Approval Date: May 27, 1997

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 141-051

B. Sponsor

Fort Dodge Animal Health
9401 Indian Creek Parkway
Overland Park, Kansas 66210-5945

C. Proprietary Name

ProHeart™ for Dogs

D. Established Name

moxidectin heartworm prevention tablets

E. Dosage Form, Route of Administration and Recommended Dose Rate

ProHeart™ tablets for Dogs are available in three tablet sizes. Tablets are administered by mouth (swallowed) at one-month intervals during times when mosquitoes, which serve as the intermediate host of the canine heartworm, are active. ProHeart™ is recommended for dogs eight weeks of age and older. The recommended dose rate of 3 mcg moxidectin/kg (1.36 mcg/lb) body weight is achieved as follows:

Weight of Dog	Tablets/Month	Moxidectin/Tablet	Tablet Weight
Up to 22 pounds	1	30 mcg	183 mg
23 to 50 pounds	1	68 mcg	412 mg
50 to 100 pounds	1	136 mcg	824 mg

Large dogs over 100 pounds body weight should be administered an appropriate combination of these tablets.

F. Indication

ProHeart™ (moxidectin) heartworm prevention tablets are indicated for once-a-month use in dogs to prevent infections by the canine heartworm, *Dirofilaria immitis*, and the subsequent development of canine heartworm disease.

II. EFFECTIVENESS

The New Animal Drug Application for moxidectin tablets contains adequate and well controlled studies which demonstrate efficacy in preventing heartworm disease in dogs.

A. Dose Establishment

Three controlled studies were conducted to establish and confirm that 3mcg moxidectin/kg body weight administered monthly prevents the development of *Dirofilaria immitis* larvae and the subsequent development of heartworm disease. These three pivotal studies are individually summarized below. Please note that where percent efficacy of moxidectin is used to characterize the results of a study, the percentage was calculated using the following formula:

% Efficacy = Geometric Mean Worm Count Control - Geometric Mean Worm Count Treated / Geometric Mean Worm Count Control X 100

Dose Determination: C-91-1 Efficacy of Moxidectin Against Experimentally Induced One -Month Old Heartworm Infections (**Dirofilaria immitis**) in Dogs. Investigator:

John W. McCall, Ph.D.
TRS Labs, Inc.
Athens, Georgia 30604

a. Purpose: To verify the recommended effective dose rate of moxidectin tablets against one-month heartworm infections in dogs.

b. Animals: Beagle dogs (20 males and 20 females), 6 to 10 months of age, 6 to 11 kg, 10 dogs per group. All test animals were heartworm-free at the time of enrollment in this study.

c. Control: placebo tablets

d. Diagnosis: Dogs were experimentally infected with 50 L3 larvae of *Dirofilaria immitis* on 30 days prior to treatment.

e. Dosage form: tablets

f. Route of administration: oral

g. Dosages: 1.5, 3 or 6 mcg/kg body weight starting 31 days after artificial infection.

h. Test duration: Dogs were necropsied on day 150.

i. Pertinent parameters measured: Worm counts at necropsy.

Results: Efficacy of moxidectin was 100% at 1.5, 3 or 6 mcg. In contrast, all placebo treated dogs harbored active heartworm infections.

Conclusions: Moxidectin was 100% effective in preventing the development of a one month-old heartworm infection of 50 L3 larvae of *D. immitis* in dogs when administered as a single oral treatment at 1.5, 3.0, and 6.0 mcg/kg.

Adverse reactions: There were no adverse reactions.

Dose Determination Study: C-90-4 Efficacy of Moxidectin Against Two and Three Month Old Heartworm Infections (*Dirofilaria Immitis*) in Dogs.

Investigator:

John W. McCall, Ph.D.
TRS Labs, Inc.
Athens, Georgia 30604

a. Purpose: To evaluate the effectiveness of moxidectin tablets against heartworm infections of two and three months duration in dogs.

b. Animals: Beagle dogs (10 males, 10 females), 13 to 14 months of age, 9 to 12 kg, 5 animals per group. All test animals were heartworm-free at the time of enrollment in this study.

c. Control: placebo tablets

d. Diagnosis: Dogs were experimentally infected with 50 L3 larvae of *Dirofilaria immitis* 60 to 90 days prior to treatment.

e. Dosage form: tablets

f. Route of administration: oral

g. Dosages: 1 or 3 mcg/kg body weight starting at 90 days after artificial infection and 0.5 mcg/kg body starting at 60 days after artificial infection.

h. Test duration: Dogs were necropsied on day 140.

i. Pertinent parameters measured: Worm counts at necropsy.

Results: The 0.5 mcg moxidectin/kg body weight dose level was 100% effective against the two-month heartworm infections. However, the single 1 and 3 mcg moxidectin/kg body weight dose level treatments were only 63% and 69% effective (respectively) against the heartworm infections of three-month duration. In contrast, all placebo treated dogs harbored active heartworm infections.

Conclusions: Moxidectin was 100% effective in preventing the development of a two month-old heartworm infection of 50 L3 larvae of *D. immitis* in dogs when administered as a single oral treatment at 0.5 mcg/kg.

Adverse Reactions: There were no adverse reactions.

Dose Confirmation Study: C-90-3 Field Study of Moxidectin Dog Heartworm Tablets in Dogs.

Investigator:

Robert A. Holmes, DVM, Ph.D.
School of Veterinary Medicine
Louisiana State University

Baton Rouge, Louisiana 70803

a. Purpose: To confirm the efficacy of different dose levels and re-treatment intervals of the moxidectin heartworm prevention tablet formulation under typical use conditions.

b. Animals: Mixed-breed dogs (14 males and 13 females), 10 to 30 months of age, 9 to 22 kg, 4 treatment groups [Group 1 (7), Group 2 (6), Group 3 (7), Group 4 (7)]. All test animals were heartworm-free at the time of enrollment in this study.

c. Control: no treatment

d. Diagnosis: Dogs were housed outdoors and exposed to mosquitoes for 269 days in a test facility located in Maringouin, Louisiana. Dogs were then enclosed in screened in runs for 139 days. Heartworm-positive dogs with known circulating levels of microfilaria were housed with the test animals to serve as sources of *Dirofilaria immitis* infection.

e. Dosage form: tablets

f. Route of administration: oral

g. Dosages: 1 or 3 mcg /kg body weight monthly for 12 months or 3 mcg/kg body weight every two months for 7 months starting at 28 days of exposure to mosquitoes.

h. Test duration: Dogs were necropsied at 13 months.

i. Pertinent parameters measured: Worm counts at necropsy.

Results: The 1 or 3 mcg moxidectin/kg body weight dose administered monthly and 3 mcg/kg administered every two months was 100% effective in preventing the occurrence of heartworm infection. In contrast, all seven dogs in the untreated control group developed heartworm infection.

Conclusions: Moxidectin was 100% effective when administered at 1 or 3 mcg/kg monthly or 3 mcg/kg every two months to dogs naturally exposed to heartworm infection.

Adverse Reactions: There were no adverse reactions.

B. Clinical Field Trials

A multi-site clinical field study was conducted in four different heartworm endemic locations (New Jersey, Illinois, California and Florida) during 1990 and 1991 to evaluate the use of ProHeart under typical treatment conditions. The principal clinical investigators, participating veterinary clinics and number of moxidectin-treated and positive control dogs initially enrolled and completing these five separate trials are summarized below.

Pivotal field Clinical Studies Conducted in the US

STUDY NUMBER	PRINCIPAL INVESTIGATOR(S) & PARTICIPATING CLINIC LOCATIONS	NUMBER OF DOGS STARTING & (FINISHING) TRIAL	
		MOXIDECTIN	IVERMECTIN
C-90-7	John J. Kazmierczak, DVM West Trenton Animal Hospital West Trenton, New Jersey 08628	51 (43)	--- ---
C-90-8	Bernard G. Levine, VMD Toms River Veterinary Hospital Toms River, New Jersey 08755 & Crestwood Veterinary Clinic Whiting, New Jersey 08759	46 (40)	10 (10)
C-90-9	Jack D. Noyes, DVM Noyes Animal Hospital Barrington, Illinois 60010 Cary Animal Hospital Cary, Illinois 60013 & South Barrington Animal Hospital South Barrington, Illinois 60010	50 (44)	15 (13)
C-90-10	Scott A. Thompson, DVM Asher Veterinary Clinic Redding, California 96002	50 (36)	15 (14)
C-90-11	Robert R. King, DVM, PhD & Charles H. Courtney, DVM, PhD College of Veterinary Medicine University of Florida Gainesville, Florida 32610	80 (73)	20 (20)
Total Dogs Starting Trial Program		280	65
Total Dogs Completing Trial Program		236	57

a. Purpose

b. Animals: At trial initiation the dogs ranged from 2 months to 16 years of age and weighed 3 to 160 pounds.

Trial	Males	Females	Total
C-90-7	17	34	51
C-90-8	23	33	56
C-90-9	35	30	65
C-90-10	33	32	65
C-90-10	44	56	100

c. Control: With the exception of Trial #C-90-7, the control group received ivermectin according to label directions. In Trial #C-90-7, animals were used as their own control and tested prior to treatment and at four and six months following the initial treatment. Efficacy was demonstrated at 100% for Trial

#C-90-7. This is consistent with the other clinical test sites which used a positive control, in particular, Trial #C-90-8 (same geographical location). The same results were obtained with the positive control as when animals were used as their own control.

d. Diagnosis: Dogs were tested for heartworms prior to trial initiation (modified Knott's test and ELISA test). Only heartworm-negative dogs were enrolled in these trials.

e. Dosage form: tablets

f. Route of administration: oral. The first administration was given by the attending veterinary clinician. The pet owner was then dispensed an adequate amount of medication to enable treatment at home for the remainder of the study.

g. Dosages: 3 mcg moxidectin/kg body weight or 6 mcg ivermectin/kg body weight. Dogs in excess of 100 pounds were given a combination of tablets in accordance with product labeling instructions.

h. Test duration: 10 months

i. Pertinent parameters measured: Dogs were tested for heartworm infection at four and six to ten months following the initial treatment (modified Knott's test and ELISA test). Feedback from the pet owner regarding the ease of administration of the tablets and their observations of any unusual behavior or signs of ill-health was documented throughout the treatment period.

Results: None of the dogs participating in this study developed heartworm infections during the treatment period. Test animals were exposed to the usual array of veterinary products and pet preparations including various shampoos, flea and tick control products, antibiotics, antimicrobials, anthelmintics, vaccines, hormones, steroids, ophthalmic treatments and nutritional supplements. Concurrent use of these products produced no observable effect on either the safety or effectiveness of moxidectin. Tablet acceptance was good for all except four animals.

Conclusions: These field trials demonstrate that moxidectin tablets are effective, safe and easy to use at the recommended dose of 3 mcg/kg body weight per month.

Adverse Reactions: Pet owners noted isolated instances of lethargy, vomiting, ataxia, anorexia, diarrhea, nervousness, weakness, increased thirst, and itching which they associated with treatment.

III. ANIMAL SAFETY

Controlled studies were conducted in dogs to address the safety of moxidectin tablets. Studies were designed to evaluate the safety of moxidectin in breeding males, breeding females, puppies, sensitive collie dogs with a previously demonstrated sensitivity to treatment with ivermectin and dogs with patent heartworm infections. A one-year feeding

study was conducted in which dogs were given daily oral administrations of moxidectin in their food.

These studies demonstrate that moxidectin has a wide therapeutic index when administered orally to dogs at the minimum recommended monthly dosage of 3 mcg/kg. The oral no-effect-level for moxidectin in dogs was established between 1120 to 1150 mcg/kg, (1.12 to 1.15 mg/kg) an excess of 300 times the recommended monthly dose level.

A. Chronic Toxicity:

Chronic Toxicity Study: Study No. HWA 362-200 One-Year Dietary Toxicity Study in Purebred Beagle Dogs

Investigator:

Gene E. Schulze, Ph.D.
Hazelton Washington, Inc.
Vienna, Virginia 22182

a. Purpose: To evaluate the toxicity of moxidectin administered daily to beagle dogs for a one-year period.

b. Animals: Purebred beagle dogs (24 males and 24 females), 5 to 7 months of age, 12 animals per group.

c. Dosage form: Different formulations were accepted based on bioavailability comparisons with the final market formulation.

d. Dosage used: Approximately 0, 10 (250 mcg/kg/day), 20 (500 mcg/kg) or 45 (1130 mcg/kg) ppm.

e. Route of administration: oral, moxidectin was ground to a fine powder before being weighed and mixed into the animal's feed.

f. Test duration: 1 year

g. Pertinent Observations and Measurements: clinical signs (observations were made twice daily), food consumption (daily), body weight and physical examinations (weekly), ophthalmoscopy (prior to treatment and during weeks 13, 26, 52), hematology, clinical chemistry and urinalysis (prior to treatment and during weeks 6, 13, 26, 52), and organ weights, gross or microscopic pathology were collected at week 52.

Results: No effects were noted in clinical signs, food consumption, body weight, physical examinations and ophthalmoscopic examinations and in the hematology, clinical chemistry and urinalysis parameters monitored throughout the trial.

No treatment-related post mortem effects, organ weight disparities or histopathological findings were observed.

Conclusions: There were no treatment-related clinical effects observed at any dose level during the course of this 52-week study.

B. Reproductive Safety

Male Reproductive Study: Study No. HRP-MI 081-04 The Safety of Moxidectin in the Breeding Male Dog

Investigators:

Martin R. Gilman, Ph.D. & William R. Voss, DVM
Hazelton Research Products, Inc.
Kalamazoo, Michigan 49009

a. Purpose: To evaluate the effect of moxidectin on male fertility, general reproductive performance and the prenatal and postnatal effects on the sired litters.

b. Animals: Fourteen male beagle dogs, 2 to 7 years of age, 9 to 15 kg, 7 animals per group. Twelve, females (Group 1) and fourteen females (Group 2), (2 to 4 years of age, 8-17 kg).

c. Dosage form: tablets

d. Dosage used: Male dogs were administered placebo tablets (Group 1) or 9 mcg moxidectin/kg body weight (Group 2) monthly for 4 consecutive months, then daily for 3 months pre-breeding period, and for 3 months post-breeding.

e. Route of administration: oral

f. Test duration: 1 year

g. Pertinent parameters measured: clinical signs (observations were made twice daily), physical examinations (males: beginning and end of trial, females: trial entry, day 30 postbreeding and weaning; pups: within 24 hours of birth and weekly until weaning), body weights (weekly for all animals) , hematology , clinical chemistry and urinalysis (males: at study initiation, 3 months, and termination, pups: weaning), semen evaluations (days 14 and 17 prior to initial dosing and ten additional times at monthly intervals). Males were euthanized following the last treatment and tissues examined microscopically.

Results: Control and treated males had similar reproductive performance. All males, with the exception of one control animal removed during the course of the study due to low sperm count, successfully bred two bitches. One bitch bred to a treated animal did not conceive. All animals (males, females, pups) remained in good health throughout the study. All parameters remained within normal reference ranges during the trial and there were no abnormal findings during the postmortem examination.

Reproduction Summary

	Group 1	**Group 2**
Fertility Index	100%	92%
Whelping Index	6.0	6.1
Whelping Index	89.7%	96.0%

FERTILITY INDEX = # CONCEIVED/ # MATED X 100
WHELPING INDEX = # LIVE PUPS/ # PREGNANT BITCHES
WEANING INDEX= # PUPS WEANED/ # LIVE PUPS DAY 1 X 100

Conclusions: There were no adverse effects on fertility, reproductive performance, or offspring of male dogs treated with moxidectin at 3 times the recommended dose level.

Female Reproductive Safety: HRP-MI 081-05 - The Safety of Moxidectin in the Breeding Female Dog

Investigators:

Martin R. Gilman, Ph.D. & William R. Voss, DVM
Hazelton Research Products, Inc.
Kalamazoo, Michigan 49009

a. Purpose: To evaluate the effect of moxidectin on pregnancy in female dogs and prenatal and postnatal effects on their offspring.

b. Animals: Twenty purebred intact female beagle dogs, 3 to 5 years of age, 7 to 13 kg, 10 animals per group., Nineteen male beagles (Group 1) and males (Group 2), (1 to 5 years of age).

c. Dosage form: tablets

d. Dosage used: female dogs were administered placebo tablets (Group 1) or 9 mcg moxidectin/kg body weight (Group 2) twice prior to breeding, then daily starting at day 12 of gestation until day 42 of lactation.

e. Route of administration: oral

f. Test duration: 9 months

g. Pertinent parameters measured: clinical signs (observations were made twice daily), physical examinations (females: day 30 postbreeding, at whelping and weaning; pups: within 24 hours of birth and at weaning), body weights (weekly for all animals) , hematology , clinical chemistry and urinalysis (females: at study initiation, prebreeding, weaning, pups: weaning). Females were euthanized within 17 days following weaning and tissues examined grossly and microscopically.

Results: All females were sucessfully bred, although one control female did not conceive and one treated female aborted at approximately 40 days of gestation. All of the remaining animals (males, females, pups) remained in good health throughout the study. All parameters remained within normal reference ranges

during the trial and there were no abnormal findings during the postmortem examination.

Reproduction Summary

	Group 1	**Group 2**
Fertility Index	90%	100%
Whelping Index	5.5	5.1
Weaning Index	81.2%	97.8%

Conclusions: The incidence of abortion was considered an incidental finding. There were no drug related adverse effects on fertility, reproductive performance, or offspring of female dogs treated with moxidectin at 3 times the recommended dose level.

Female Breeding Study: Study No. HRP-MI 081-07 - Reproduction Evaluation of Moxidectin in the Breeding Female Dog

Investigators:

Martin R. Gilman, Ph.D. & William R. Voss, DVM
Hazelton Research Products, Inc.
Kalamazoo, Michigan 49009

a. Purpose: To evaluate the effect of moxidectin on female fertility, general reproductive performance and the prenatal effects on the offspring.

b. Animals: Twenty purebred intact female beagle dogs, 2 to 4 years of age, 8 to 15 kg, 10 animals per group. Ten, males (1 to 4 years).

c. Dosage form: tablets

d. Dosage used: 0 (Group 1) or 9 mcg moxidectin/kg body weight (Group 2) in tablet form daily throughout a three-month pre-breeding period. This daily 3X treatment regimen continued throughout the gestation until whelping occurred. Identically formulated placebo tablets were administered to female dogs in the control group using the same treatment regimen.

e. Route of administration: oral

f. Test duration: 18 months

g. Pertinent Observations and Measurements: clinical signs (observations were made twice daily), physical examinations (females: prior to study initiation, day 30 of gestation and after whelping), body weights (weekly for all animals), hematology , clinical chemistry and urinalysis (females: at study initiation and within 72 hours of whelping). Females were euthanized within 96 hours following whelping and tissues examined grossly and microscopically.

Results: All females were successfully bred, although one treated female did not conceive. All of the remaining animals (males, females, pups) remained in good health throughout the study. All parameters remained within normal reference ranges during the trial and there were no abnormal findings during the postmortem examination.

Conclusions: The incidence of one female not conceiving was considered an incidental finding. There were no adverse effects on fertility, reproductive performance, or offspring of female dogs treated with moxidectin at

3 times the recommended dose level.

Reproduction Summary

	Group 1	**Group 2**
Fertility Index	100%	90%
Whelping Index	6.9	5.7
Proportion of Live Births	1.00	0.96

PROPORTION OF LIVE BIRTHS = # OF LIVE BIRTHS/ TOTAL LITTER SIZE

C. Safety in Sensitive Collie Dogs

Collie Study: Study No. C-90-12 Evaluation of the Safety of Moxidectin in Collie Dogs

Investigator:

Allen J. Paul, DVM, MS
University of Illinois
College of Veterinary Medicine
Urbana, Illinois 61801

a. Purpose: To evaluate the potential for adverse reactions to multiple overdose treatments of moxidectin in collie dogs previously shown to be sensitive to ivermectin-containing heartworm preventative products.

b. Animals: twenty-seven collie dogs (nine adult males, nine adult females, and nine collie puppies, 9 animals per group). The adults ranged from 1 to 8 years of age and weighed 17 to 28 kg,while the puppies ranged between 3 to 4 months of age and weighed 6-12 kg.

c. Dosage form: tablets

d. Dosages: placebo or moxidectin tablets were administered at 0, 3 or 15 mcg/kg body weight for three times at successive monthly intervals.

e. Route of administration: oral

f. Test duration: 3 months

g. Pertinent parameters measured: Daily observations for clinical signs (for the first eight hours following treatment, then twice daily), physical examinations (prior to each treatment) and hematology, clinical chemistry and urinalysis assessments (24 hours prior to and after each treatment).

Results: No signs of toxicity were observed in any of the test animals (adults or puppies) at any time during the study. All measured hematology, clinical chemistry and urinalysis parameters remained within normal reference ranges for all dogs throughout the test period.

Conclusions: There were no adverse effects demonstrated in cCollie dogs administered moxidectin at 1one and at 5 times the recommended dose recommended level.

Collie Study: Study No. C-91-3 The Safety of Moxidectin at 10, 20 and 30 Times the Recommended Use Level in Avermectin-Sensitive Collie Dogs

Investigator:

Allen J. Paul, DVM, MS
University of Illinois
College of Veterinary Medicine
Urbana, Illinois 61801

a. Purpose: To evaluate the potential for adverse reactions to single large overdose treatments of moxidectin in collie dogs previously shown to be sensitive to ivermectin-containing heartworm preventative products.

b. Animals: Twenty-four collie dogs (eight adult males, eight adult females, and eight collie puppies), 6 animals per group. The adults ranged from 1 to 8 years of age and weighed 17 to 28 kg, the puppies ranged between 3 to 4 months of age and weighed 6-12 kg. The animals used in this study participated in the previously described safety study (C-90-12), The adults ranged from 1 to 8years of age while the puppies ranged between 6 and 8 months of age. All of these test animals following a six week interval.

c. Dosage form: tablets

d. Dosages: Placebo or moxidectin tablets were administered at 0, 30, 60 or 90 mcg/kg body weight for one treatment. Thirty days following moxidectin treatment, all dogs were administered liquid ivermectin orally at a dose of 120 mcg/kg body weight to reconfirm sensitivity to this compound.

e. Route of administration: oral

f. Test duration: 1 month

g. Pertinent parameters measured: Daily observations for clinical signs (hourly for up to ten hours following treatment, then twice daily). The ivermectin animals were observed for six days following treatment. Clinical signs (depression, ataxia, mydriasis, salivation or drooling) were scored as follows:

0= normal, 1=mild reaction, 2=moderate reaction, 3=severe reaction.

Results: No signs of toxicity were observed in dogs admininstered moxidectin at 10 or 20 times the recommended use level. One of six dogs receiving the 30X dose of moxidectin showed mild signs of depression and ataxia for approximately six to ten hours, and mild salivation at eight hours following treatment. These signs disappeared by 24 hours post-treatment. Within 36 hours following ivermectin administration, all of the adults and 6 of 8 puppies exhibited signs of toxicity (depression, ataxia, and/or salivation). These toxic signs decreased in all dogs by day 5 and there were no signs displayed by day 7.

Conclusions: There were no adverse effects demonstrated in Collie dogs administered moxidectin at 10 or 20 times the recommended dose level. Mild signs of depression, ataxia and salivation were observed at 30 times the recommended dose level.

D. Safety in Dogs with Patent Heartworm Infections

Heartworm Infected Dogs: Study No. C-90-13 - The Safety of Moxidectin in Dogs Infected With Dog Heartworm, *Dirofilaria immitis*

Investigator:

Byron L. Blagburn, PhD.
College of Veterinary Medicine
Auburn University, Alabama 36849

a. Purpose: To demonstrate the safety of moxidectin administered to dogs with patent heartworm infections of *Dirofilaria immitis*.

b. Animals: Twenty-four adult beagle, beagle-cross and mixed-breed heartworm infected dogs (12 males and 12 females), 6 months of age and older, 6 to 34 kg, 8 per group.

c. Dosage form: tablets

d. Dose Levels and Regimen: Placebo tablets or moxidectin were administered at 0, 3 or 15 mcg /kg body weight for three times at successive monthly intervals.

e. Route of administration: oral

f. Test duration: 3 months

g. Pertinent parameters measured: Daily observations for clinical signs (hourly for up to eight hours following treatment, then twice daily), hematology, clinical chemistry and urinalysis assessments (within 24 hours prior to and following each treatment).

Results: There were no adverse reactions noted in any of the dogs throughout the test period. Hematology, clinical chemistry and urinalysis parameters were not affected. One animal in the placebo group died due to complications of dirofilariasis.

Conclusions: There were no adverse effects of treatment with moxidectin administered at 1one and at 5 times the recommended dose level to dogs with patent infections of *D. immitis*.

E. Safety in Puppies

Clinical field trial and safety data were compiled to demonstrate the safety of moxidectin in puppies.

Clinical Field Trials: Five clinical field trials were conducted in the United States, Japan and Australia. Animals selected from these trials were 6, 7 or 8 weeks of age.

Name and address of investigators:

Country	**Trial**	**Investigator**	**Address**
US	C-90-10	Dr. S. Thompson	Asher Veterinary Clinic Redding, CA 96002
Japan	28-1	Dr. Yamane	Clinical Research Laboratory for Small Animals Tottori, Japan
Japan	28-1	Dr. Yoshida	Mito Animal Hospital Ibaragi, Japan
Japan	28-1	Nobushi Group	Saitama, Japan
Australia	27-20	Dr. R. Barbero	Indooroopilly Veterinary Clinic Queensland, Australia
Australia	27-21	Dr. G. Hutchinson	Graduate School of Tropical Veterinary Science and Agriculture Queensland, Australia
Australia	27-22	Dr. C. F. Smith	Bulimba Veterinary Clinic Queensland, Australia

a. Purpose: To determine the effectiveness and safety of moxidectin tablets in puppies in relationaccording to the proposed label dosedirections.

b. Animals: 15 Purebred and mixed breed dogs, 1 to 8 kg.

Trial	**Sex**	**Age**	**mcg Moxidectin/kg body weight and Regimen**	**Test Duration**
C-90-10	M	8 weeks	3.9 mcg/kg monthly	10 months
28-1	M	8 weeks	4.4 mcg/kg monthly	6 months
28-1	F	8 weeks	3.0 mcg/kg monthly	6 months
28-1	F	8 weeks	3.4 mcg/kg monthly	6 months
27-20	F	8 weeks	5.0 mcg/kg monthly	12 months
27-20	M	7 weeks	30 mcg/kg monthly	12 months
27-20	M	7 weeks	8.6 mcg/kg monthly	12 months
27-20	M	6 weeks	12 mcg/kg monthly	12 months
27-21	M	7 weeks	5.7 mcg/kg monthly	12 months
27-21	F	6 weeks	8.1 mcg/kg monthly	12 months
27-21	F	8 weeks	4.1 mcg/kg monthly	12 months
27-21	F	6 weeks	7.1 mcg/kg monthly	12 months
27-21	F	6 weeks	10 mcg/kg monthly	12 months
27-21	F	6 weeks	8.8 mcg/kg monthly	12 months
27-22	M	8 weeks	10 mcg/kg monthly	12 months

c. Dosage form: tablets

d. Route of administration: oral

e. Pertinent parameters measured: Treatment dates, concurrent treatments, adverse reactions, and other observations were recorded on individual animal data sheets.

Safety Tolerance study: Study No. 28-2 - A Safety Test of 30 mcg/kg Moxidectin Administered Daily for 12 days in Dogs

Investigator:

Dr. S. Yamasawa
Central Research Laboratories
Singapore

a. Purpose: To determine the effects on dogs of prolonged administration of moxidectin tablets at ten times the recommended an elevated dose.

b. Animals: Two collies (1 male, 1 female), eight weeks of age.

c. Dosage form: tablets

d. Dose Levels and Regimen: moxidectin was administered at 30 mcg /kg body weight for twelve days.

e. Route of administration: oral

f. Test duration: 12 days

g. Pertinent parameters measured: Daily observations for clinical signs, body weights (days -1, 5, 12), hematology and clinical chemistry (days -14, -7, -1, 12).

Results: Adverse reactions in the clinical field trials included sporadic vomiting, diarrhea, and lethargy. There were no adverse reactions noted in the two dogs in thise safety study.

Conclusions: Moxidectin iwas is safe when administered for 12 days at 10 times the recommended dose to two 8 week old collie puppies.

IV. 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 to be labeled for use in dogs, which are non-food animals.

V. AGENCY CONCLUSIONS

The data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. It demonstrates that ProHeart™ Tablets (moxidectin), when used under labeled conditions of use, are safe and effective.

Under Section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient of the drug (including any ester or salt of the active ingredient) has been approved in any other application.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is required to determine the existence of heartworm infection, and to

then properly treat existing heartworm infection prior to starting treatment with ProHeart™ Tablets (moxidectin) tablets in a prevention program.

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.