomas R. Klei, Ph.D.
Louisiana State University
Baton Rouge, LA 70803

Test Animals/Source of Infection: Naturally-infected, mixed-breed ponies
Treatment Design:

Treatment Groups	**Number Treated**
Control (received placebo treatment)	10
Moxidectin Equine Gel, 0.3 mg/kg body weight	10
Moxidectin Equine Gel, 0.4 mg/kg body weight	10
Moxidectin Equine Gel, 0.5 mg/kg body weight	10

Test Duration: Necropsy on Day 14 posttreatment

Observations: No adverse reactions to treatment were observed.

(iii) Study Designation: EQ-90-2

Clinical Investigator:

Joseph A. DiPietro, DVM, MS
University of Illinois
Urbana, IL 61801

Test Animals/Source of Infection: Naturally-infected, mixed-breed horses

Treatment Design:

Treatment Groups	**Number Treated**
Control (received placebo treatment)	10
Moxidectin Equine Gel, 0.3 mg/kg body weight	10
Moxidectin Equine Gel, 0.4 mg/kg body weight	10
Moxidectin Equine Gel, 0.5 mg/kg body weight	10

Test Duration: Necropsy on Day 14 posttreatment

Observations: No adverse reactions to treatment were observed.

(iv) Study Designation: EQ-91-6

Clinical Investigator:

Thomas R. Klei, Ph.D.
Louisiana State University
Baton Rouge, LA 70803

Test Animals: Artificially-infected, mixed-breed ponies

Source of Infection: Ponies (94-124 days of age) were experimentally infected by oral inoculation of 600 *Strongylus vulgaris* infective larvae 56 days prior to treatment and 3000 embryonated *Parascaris equorum* eggs 11 days prior to treatment. The *Strongylus vulgaris* larvae were obtained from cultures of feces from ponies with surgically-induced monospecific infections of adult parasites. Ponies were treated on Day 0 and necropsied on Day 35.

Treatment Design:

Treatment Groups	**Number Treated**
Control (received placebo treatment)	6
Moxidectin Equine Gel, 0.3 mg/kg body weight	6
Moxidectin Equine Gel, 0.4 mg/kg body weight	6
Moxidectin Equine Gel, 0.5 mg/kg body weight	6

Test Duration: Necropsy on Day 35 posttreatment

Observations: No adverse reactions to treatment were observed.

(v) Study Designation: EQ-91-5

Clinical Investigator:

Owen Slocombe, DVM, Ph.D.
University of Guelph
Guelph, Ontario, Canada

Test Animals: Artificially-infected, mixed-breed ponies

Source of Infection: Ponies were reared under parasite free conditions and ranged from 48 to 78 days of age at the time of animal allocation. Infective larvae for inoculation into the ponies were cultured from feces containing eggs of *Strongylus vulgaris*. The animals were experimentally infected by oral inoculation of *S. vulgaris* infective larvae. The foals in Replicate 1 received 600 larvae, and each foal in subsequent replicates received 500 larvae.

Treatment Design:

Treatment Groups	**Number Treated**
Control (received placebo treatment)	6
Moxidectin Equine Gel, 0.3 mg/kg body weight	6
Moxidectin Equine Gel, 0.4 mg/kg body weight	6
Moxidectin Equine Gel, 0.5 mg/kg body weight	6

Test Duration: Necropsy on Day 27 posttreatment

Observations: No adverse reactions to treatment were observed.

2. Results of Dose Determination Studies with Moxidectin 2% Equine Oral Gel.

The dose limiting parasite was found to be *Gasterophilus intestinalis* instars recovered from the stomach. Both studies EQ-90-1 and EQ-91-4 exhibited a dose effect, with the 0.4 mg/kg dose showing statistically significant improved efficacy as compared to the 0.3 mg/kg dose.

The efficacy against late L3 and L4 encysted mucosal cyathostome larvae was determined using the mural transillumination technique. Moxidectin appeared to exhibit a dose effect in study EQ-90-2; however, this was not true for study EQ-91-4.

Experiment Number	Parasite	Percent Efficacy[a] at Moxidectin Dose Levels (mg/kg)		
		0.3	**0.4**	**0.5**
EQ-90-1	*Gasterophilus intestinalis* (2nd & 3rd instars)	84.0	96.2	97.8
EQ-91-4	*Gasterophilus intestinalis* (2nd & 3rd instars)	86.1	93.4	94.3
EQ-90-2[b]	Late L_3 and L_4 mucosal cyathostome larvae	62.0	92.4	92.8
EQ-91-4[b]	Late L_3 and L_4 mucosal cyathostome larvae	96.7	85.5	86.3

[a]All listed percent efficacy values calculated on the basis of geometric means.
[b]Efficacy was determined using mural transillumination technique.

3. Efficacy against other gastrointestinal parasites:

   The efficacy at 0.4 mg/kg was found to be greater than 90% for the following list of internal parasites as determined by the dose determination studies.

   - *Strongylus vulgaris* (adults)
   - *Strongylus vulgaris* (L_4/L_5 arterial larvae)
   - *Strongylus edentatus* (adults)
   - *Triodontophorus brevicauda* (adults)
   - *Triodontophorus serratus* (adults)
   - *Cyathostomum* spp. (adults)
   - *Cylicocyclus* spp. (adults)
   - *Cyclicostephanus* spp. (adults)
   - *Gyalocephalus capitatus* (adults)
   - *Oxyuris equi* (adults)
   - *Oxyuris equi* (L_4 larvae)
   - *Parascaris equorum* (adults)
   - *Trichostrongylus axei* (adults)
   - *Habronema muscae* (adults
   - Small strongyle larvae (lumenal undifferentiated)

B. Dose Confirmation Studies:

Six dose confirmation trials were conducted in different geographic locations in North America: Cyanamid Experiments EQ-92-1 (Ohio), EQ-92-2 (Louisiana), EQ-92-3 (Tennessee), 0876-E-10-95 (Louisiana), 0876-E-11-95 (Texas) and 0876-E-CN-4-95 (Canada). In studies EQ-92-1, EQ-92-2 and EQ-92-3, 0.3 and 0.4 mg moxidectin/kg body weight dose levels were tested in horses and ponies with naturally-acquired endoparasitic infections. Special attention was directed in each study to an evaluation of the efficacy against the late L3 and L4 cyathostome (small strongyle) larvae which characteristically encyst in the equine gut mucosa. In studies 0876-E-10-95, 0876-E-11-95, and 0876-E-CN-4-95, a 0.4 mg moxidectin/kg body weight dose was tested to determine efficacy against *Gasterophilus intestinalis*.

Five foreign studies 0876-E-FR-01-92, 0876-E-NL-01-94, 0876-E-BR-02-93, 0876-E-UK-04-94 and 0876-E-AR-01-94 also support the efficacy of the 0.4 mg moxidectin/kg body weight dose.
Efficacy against encysted cyathostome larvae was evaluated with the mural transillumination technique. In the mural transillumination technique (Reinemeyer, C. R.

and R. P. Herd. 1986. "Comparison of Two Techniques for Quantification of Encysted Cyathostome Larvae in the Horse". Am. J. Vet. Res. 47:507-509) uniform sections from the cecum and ventral colon are cut and illuminated from the serosal side with a strong light source. Cyathostome larvae encysted in the mucosa and submucosa can be observed at 15X magnification and counted. All test animals were necropsied and parasite collection and identification accomplished. Determination of effectiveness was accomplished using two-way analysis of variance (ANOVA). The results of these experiments confirmed that moxidectin 2% Equine Oral Gel when given at the recommended 0.4 mg moxidectin/kg body weight was effective in the treatment and control of encysted cyathostomes and other equine gastrointestinal parasites listed in the product labeling.

1. Six North American Dose Confirmation Studies:

(i) Study Designation: EQ-92-1

Clinical Investigator:

Rupert P. Herd, MVSc, Ph.D.
The Ohio State University
Columbus, OH 43210

Test Animals/Source of Infection: Naturally-infected, mixed-breed ponies

Treatment Design:

Treatment Groups	**Number Treated**
Control (received placebo treatment)	***8***
Moxidectin Equine Gel, 0.3 mg/kg body weight	***8***
Moxidectin Equine Gel, 0.4 mg/kg body weight	***8***
Ivermectin, 0.2 mg/kg body weight	***8***

Test Duration: Necropsy on Day 14 posttreatment

Observations: No adverse reactions to treatment were observed.

(ii) Study Designation: EQ-92-3

Clinical Investigator:

Craig R. Reinemeyer, DVM, Ph.D.
University of Tennessee
Knoxville, TN 37996

Test Animals/Source of Infection: Naturally-infected, mixed-breed yearling horses

Treatment Design:

Treatment Groups	**Number Treated**
Control (received placebo treatment)	8
Moxidectin Equine Gel, 0.3 mg/kg body weight	8
Moxidectin Equine Gel, 0.4 mg/kg body weight	8
Ivermectin, 0.2 mg/kg body weight	8

Test Duration: Necropsy on Day 14 posttreatment

Observations: No adverse reactions to treatment were observed.

(iii) Study Destination: 0876-E-US-10-95

Clinical Investigator:

Thomas R. Klei, Ph.D.
Louisiana State University
Baton Route, LA 70803

Test Animals/Source of Infection: Naturally-infected, mixed-breed ponies

Treatment Design:

Treatment Groups	**Number Treated**
Control (received placebo treatment)	7
Moxidectin Equine Gel, 0.4 mg/kg body weight	7

Test Duration: Necropsy on Day 14 posttreatment

Observations: No adverse reactions to treatment were observed.

(iv) Study Destination: 0876-E-US-11-95

Clinical Investigator:

Thomas M. Craig, DVM, Ph.D.
Texas A&M University
College Station, TX 77836

Test Animals/Source of Infection: Naturally-infected, mixed-breed ponies and horses

Treatment Design:

Treatment Groups	**Number Treated**
Control (received placebo treatment)	7
Moxidectin Equine Gel, 0.4 mg/kg body weight	7

Test Duration: Necropsy on Day 14 posttreatment

Observations: No adverse reactions directly attributed to treatment were observed. Lip smacking and chewing following treatment were noted among animals in both treated and control groups.

(v) Study Destination: 0876-E-CN-4-95

Clinical Investigator:

Owen Slocombe, DVM, Ph.D.
University of Guelph
Guelph, Ontario, Canada

Test Animals/Source of Infection: Naturally-infected, mixed-breed ponies and one light horse
Treatment Design:

Treatment Groups	**Number Treated**
Control (received placebo treatment)	7
Moxidectin Equine Gel, 0.4 mg/kg body weight	7

Test Duration: Necropsy on Day 14 posttreatment

Observations: No adverse reactions to treatment were observed.

Five Foreign Dose Confirmation Studies

(vi) Study Designation: 0876-E-FR-01-92

Clinical Investigator:

Prof. P. Dorchies, Ph.D.
Veterinary School of Toulouse
Toulouse, France

Test Animals/Source of Infection: Naturally-infected Pottock ponies

Treatment Design:

Treatment Groups	**Number Treated**
Control (received placebo treatment)	6
Moxidectin Equine Gel, 0.4 mg/kg body weight	6

Test Duration: Necropsy was performed 14 days posttreatment

Observations: One moxidectin-treated pony exhibited signs of colic four days after treatment, which subsided. No other clinical signs were noted in any of the other test animals.

(vii) Study Designation: 0876-E-NL-01-94

Clinical Investigator:

M. Eysker, Ph.D.
Utrecht University
Utrecht, The Netherlands

Test Animals/Source of Infection: Naturally-infected Shetland ponies

Treatment Design:

Treatment Groups	**Number Treated**
Control (received placebo treatment)	6
Moxidectin Equine Gel, 0.4 mg/kg body weight	6

Test Duration: Necropsy was performed 35 days posttreatment

Observations: No adverse reactions to treatment were observed.

(viii) Study Designation: 0876-E-BR-02-93

Clinical Investigator:

Alvimar José Da Costa, DVM, M.Sc., Ph.D.
Faculdade de Ciências Agrárias e Veterinárias-
de Jaboticabal-Universidade
Jaboticabal, São Paulo State, Brazil

Test Animals/Source of Infection: Naturally-infected mixed-breed horses

Treatment Design:

Treatment Groups	**Number Treated**
Control (untreated)	8
Moxidectin Equine Gel, 0.4 mg/kg body weight	8
Ivermectin, 0.2 mg/kg body weight	8

Test Duration: Necropsy was performed 14 days posttreatment

Observations: No adverse reactions to treatment were observed.

(ix) Study Designation: 0876-E-UK-04-94

Clinical Investigator:

Ken Bairden, M.Sc., Ph.D.
Glasgow Veterinary College
Glasgow, Scotland

Test Animals/Source of Infection: Naturally-infected mixed-breed ponies

Treatment Design:

Treatement Groups	**Number Treated**
Control (untreated)	8
Moxidectin Equine Gel, 0.4 mg/kg body weight	8

Test Duration: Necropsy was performed 80 days posttreatment

Observations: One horse in the control group died due to colic four days after treatment.
No other adverse reactions to treatment were observed.

(x) Study Designation: 0876-E-AR-01-94

Clinical Investigator:

Jose Tolosa, DVM
Universidad Nacional de Rio Cuarto
Rio Cuarto Cordoba, Argentina

Test Animals/Source of Infection: Naturally-infected mixed-breed horses

Treatment Design:

Treatment Groups	**Number Treated**
Control (untreated)	8
Moxidectin Equine Gel, 0.4 mg/kg body weight	8

Test Duration: Necropsy was performed 14 days posttreatment

Observations: One horse died three days after receiving moxidectin treatment. Necropsy did not reveal the cause of death; however, thromboembolism was suspected. The association of death and treatment with moxidectin could not be determined. No other adverse reactions to treatment were observed.

2. Results of Dose Confirmation Studies with Moxidectin 2% Equine Oral Gel.

***Gasterophilus intestinalis* (2nd & 3rd instars):** The dose limiting parasite was found to be *Gasterophilus intestinalis* instars recovered from the stomach. In studies EQ-92-2 and EQ-92-3 a dose effect consisting of improved efficacy at the 0.4 mg moxidectin/kg body weight dose level was demonstrated. The efficacy of the 0.4 mg moxidectin/kg body weight dose level was subsequently confirmed in three additional studies (0876-E-US-10-95, 0876-E-US-11-95 and 0876-E-CN-4-95).

Late L_3 and L_4 mucosal cyathostome larvae: The efficacy against late L_3 and L_4 encysted mucosal cyathostome larvae was confirmed using the mural transillumination technique. A dose effect was exhibited in two studies (EQ-92-1 and EQ-92-2). Efficacy at the recommended dose level of 0.4 mg moxidectin/kg body weight against encysted cyathostomes was subsequently confirmed in two additional studies (0876-E-UK-04-94 and 0876-E-AR-01-94).

Experiment Number	Parasite	Percent Efficacy[a] at Moxidectin Dose Levels (mg/kg)	
		0.3	**0.4**
EQ-92-2	Gasterophilus intestinalis (2nd & 3rd instars)	34.3	75.2
EQ-92-3	Gasterophilus intestinalis (2nd & 3rd instars)	87.3	93.4
0876-E-US-10-95	Gasterophilus intestinalis (2nd & 3rd instars)	-	99.5
0876-E-US-11-95	Gasterophilus intestinalis (2nd & 3rd instars)	-	85.5
0876-E-CN-4-95	Gasterophilus intestinalis (2nd & 3rd instars)	-	99.5
EQ-92-1[b]	Late L_3 and L_4 mucosal cyathostome larvae	62.6	79.1
EQ-92-2[b]	Late L_3 and L_4 mucosal cyathostome larvae	61.0	88.3
0876-E-UK-04-94[b]	Late L_3 and L_4 mucosal cyathostome larvae	-	94.8
0876-E-AR-01/94[b]	Late L_3 and L_4 mucosal cyathostome larvae	-	97.4

[a]All listed percent efficacy values calculated on the basis of geometric means.
[b]Efficacy was determined using mural transillumination technique.

3. Efficacy against other gastrointestinal parasites:

   The efficacy of moxidectin gel at 0.4 mg/kg was found to be greater than 90% for the following list of internal parasites as determined by the dose confirmation studies.

   - *Strongylus vulgaris* (adults)
   - *Strongylus edentatus* (adults)
   - *Strongylus edentatus* (visceral larvae)
   - *Triodontophorus brevicauda* (adults)
   - *Triodontophorus serratus* (adults)
   - *Cyathostomum* spp. (adults)
   - *Cylicocyclus* spp. (adults)
   - *Cyclicostephanus* spp. (adults)
   - *Oxyuris equi* (adults)
   - *Oxyuris equi* (L4 larvae)
   - *Parascaris equorum* (adults)
   - *Parascaris equorum* (L4 larvae)
   - *Habronema muscae* (adults)
   - Small strongyle larvae (lumenal undifferentiated)

C. Field Efficacy Trials:

The efficacy and safety of moxidectin 2% Equine Oral Gel at the recommended 0.4 mg moxidectin/kg body weight dose level was demonstrated under a variety of field conditions representative of the intended use of the product in three geographic locations in the US. These three field trials included Cyanamid Experiments 0876-E-US-8-94 (Florida), 0876-E-US-5-94 (Texas) and 0876-E-US-6-94 (Illinois). The syringe

applicator in which the product is to be marketed was used in all trials and included hands-on evaluation of the ease of administration and acceptability of the gel formulation. Performance was evaluated against control animals receiving placebo-treatments of the excipient components of the gel formulation or positive controls receiving the recommended level of a currently approved equine endectocide product on the basis of fecal egg count data collected at points throughout the experimental periods. Efficacy was calculated using the geometric means of egg counts as percent reduction in comparison to control animals. Since the control animals were removed from the trial following the Day 14 fecal sampling, the % reduction of fecal eggs for the moxidectin and ivermectin treatment groups beyond 14 days was calculated by comparing to pretreatment egg counts using arithmetric means.

No adverse reactions to treatment were observed in any of the 305 horses treated at the recommended 0.4 mg moxidectin/kg body weight dose level in these three studies. The data from these trials demonstrated that QUEST™ moxidectin 2% Equine Oral Gel is easily administered, readily accepted by the treated animals, and is both safe and effective when used in accordance with label directions. The results of these three experiments are included in the individual study summaries which follow.

1. Three Field Efficacy Studies

(i) Study Designation: 0876-E-US-8-94

Clinical Investigator:

Bill C. Clymer, Ph.D.
CAVL, Inc. & CRC
Amarillo, TX 79118 (Trial location: Florida)

Test Animals/Source of Infection: Naturally-infected, mixed-breed horses

Treatment Groups	**Number Treated**
Control (received placebo treatment)	25
Moxidectin Equine Gel, 0.4 mg/kg body weight	100

Test Duration: Fecal egg counts through 14 days posttreatment Egg/Larvae

Determination: Eggs per gram (EPG) determination was by modified Wisconsin sugar flotation procedures with double centrifugation. Larvae identification was by pooled coproculture.

Results: Moxidectin was effective in reducing fecal egg shedding at 14 days posttreatment. Percent efficacy was >99.9% for strongyle eggs. Identification of larvae by coproculture on Day 14 indicated that there were no larvae in feces from moxidectin-treated horses. Cyathostome larvae were isolated from the feces from control horses.
Observations: No adverse reactions to treatment were observed.

(ii) Study Designation: 0876-E-US-5-94

Clinical Investigator:

Bill C. Clymer, Ph.D.
CAVL, Inc. & CRC
Amarillo, Texas 79118 (Trial location: Texas)

Test Animals/Source of Infection: Naturally-infected, mixed-breed horses

Treatement Groups	**Number Treated**
Control (received placebo treatment)	25
Moxidectin Equine Gel, 0.4 mg/kg body weight	105
Ivermectin, 0.2 mg/kg body weight	26

Test Duration: Fecal egg counts through 84 days posttreatment Egg/Larvae

Determination: Eggs per gram (EPG) determination was by modified Wisconsin sugar flotation procedures with double centrifugation. Larvae identification was by pooled coproculture.

Results: Moxidectin and ivermectin were effective in reducing fecal egg counts at 14 days posttreatment. Percent efficacies were >99.9 and 100% for horses treated with moxidectin and ivermectin, respectively. Efficacies at day 84 were 100 and 99.8% for moxidectin and ivermectin when compared to pretreatment infection levels. Fecal coproculture indicated cyathostome larvae were the primary endoparasite present in control and pretreatment samples.

Observations: No adverse reactions to treatment with moxidectin were observed.

(iii) Study Designation: 0876-E-US-6-94

Clinical Investigator:

Joseph A. DiPietro, DVM, MS
University of Illinois
School of Veterinary Medicine
Urbana, Illinois 61801 (Trial location: Illinois)

Test Animals/Source of Infection: Naturally-infected Standardbred horses

Treatment Groups	**Number Treated**
Control (received placebo treatment)	24
Moxidectin Equine Gel, 0.4 mg/kg body weight	105
Ivermectin, 0.2 mg/kg body weight	26

Test Duration: Fecal egg counts through 84 days posttreatment

Egg/Larvae Determination: Eggs per gram (EPG) determination was by modified Wisconsin sugar flotation procedures with double centrifugation. Larvae identification was by pooled coproculture.

Results: Moxidectin and ivermectin were effective in the suppression of fecal egg counts at 14 days posttreatment. Percent efficacy against strongyle eggs was >99.9 and 100%, and efficacy against eggs of *Parascaris equorum* was 98.8 and 99.5%, for the moxidectin- and ivermectin-treated horses, respectively. The moxidectin strongyle counts remained low throughout the trial with 94% efficacy at day 84 when compared to pretreatment infection levels. The ivermectin group strongyle egg counts had begun to rise by Day 42, and exceeded pretreatment levels by Day 70.

Observations: No adverse reactions to treatment with moxidectin were observed.

III. TARGET ANIMAL SAFETY

Five experiments were carried out in accordance with the applicable Good Laboratory Practices (GLP) regulations (i.e., 21 CFR Part 58) to demonstrate that QUEST™ moxidectin 2% Equine Oral Gel can be administered safely to horses and ponies at the recommended dose level of 0.4 mg moxidectin/kg body weight. Each study was specifically designed to determine the product's margin of safety and document the signs of toxicity in foals (the most sensitive class of the target species), pregnant mares or mature breeding stallions in separate studies with multiple, elevated dose levels of the animal drug product. With the exception of the change in dose level and dosing regimen necessitated by the studies, all test animals were treated per label directions with the final moxidectin 2% Equine Oral Gel formulation. The results of these five studies show that moxidectin 2% Equine Oral Gel when used in accordance with label directions has an adequate therapeutic index (ratio between effective and toxic dose levels) to enable efficacious treatment of indicated equine parasites without evoking drug-related adverse reactions in
the treated animal. These five target animal safety (TAS) evaluations are summarized below under separate headings.

A. Target Animal Safety Tests in Foals

A series of three separate experiments were performed in foals of various ages to evaluate the safety of the recommended 0.4 mg/kg body weight dose level of moxidectin 2% Equine Oral Gel and determine the characteristic clinical signs associated with an overdose of this animal drug.

1. Foal Safety Study 0876-E-US-4-94

   (i) Type of Study: Target Animal Safety

   (ii) Investigator:

   Larry R. Cruthers, Ph.D.
   Professional Laboratory and Research Services, Inc.
   Corapeake, North Carolina

   (iii) General Design:

   a. Purpose: This study was designed to evaluate the clinical and pathological effects of administering 1X, 3X and 5X dose levels of moxidectin 2% Equine Oral Gel to one- to two-week old foals for three consecutive days.

b. Animals: Eight mixed-breed foals between seven and 13 days of age with body weights ranging from 49.4 to 81.3 kg.

c. Dose Levels:

- Group A - 5X volume of the placebo gel vehicle (0 mg moxidectin/kg body weight) administered daily for three consecutive days. Two foals.
- Group B - 1X dose level (0.4 mg moxidectin/kg body weight) administered daily for three consecutive days. Two foals.
- Group C - 3X dose level (1.2 mg moxidectin/kg body weight) administered daily for three consecutive days. Two foals.
- Group D - 5X dose level (2 mg moxidectin/kg body weight) administered daily for three consecutive days. Two foals.

d. Pertinent Measurements/Observations: Physical examinations and blood sample collection for hematology, serum chemistry and coagulation profile analysis (prior to the initial treatment and before necropsy). Behavioral observation for clinical signs (hourly for first six hours following each treatment and at least twice daily for 14 days following the last treatment). Post mortem examination and histopathological analysis of selected tissue.

(iv) Results:

a. Clinical Observations: Foals given the placebo gel and 1X dose level for three consecutive days demonstrated no signs of adverse reaction throughout the treatment period. None of the foals given the 3X dose level demonstrated any signs of adverse reaction after the first treatment. Following the second treatment and intensifying after the last administration, one foal in the 3X group exhibited clinical signs of depression and ataxia (incoordination) which progressed in severity to difficulty rising, droopy lip, protruding tongue, tremors, vacant eye stare and recumbency. Because the foal was unable to nurse, it was given mare's milk by nasogastric tube. The other 3X foal exhibited similar, less severe signs beginning shortly before the third treatment and was also administered mare's milk via nasogastric tube. Both 3X foals resumed nursing on their own within three days following the last treatment. Foals in the 5X group became ataxic and depressed following the initial administration. These clinical signs intensified after the second and third 5X treatments. The 5X foals were given mare's milk via nasogastric tube and resumed feeding on their own within two days following the last treatment. There were no treatment-related findings detected in the physical exams performed on all foals 14 days posttreatment.

b. Hematology/Serum Chemistry/Coagulation Parameters: Values for all animals were within accepted normal ranges.

c. Gross Pathology and Tissue Histopathology: No treatment-related gross pathology or microscopic findings were reported.

(v) Conclusion: One to two week old foals given either the recommended dose level of moxidectin 2% Equine Oral Gel for three consecutive days or a single 3X treatment showed no clinical signs of toxicity. Foals treated with 3X levels on multiple occasions and a single 5X treatment exhibited clinical signs indicative of toxicity which included depression and incoordination, abnormal head carriage, droopy lips and ears, protruding tongue, vacant eye stare, tremors, recumbency

and inability to nurse. These signs were reversible with time and supportive nutrient therapy.

2. Foal Safety Study 0876-E-US-7-94

(i) Type of Study: Target Animal Safety Test

(ii) Investigator:

Larry R. Cruthers, Ph.D.
Professional Laboratory and Research Services, Inc.
Corapeake, North Carolina

(iii) General Design:

a. Purpose: This study was designed to evaluate the clinical and pathological effects of administering 3X and 5X dose levels of moxidectin 2% Equine Oral Gel to foals four months of age and older for three consecutive days.

b. Animals: Eighteen mixed-breed, weanling foals between four and seven months with body weights ranging from 120 to 275 kg.

c. Dose Levels:

- Group A - 3X dose level (1.2 mg moxidectin/kg body weight) administered daily for three consecutive days. Eight foals.
- Group B - 5X dose level (2.0 mg moxidectin/kg body weight) administered daily for three consecutive days. Two foals.
- Group C - Untreated controls. Eight foals.

d. Pertinent Measurements/Observations: Physical examinations and blood sample collection for hematology and serum chemistry analysis (prior to the initial treatment and before necropsy). Neurological examinations (prior to the initial treatment and the day after the last treatment). Behavioral observation for clinical signs (hourly for first six hours following each treatment and at least twice daily for six days following the last treatment). Post mortem examination and histopathological analysis of selected tissues.

(iv) Results:

a. Clinical Observations: Three of eight foals given the 3X dose became depressed or ataxic after one treatment. The signs observed included incoordination, abnormal tail carriage, droopy lip and eyelids and slow movement. Three more foals were similarly affected following a second 3X treatment, and all foals exhibited clinical signs after being given the last 3X treatment. Six of the eight foals demonstrated no effects on the neurologic examination performed on the day following the last treatment. The remaining two foals exhibited signs including unresponsiveness to surroundings, abnormal head and ear carriage and occasional dragging of hindlimbs when walking (not trotting). All eight 3X foals were normal on the physical exam carried out six days posttreatment. Both 5X foals exhibited signs of toxicity consisting primarily of incoordination, depression and weakness following the first treatment. The severity of these signs intensified

with subsequent 5X treatments. Both foals became recumbent and required fluid supplementation. The foal receiving fluids via nasogastric tube died of aspiration pneumonia resulting from this therapy. The other foal was administered intravenous fluids and was normal on the physical exam performed six days posttreatment.

b. Hematology and Serum Chemistry Parameters: Values for all animals were within accepted normal ranges.

c. Gross Pathology and Tissue Histopathology: No treatment-related gross pathology or microscopic findings were reported.

(v) Conclusion: The clinical signs indicative of toxicity were identified in older foals receiving three times the recommended dose level of moxidectin 2% Equine Oral Gel on one or more occasions. These signs include depression, droopy eyelids, abnormal head, ear and tail carriage, vacant eye stare, slow movement, twitching, incoordination and recumbency. These foals returned to normal health without supportive treatment. Foals given five times the recommended level showed similar signs after one administration. These signs increased in severity with additional daily treatments.

3. Foal Safety Study 0876-E-US-9-95

(i) Type of Study: Target Animal Safety Test

(ii) Investigator:

Sarah Ralston, VMD, Ph.D.
Rutgers University
New Brunswick, New Jersey

(iii) General Design:

a. Purpose: This study was designed to evaluate the clinical and pathological effects of administering single 2X and 3X dose levels of moxidectin 2% Equine Oral Gel to foals four months of age and older.

b. Animals: Thirty Standardbred foals between four and six months of age with body weights ranging from 179 to 288 kg.

c. Dose Levels:

- Group A - Untreated controls. Ten foals.
- Group B - Single 2X dose level (0.8 mg moxidectin/kg body weight) administration. Ten foals.
- Group C - Single 3X dose level (1.2 mg moxidectin/kg body weight) administration. Ten foals.

d. Pertinent Measurements/Observations: Physical and neurological examinations were performed twice pretreatment and at eight hours posttreatment. Behavioral observation for clinical signs were performed hourly for the initial eight hours, and then at 12 and 24 hours posttreatment.

(iv) Results:

a. Clinical Observations: None of the moxidectin-treated foals showed any signs of clinical neurological signs attributable to moxidectin treatment.

(v) Conclusion: Single treatments of up to three times the recommended dose level of moxidectin 2% Equine Oral Gel can be safely administered to foals as young as four months of age.

4. Breeding/Pregnant Mare and Unborn/Newborn Foal Safety Study EQ-92-4

(i) Type of Study: Female Reproductive and Unborn/Newborn Foal Safety

(ii) Investigator:

Richard L. Asquith, DVM
University of Florida
Gainesville, Florida

(iii) General Design:

a. Purpose: To evaluate the clinical and reproductive performance effects in mares treated every 14 days with three times the recommended dose level of moxidectin 2% Equine Oral Gel for two consecutive gestation periods and assess the clinical health of the foals produced by these mares during the treatment period.

b. Animals: Forty mares (Quarter Horse, Thoroughbred, Saddlebred, Standardbred and Morgan breeds) between four and 26 years of age. Four mares (two treated and two control) did not complete this two-gestation study for reasons unrelated to drug treatment.

c. Dose Levels:

- Group A - 3X volume of placebo vehicle gel (0 mg moxidectin/kg body weight) at 14-day intervals for two consecutive gestations. Eighteen mares.
- Group B - 3X dose level (1.2 mg moxidectin/kg body weight) at 14-day intervals for two consecutive gestations. Eighteen mares.

d. Pertinent Measurements/Observations: Mares and foals received periodic physical examinations. Behavioral observation of mares for clinical signs of toxicity were performed hourly for six hours, and then daily for one week following each treatment. Mares were examined by palpation for estrus, conception and maintenance of pregnancy at regular intervals.

(iv) Results:

a. Clinical Observations: No clinical signs indicative of toxicity were observed in either the mares or their foals during the course of this experiment. Transient anorexia was sporadically reported in treated mares following initial treatments.

b. Hematology and Serum Chemistry: Hematology and serum chemistry parameters were within normal physiological limits for all mares in this study.

c. Reproductive Parameters: All reproductive parameters were within normal limits.

Parameter	**Control**	**Moxidectin**
Live Foal Index[1] - 1993	0.92 (11/12)	0.79 (11/14)
Live Foal Index - 1994	0.81 (13/16)	0.76 (13/17)
Fertility Index[2] - 1994	0.89 (16/18)	0.94 (17/18)
Services per conception - 1994	1.67	1.89

[1] Live foal index = number of live foals per number of pregnant mares (# live foals/# mares conceived)
[2] Fertility index = number of pregnant mares per total number of mares (# mares conceived/total # mares)

(v) Conclusion: Mares can be administered up to three times the recommended dose level of moxidectin 2% Equine Oral Gel on multiple occasions throughout their gestation periods without clinical reactions, impairment of reproductive performance or any adverse effects on the health of their foals.

5. Breeding Stallion Safety Study EQ-93-3

(i) Type of Study: Male Reproductive Safety

(ii) Investigator:

E. L. Squires, Ph.D.
Colorado State University
Fort Collins, Colorado

(iii) General Design:

a. Purpose: To evaluate the clinical and reproductive performance effects in breeding stallions treated three times at seven-day intervals with three times the recommended dose level of moxidectin 2% Equine Oral Gel.

b. Animals: Twenty-four mature stallions (Quarter Horse, Thoroughbred, Arabian, Appaloosa and other breeds) between three and 18 years of age.

c. Dose Levels:

- Group A - Single administration of 3X volume of placebo gel. Castration 61 days posttreatment. Six stallions.
- Group B - 3X dose level administered three times at seven-day intervals. Castration 61 days following initial treatment. Six stallions.
- Group C - Single administration of 3X volume of placebo gel. Castration 75 days posttreatment. Six stallions.
- Group D - 3X dose level administered three times at seven-day intervals. Castration 75 days following initial treatment. Six stallions.

d. Pertinent Measurements/Observations: Physical examinations; posttreatment clinical observations for signs of adverse reactions; testicular measurements; breeding behavior observations (time to first mount and first ejaculation and number of mounts); semen collection and evaluation (gel and gel-free volume, and sperm concentration, motility and morphology); blood collection

for hematology, serum chemistry, LH (luteinizing hormone) and testosterone analysis; post-castration evaluations of testicle weight and microscopic examination of testicular tissues.

(iv) Results:

a. Clinical Observations: No clinical signs indicative of adverse reaction were observed in any of the moxidectin-treated stallions throughout the course of this experiment.

b. Breeding Behavior and Semen Analysis: Although minor differences attributable to individual stallion variability were noted, all breeding behavior, semen evaluation and sperm morphology data were within normal physiological limits.

c. Hematology/Serum Chemistry/Hormone Level Parameters: Hematology and serum chemistry parameters and LH levels were not affected by moxidectin treatment. Two stallions with consistently low testosterone levels throughout both the pre- and postreatment periods accounted for the overall decreased serum testosterone levels observed in moxidectin-treated stallions.

d. Post-Castration Testicular Evaluation: Microscopic examination of testicular tissues revealed no histopathology. Although moxidectin-treated stallions had lower testes weights than controls, individual values were never below physiological limits. Daily sperm production as determined histologically was also lower in moxidectin-treated stallions, however, this was related to testes weight which is used in the calculation of this parameter.

(v) Conclusion: Breeding stallions can be administered up to three times the recommended dose level of moxidectin 2% Equine Oral Gel on multiple occasions without adverse clinical reactions or impairment of reproductive performance.

IV. HUMAN FOOD SAFETY

A. Human Food Safety

Data on human safety pertaining to the consumption of drug residues in food were not required for approval of this NADA. This drug is labeled for use in horses and ponies which are non-food animals. The following "Warning" statement appears on the product label: "Do not use in horses or ponies intended for food."

B. User Safety

Product labeling contains adequate "Precaution" and "Warning" statements to insure human safety relative to possession, handling, and administration of this animal drug product.

V. AGENCY CONCLUSIONS

The data in support of this NADA comply with the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and Section 514.111 of the implementing regulations. The data demonstrate that QUEST™ moxidectin 2% Equine Oral Gel, when used under labeled conditions, is safe and effective.

The drug is labeled for Over the Counter use. Routine deworming of horses is a widely accepted and recommended practice performed by the layperson. A diagnosis of parasite infection prior to deworming is not necessary.

The package insert contains a detailed diagram of the syringe accompanied by adequate directions for use by the layperson.

Under section 512(c)(2)(F)(ii) of the FFDCA, this approval for non food producing animals qualifies for three years of marketing exclusivity beginning on the date of approval because the application contains substantial evidence of the effectiveness of the drug involved, or studies of animal safety required for the approval of the application and conducted or sponsored by the applicant.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.