Date of Approval: May 9, 2008

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-286

PANACUR Plus

fenbendazole/ivermectin/praziquantel

Chewable Tablets

Dogs

For the treatment and control of adult *Toxocara canis* (roundworm), *Ancylostoma caninum* (hookworm), *Trichuris vulpis* (whipworm), and *Dipylidium caninum* (tapeworm), and for the prevention of heartworm disease caused by *Dirofilaria immitis* in adult dogs.

Sponsored by:

Intervet Inc.

TABLE OF CONTENTS

I. GENERAL INFORMATION:

A. File Number: NADA 141-286

B. Sponsor: Intervet Inc.
P.O. Box 318
29160 Intervet Lane
Millsboro, DE 19966

Drug Labeler Code: 057926

C. Proprietary Name(s): PANACUR Plus Soft Chews

D. Established Name(s): Fenbendazole/ivermectin/praziquantel

E. Pharmacological Category: Antiparasitic

F. Dosage Form(s): Chewable tablets

G. Amount of Active Ingredient(s):

2.16 g small chews:	454 mg fenbendazole 27 mcg ivermectin 23 mg praziquantel
5.4 g large chews:	1,134 mg fenbendazole 68 mcg ivermectin 57 mg praziquantel

H. How Supplied: Each of the two dosage strengths comes in blister packages of 6 soft chews that are packaged in dispensing cartons of 60 soft chews.

I. How Dispensed: Rx

J. Dosage(s): PANACUR Plus Soft Chews should be administered orally at monthly intervals at the recommended minimum dose level of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg of body weight.

K. Route(s) of Administration: Oral

L. Species/Class(es): Dogs

M. Indication(s): For the treatment and control of adult *Toxocara*

canis (roundworm), *Ancylostoma caninum* (hookworm), *Trichuris vulpis* (whipworm), and *Dipylidium caninum* (tapeworm), and for the prevention of heartworm disease caused by *Dirofilaria immitis* in adult dogs.

II. EFFECTIVENESS:

A. Dosage Characterization:

The effectiveness of 6 mcg ivermectin per kg body weight against *Dirofilaria immitis* is well documented in the literature.[1,2] The effectiveness of 5 mg praziquantel per kg body weight against *D. caninum* is also documented in the literature.[3] Two dose characterization studies were done to assess the effectiveness of a single dose of 100 mg per kg fenbendazole when administered in combination with 6 mcg ivermectin and 5 mg praziquantel per kg against *Ancylostoma caninum* (dose-limiting species) and *Trichuris vulpis* infections in dogs.

B. Substantial Evidence:

1. Dose Confirmation-*Toxocara canis*

Study No. 2045-009-01

Title: Dose confirmation study to confirm the efficacy of a palatable fenbendazole, ivermectin, and praziquantel combination soft chew product (PANACUR Plus) when administered to dogs as a single treatment against natural *Toxocara canis* infections.

Type of Study: Laboratory effectiveness study

Purpose: This study was performed to assess the effectiveness of a fenbendazole, ivermectin, and praziquantel combination soft chew product administered as a single dose of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg body weight against natural infections of *T. canis* in dogs.

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[1] Ohishi I, Katae H, Hayasaki K, et al. Prophylactic activity of ivermectin against *Dirofilaria immitis* infection in dogs: Establishment of effective dose and administration schedule. *Jpn J Vet Sci* 1987;49:439-445.

[2] Paul AJ, Todd KS, Acre Sr, KE, et al. Efficacy of ivermectin chewable tablets and two new ivermectin tablet formulations against *Dirofilaria immitis* larvae in dogs. *Am J Vet Res* 1991;52:1922-1923.

[3] Kruckenberg SM, Meyer AD, Eastman WR, et al. Preliminary Studies on the effect of praziquantel against tapeworms in dogs and cats. *Vet Med Small Anim Clin* 1981;76:689-693.

Clinical Investigator: Dwight D. Bowman, Ph.D.
College of Veterinary Medicine
Cornell University
Ithaca, NY

Animals: A total of 20 mixed-breed dogs (10 males and 10 females) over three months of age and weighing 6.86 to 35.82 kg (15.1 to 78.8 pounds) at the time of treatment were used in this study.

Dosage Groups (10 dogs per group):

Group 1: (5 males, 5 females) PANACUR Plus Soft Chew (a minimum of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg bodyweight).

Group 2: (5 males, 5 females) Control (0 mg/kg delivered in the tablet formulation without active ingredients).

Route of Administration: Oral

Test Duration: 8 days

Study Design: Dogs with natural *T. canis* infections were acquired. Dogs qualified for the study by Day 2 based upon physical examination, serum chemistry, hematology and positive *T. canis* fecal samples. Dogs were randomly assigned to either the treatment or control group. Treatment (either test article or control) was administered orally on Day 0 and dogs were necropsied on Day 7.

Statistical Methods: For log worm counts, ANOVA was used to compare treatments and contrasts were used to make pairwise comparisons where appropriate.

Results: The results of the worm counts at necropsy demonstrate that the control dogs were adequately infected with *T. canis*, the geometric mean worm count for the PANACUR Plus Soft Chew group was significantly less than the geometric mean worm count of the control group ($p < 0.001$), and the PANACUR Plus Soft Chew was 94.8% ($\geq$ 90%) effective against natural *T. canis* infections. See Table 1 below.

Table 1. Effectiveness of PANACUR Plus Soft Chew against natural *T. canis* infection

Treatment	Geometric Mean	% Effectiveness
IFP* combination	0.2	94.8%
Control	4.4	---

*IFP-ivermectin, fenbendazole, praziquantel

Conclusions: This study demonstrated that the PANACUR Plus Soft Chews were effective against natural infections of *T. canis* in dogs.

Adverse Reactions: There were no adverse reactions reported in this study.

Study No. 2045-014-01

Title: Dose confirmation study to confirm the efficacy of a palatable fenbendazole, ivermectin, and praziquantel combination soft chew product (PANACUR Plus) when administered to dogs as a single treatment against induced *Toxocara canis* infections.

Type of Study: Laboratory effectiveness study.

Purpose: This study was performed to assess the effectiveness of a fenbendazole, ivermectin, and praziquantel combination soft chew product administered as a single dose of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg body weight against induced infections of *T. canis* in dogs.

Clinical Investigator: Ms. Robyn Slone
PLRS, Inc.
Corapeake, NC

Animals: A total of 12 purpose-bred Beagles (6 males and 6 females) approximately five months of age and weighing 4.1 to 8.8 kg (9.0 to 19.4 pounds) at the time of treatment were used in this study.

Dosage Groups (6 dogs per group):

Group 1: (3 male, 3 female) PANACUR Plus Soft Chew (a minimum of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg bodyweight).

Group 2: (3 male, 3 female) Control (0 mg/kg delivered in the tablet formulation without active ingredients).

Route of Administration: Oral.

Test Duration: 8 days

Study Design: Dogs were determined to be free of intestinal parasites and were inoculated orally with approximately 300 *T. canis* eggs on Day -49. Dogs qualified for the study by Day -4 based upon physical examination, hematology, and serum chemistry and presence of induced infection with *T. canis*. Dogs were randomly assigned to either the treatment or control group. Treatment (either test article or control) was administered on Day 0 and dogs were sacrificed and necropsied on Day 7.

Statistical Methods: For log worm counts, ANOVA was used to compare treatments and contrasts were used to make pairwise comparisons where appropriate.

Results: The results of the worm counts at necropsy demonstrate that the control dogs were adequately infected with *T. canis*. The geometric mean worm count in the PANACUR Plus Soft Chew group was significantly less than the geometric mean worm count of the control ($p < 0.001$), and the PANACUR Plus soft chew was 92.9% (≥ 90%) effective against induced infections of *T. canis.* See Table 2 below.

Table 2. Effectiveness of PANACUR Plus Soft Chew against induced *T. canis* infection

Treatment	Geometric Mean	% Effectiveness
IFP* combination	0.9	92.9%
Control	12.8	---

*IFP-ivermectin, fenbendazole, praziquantel

Conclusions: This study demonstrated that the PANACUR Plus Soft Chews were effective against induced infections of *T. canis* in dogs.

Adverse Reactions: Self-limiting loose watery stool occurred twice in one dog receiving the PANACUR Plus Soft Chews.

2. Dose Confirmation–*Ancylostoma caninum*

Study Number 2045-006-03

Title: Dose confirmation study to confirm the efficacy of a palatable fenbendazole, ivermectin and praziquantel combination soft chew product when administered to dogs as a single treatment against natural *Ancylostoma caninum* infections.

Type of Study: Laboratory effectiveness study

Purpose: This study was performed to assess the effectiveness of a fenbendazole, ivermectin, and praziquantel combination soft chew product administered as a single dose of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel minimum per kg bodyweight against natural infections of *A. caninum* in dogs.

Clinical Investigator: Prof. Dawie Kok
ClinVet International (Pty) Ltd
Bloemfontein, Republic of South Africa

Animals: A total of 24 adult mixed-breed dogs (11 males and 13 females) weighing 4.95 to 16.68 kg (10.9 to 36.7 pounds) at the time of treatment were used in this study.

Dosage Groups (12 dogs per group):

Group 1: (6 male and 6 female) PANACUR Plus Soft Chew (a minimum of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg bodyweight).

Group 2: (5 male and 7 female) Control (0 mg/kg delivered in the tablet formulation without active ingredients).

Route of Administration: Oral

Test Duration: 7 days

Study Design: Dogs were identified as naturally infected with *A. caninum* by fecal examination for the presence of eggs. They were then ranked by mean fecal egg count in descending order and randomly assigned to either the treatment or control group. Treatment (either test article or control) was administered on Day 0 and dogs were sacrificed and necropsied on Day 7.

Statistical Methods: For log worm counts, ANOVA was used to compare treatments and contrasts were used to make pairwise comparisons where appropriate.

Results: The results of the worm counts at necropsy demonstrate that the control dogs were adequately infected by *A. caninum.* The geometric mean worm count in the PANACUR Plus Soft Chew group was significantly less than the geometric mean worm count of the control group ($p < 0.001$), and the PANACUR Plus Soft Chew was 94.6% ($\geq$ 90%) effective against natural infections of *A. caninum*. See Table 3 below.

Table 3. Effectiveness of PANACUR Plus Soft Chew against natural *A. caninum* infection

Treatment	Geometric Mean	% Effectiveness
IFP* combination	1.4	94.6%
Control	25.6	---

*IFP-ivermectin, fenbendazole, praziquantel

Conclusions: This study demonstrated that the PANACUR Plus Soft Chews were effective against natural infections of *A. caninum* in dogs.

Adverse Reactions: One dog administered the PANACUR Plus Soft Chews experienced loose stool on three separate days post-treatment.

Study Number 2045-007-01

Title: Dose confirmation, non-interference study to evaluate the efficacy of a palatable fenbendazole, ivermectin and praziquantel combination soft chew product when administered to dogs as a single treatment against induced *Ancylostoma caninum* infections.

Type of Study: Laboratory effectiveness and non-interference study.

Purpose: The objectives of this study were to a) assess the effectiveness of a fenbendazole, ivermectin and praziquantel combination soft chew product administered as a single dose of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel minimum per kg bodyweight against induced infections of *A. caninum* in dogs, b) demonstrate that praziquantel alone is not effective against induced *A. caninum* infections in dogs, and c) demonstrate that ivermectin alone is not effective against induced *A. caninum* infections in dogs.

Clinical Investigator: Dr. Brian Schricker
Liberty Research Inc.
Waverly, NY

Animals: A total of 40 adult purpose-bred Beagles (20 males and 20 females) weighing 8 to 17 kg (17.6 to 37.4 pounds) at the time of treatment were used in this study.

Dosage Groups (10 dogs per group):

Group 1: (5 male, 5 female) PANACUR Plus Soft Chew (a minimum of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg bodyweight).

Group 2: (5 male, 5 female) Ivermectin soft chew (a minimum of 6 mcg ivermectin per kg bodyweight).

Group 3: (5 male, 5 female) Praziquantel soft chew (a minimum of 5 mg praziquantel per kg bodyweight).

Group 4: (5 male, 5 female) Control (0 mg/kg delivered in the tablet formulation without active ingredients).

Route of Administration: Oral

Test Duration: 8 days

Study Design: Dogs were inoculated orally with approximately 300 viable L_3 *A. caninum* larvae 28 days prior to treatment. Dogs were ranked by mean fecal egg count in descending order within sex prior to randomization to treatment. Treatment (either test article, praziquantel only, ivermectin only, or control) was administered on Day 0. Necropsies and parasite counts were done on Day 7.

Statistical Methods: For log worm counts, ANOVA was used to compare treatments and contrasts were used to make pairwise comparisons where appropriate.

Results: The results of the worm counts at necropsy demonstrate that the control dogs were adequately infected with *A. caninum*. The geometric mean worm count in the PANACUR Plus Soft Chew group was significantly less than the geometric mean worm count of the control group ($p < 0.001$), and the PANACUR Plus Soft Chew was 96.2% (≥ 90%) effective against induced infection of *A. caninum*.

The worm counts at necropsy demonstrated that ivermectin alone was 95.3 % (≥ 90%) effective against *A. caninum*, and the geometric mean worm count of the combination group was not significantly greater than the geometric mean worm count of the ivermectin group ($p = 0.375$). Thus, ivermectin was effective against induced infections of *A. caninum*.

The worm counts at necropsy demonstrated that praziquantel alone was 0 % (< 90%) effective against *A. caninum*, and the geometric mean worm count of the combination group was significantly less than the geometric mean worm count of praziquantel group ($p < 0.001$). Thus, praziquantel was not effective against induced infections of *A. caninum*. See Table 4 below.

Table 4. Effectiveness of PANACUR Plus Soft Chew, praziquantel, or ivermectin against induced *A. caninum* infection

Treatment	Geometric Mean	% Effectiveness
IFP* combination	1.7	96.2%
Praziquantel	53.1	0%
Ivermectin	2.1	95.3%
Control	45.7	---

*IFP-ivermectin, fenbendazole, praziquantel

Conclusions: This study demonstrated that the PANACUR Plus Soft Chews were effective against induced infections of *A. caninum* in dogs. Praziquantel alone was not effective against induced infections of *A. caninum* in dogs. Ivermectin alone dosed at up to 11.7 mcg/kg bodyweight was effective against induced infections of *A. caninum* in dogs.

Adverse Reactions: Six of the ten dogs in each group (60 %), experienced some type of adverse reaction either the day of treatment or on Day 1 through Day 7. For the PANACUR Plus Soft Chew group, four dogs had diarrhea, and two of the dogs experienced both diarrhea and vomiting. In the ivermectin group, two dogs had diarrhea/soft stool, one dog vomited, and three dogs experienced episodes of both vomiting and diarrhea/soft stool. In the praziquantel group, three dogs had diarrhea/soft stool, two dogs experienced episodes of both vomiting and diarrhea, and one dog experienced excess salivation. In the control group, six dogs had diarrhea/soft stool. Between Days -13 and -1 of the study, 27 of the total 40 dogs experienced at least one episode of diarrhea/soft stool. Diarrhea/soft stool occurred more frequently on treatment day (Day 0) than on any other day in the study (Day -13 through Day 7). Vomiting and salivation occurred only after treatment.

3. Dose confirmation-*Trichuris vulpis*

Study No. 2045-015-01

Title: Dose confirmation study to confirm the efficacy of a palatable fenbendazole, ivermectin, and praziquantel combination soft chew product (PANACUR Plus) when administered to dogs as a single treatment against induced *Trichuris vulpis* infections.

Type of study: Laboratory effectiveness study.

Purpose: This study was performed to assess the effectiveness of a fenbendazole, ivermectin, and praziquantel combination soft chew product administered as a single dose of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg body weight against induced infections of *T. vulpis* in dogs.

Clinical Investigator: Ms. Robyn Slone
PLRS, Inc.
Corapeake, NC

Animals: A total of 20 purpose-bred Beagles (10 males and 10 females) approximately seven months of age and weighing 6.18 to 11.1 kg (13.6 to 22.2 pounds) at the time of treatment were used in this study.

Dosage Groups (10 dogs per group):

Group 1: (5 male, 5 female) PANACUR Plus Soft Chew (a minimum of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg bodyweight).

Group 2: (5 male, 5 female) Control (0 mg/kg delivered in the tablet formulation without active ingredients).

Route of Administration: Oral

Test Duration: 8 days

Study Design: Dogs were determined to be free of intestinal nematode parasite infection and then inoculated orally with approximately 700 larvated infective *T. vulpis* ova on Day -81. Dogs qualified for the study by Day -5, prior to dosing, based upon physical examination, hematology, serum chemistry, and presence of induced infection with *T. vulpis*. Dogs were randomly assigned to either the treatment or control group. Treatment (either test article or control) was administered on Day 0 and dogs were sacrificed and necropsied on Day 7.

Statistical Methods: For log worm counts, ANOVA was used to compare treatments and contrasts were used to make pairwise comparisons where appropriate.

Results: The results of the worm counts at necropsy demonstrate that the control dogs were adequately infected by *T. vulpis*. The geometric mean worm count in the PANACUR Plus Soft Chew group was significantly less than the geometric mean worm count of the control group ($p < 0.001$), and the PANACUR Plus Soft Chew was 99.2% ($\geq$ 90%) effective against induced infections of *T. vulpis* in dogs. See Table 5 below.

Table 5. Effectiveness of PANACUR Plus Soft Chew against induced *T. vulpis* infection

Treatment	Geometric Mean	% Effectiveness
IFP* combination	0.3	99.2%
Control	35.5	---

*IFP-ivermectin, fenbendazole, praziquantel

Conclusions: This study demonstrated that the PANACUR Plus Soft Chews were effective against induced infections of *T. vulpis* in dogs.

Adverse Reactions: Two adverse reactions were reported in the study. Both events were instances of self-limiting diarrhea and occurred in one dog in the PANACUR Plus Soft Chew group and one dog in the control group.

4. Dose confirmation and non-interference-*Trichuris vulpis*

Study No. 2045-018-01

Title: Dose confirmation, non-interference study to confirm the efficacy of a palatable fenbendazole, ivermectin and praziquantel combination soft chew product when administered to dogs as a single treatment against natural *Trichuris vulpis* infections.

Type of Study: Laboratory effectiveness and non-interference study.

Purpose: The objectives of this study were to a) assess the effectiveness of a fenbendazole, ivermectin, and praziquantel combination soft chew product administered as a single dose of approximately 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg body weight against natural infections of *T. vulpis* in dogs, b) demonstrate that ivermectin alone is not effective against natural *T. vulpis* infections in dogs, and c) demonstrate that praziquantel alone is not effective against natural *T. vulpis* infections in dogs.

Clinical Investigator: Dwight D. Bowman, Ph.D.
College of Veterinary Medicine
Cornell University
Ithaca, NY

Animals: A total of 40 mixed-breed dogs (20 males and 20 females) over six months of age and weighing 7.45 to 39.55 kg (16.4 to 87.0 pounds) at the time of treatment were used in this study.

Dosage Groups (10 dogs per group):

Group 1: (5 male, 5 female) PANACUR Plus Soft Chew (a minimum of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg bodyweight).

Group 2: (4 male, 6 female) Ivermectin soft chews (a minimum of 6 mcg ivermectin per kg bodyweight).

Group 3: (5 male, 5 female) Praziquantel soft chews (a minimum of 5 mg praziquantel per kg bodyweight).

Group 4: (6 male, 4 female) Control (0 mg/kg delivered in the tablet formulation without active ingredients).

Route of Administration: Oral

Test Duration: 8 days

Study Design: Dogs with natural *T. vulpis* infections were acquired. Dogs qualified for the study by Day -2 based upon physical examination, serum chemistry, hematology and positive *T. vulpis* fecal samples. Dogs were randomly assigned to

one of the four treatment groups. Treatment (either test article, ivermectin only, praziquantel only, or control) was administered on Day 0, and dogs were necropsied on Day 7.

Statistical Methods: For log worm counts, ANOVA was used to compare treatments and contrasts were used to make pairwise comparisons where appropriate.

Results: The results of the worm counts at necropsy demonstrate that the control dogs were adequately infected by *T. vulpis*, the geometric mean worm count in the PANACUR Plus Soft Chew group was significantly less than the geometric mean worm count of the control group ($p < 0.001$), and the PANACUR Plus Soft Chew was 99.6% ($\geq$ 90%) effective against natural infections of *T. vulpis*.

The worm counts at necropsy demonstrate that ivermectin alone was 76.4% effective against natural infections of *T. vulpis* ($p < 0.001$). Thus, ivermectin was not effective (< 90%) against *T. vulpis*.

The worm counts at necropsy demonstrate that praziquantel alone was 27.8% effective against natural infections of *T. vulpis* ($p < 0.001$). Thus, praziquantel was not effective (< 90%) against *T. vulpis*. See Table 6 below.

Table 6. Effectiveness of PANACUR Plus Soft Chew, praziquantel, or ivermectin against natural *T. vulpis* infection

Treatment	Geometric Mean	% Effectiveness
IFP* combination	0.3	99.6%
Praziquantel	58.7	27.8%
Ivermectin	19.2	76.4%
Control	81.3	---

*IFP-ivermectin, fenbendazole, praziquantel

Conclusions: This study demonstrated that the PANACUR Plus Soft Chews were effective against natural infections of *T. vulpis* in dogs. Ivermectin and praziquantel did not demonstrate effectiveness against natural infections of *T. vulpis* in dogs.

Adverse Reactions: There were no adverse reactions reported in this study.

5. Dose confirmation-*Dipylidium caninum*

Study Number 2045-004-01

Title: Dose confirmation study to confirm the efficacy of a palatable fenbendazole, ivermectin, and praziquantel combination soft chew product (PANACUR Plus) when administered to dogs as a single treatment against natural *Dipylidium caninum* infections.

Type of Study: Laboratory effectiveness study.

Purpose: This study was performed to assess the effectiveness of a fenbendazole, ivermectin, and praziquantel combination soft chew product administered as a single dose of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg bodyweight against natural infections of *D. caninum* in dogs.

Clinical Investigator: Dwight D. Bowman, PhD
Cheri-Hill Kennel and Supply
Stanwood, MI

Animals: A total of 20 adult mixed-breed dogs (12 males and 8 females) weighing 14.55 to 39.32 kg (32.0 to 86.5 pounds) at the time of treatment were used in this study.

Dosage Groups (10 dogs per group):

Group 1: (5 male, 5 female) PANACUR Plus Soft Chew (a minimum of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg bodyweight).

Group 2: (7 male, 3 female) Control (0 mg/kg delivered in the tablet formulation without active ingredients).

Route of Administration: Oral.

Test Duration: 12 days

Study Design: Dogs were identified as naturally infected with *D. caninum* by fecal examination for presence of proglottids, and were randomly assigned to either the treatment or control group. Treatment (either test article, ivermectin only, praziquantel only, or control) was administered on Day 0. Necropsies and parasite counts were done on Day 12.

Statistical Methods: For log scolex counts, ANOVA was used to compare treatments and contrasts were used to make pairwise comparisons where appropriate.

Results: The results of the scolex counts at necropsy demonstrated that the control animals were adequately infected with *D. caninum*. The geometric mean scolex count in the PANACUR Plus Soft Chew group was significantly less than the mean scolex count of the control group ($p = 0.002$), and the PANACUR Plus Soft Chew was 100% effective against natural infections of *D. caninum* in dogs. See Table 7 below.

Table 7. Effectiveness of PANACUR Plus Soft Chew against natural *D. caninum* infection

Treatment	Geometric Mean	Percent Effectiveness
IFP* combination	0.00	100%

Control	7.03	---

*IFP-ivermectin, fenbendazole, praziquantel

Conclusions: This study demonstrated that the PANACUR Plus Soft Chews were effective against natural infections of *D. caninum* in dogs.

Adverse Reactions: There were no adverse reactions reported in this study.

6. Dose confirmation and non-interference-*Dipylidium caninum*

Study Number 2045-005-01

Title: Dose confirmation, non-interference study to confirm the efficacy of a palatable fenbendazole, ivermectin and praziquantel combination soft chew product (PANACUR Plus) when administered to dogs as a single treatment against natural *Dipylidium caninum* infections.

Type of Study: Laboratory effectiveness and non-interference study.

Purpose: The objectives of this study were to a) assess the effectiveness of a fenbendazole, ivermectin, and praziquantel combination soft chew product administered as a single dose of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg bodyweight against natural infections of *D. caninum* in dogs, b) demonstrate that fenbendazole alone is not effective against natural *D. caninum* infections in dogs, and c) demonstrate that ivermectin alone is not effective against natural *D. caninum* infections in dogs.

Clinical Investigator: Prof. Dawie Kok
ClinVet International (Pty) Ltd
Republic of South Africa.

Animals: A total of 40 adult mixed-breed dogs (9 males and 31 females) weighing 3.77 to 13.77 kg (8.3 to 30.3 pounds) at the time of treatment were used in this study.

Dosage Groups (10 dogs per group):

Group 1: (2 male, 8 female) PANACUR Plus Soft Chew (a minimum of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg bodyweight).

Group 2: (2 male, 8 female) Fenbendazole soft chews (a minimum of 100 mg fenbendazole per kg bodyweight).

Group 3: (2 male, 8 female) Ivermectin soft chews (a minimum of 6 mcg ivermectin per kg bodyweight).

Group 4: (3 male, 7 female) Control (0 mg/kg delivered in the tablet formulation without active ingredients).

Route of Administration: Oral

Test Duration: 12 days

Study Design: Dogs were identified as naturally infected with *D. caninum* by fecal examination for presence of proglottids, and were each randomly assigned to one of the study groups. Treatment (either test article, fenbendazole only, ivermectin only, or control) was administered on Day 0. Necropsies were done on Day 12, and parasite counts were performed on fixed specimens on various days within two months of Day 12.

Statistical Methods: For log scolex counts, ANOVA was used to compare treatments and contrasts were used to make pairwise comparisons where appropriate.

Results: The results of the scolex counts at necropsy demonstrate that the control animals were adequately infected by *D. caninum.* The geometric mean scolex count in the PANACUR Plus Soft Chew group was significantly less than the geometric mean scolex count of the control group ($p < 0.001$), and the PANACUR Plus Soft Chew was 100% effective against natural infections of *D. caninum* in dogs.

The scolex counts at necropsy demonstrate that the fenbendazole alone was less than 90% effective. Thus, fenbendazole was not effective against *D. caninum.*

The scolex counts at necropsy demonstrate that the ivermectin alone was less than 90% effective. Thus, ivermectin was not effective against *D. caninum.* See Table 8 below.

Table 8. Effectiveness of PANACUR Plus Soft Chew, fenbendazole, or ivermectin against natural *D. caninum* infection

Treatment	Geometric Mean	% Effectiveness
IFP* combination	0.00	100%
Fenbendazole	19.25	0%
Ivermectin	38.22	0%
Placebo	16.46	-

*IFP-ivermectin, fenbendazole, praziquantel

Conclusions: This study demonstrated that the PANACUR Plus Soft Chews were effective against natural infections of *D. caninum* in dogs. Fenbendazole and ivermectin did not demonstrate effectiveness against natural infections of *D. caninum* in dogs.

Adverse Reactions: One dog treated with the PANACUR Plus Soft Chews developed dark diarrhea, dehydration and was euthanized six days after treatment.

Pre-treatment clinicopathological findings included hypoalbuminemia, low total protein, and low hematocrit. Necropsy revealed moderate duodenal ulceration, large numbers of *Helicobacter* organisms in the pylorus, and diffuse mild interstitial pneumonia. The relationship between the necropsy findings and the development of clinical disease after treatment with the drug product is unclear because the dog had evidence of subclinical disease upon enrollment. Diarrhea occurred in one dog in each treatment group and two dogs in the control group.

7. Dose confirmation-*Dirofilaria immitis*

Study Number 2045-010-01

Title: Dose confirmation study to confirm the efficacy of a palatable fenbendazole, ivermectin and praziquantel combination soft chew product (PANACUR Plus) when administered to dogs as a single treatment against induced *Dirofilaria immitis* infections.

Type of Study: Laboratory effectiveness study

Purpose: This study was performed to assess the effectiveness of a fenbendazole, ivermectin, and praziquantel combination soft chew product administered as a single dose of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg bodyweight for prevention of induced infections of *D. immitis* in dogs when given 30 days after infestation.

Clinical Investigator: Dr. John McCall
TRS Labs, Inc.
Athens, GA

Animals: A total of 20 purpose-bred Beagles (10 males and 10 females) approximately six to nine months of age and weighing 8.73 to 14.45 kg (19.2 to 31.8 pounds) at the time of treatment were used in this study.

Dosage Groups (10 dogs per group):

Group 1: (5 male, 5 female) PANACUR Plus Soft Chew (a minimum of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg bodyweight)

Group 2: (5 male, 5 female) Control (0 mg/kg delivered in the tablet formulation without active ingredients).

Route of Administration: Oral

Test Duration: 125 days

Study Design: Dogs were determined to be free from existing heartworm infections and healthy on physical exam, hematology and serum chemistry. Dogs were randomly allocated into either the treatment or control group, then inoculated

subcutaneously with approximately 50 viable L3 *D. immitis* larvae 30 days prior to administration of the test article or control (Day 0). Antigen testing for *D. immitis* was performed again on Day 90 of the study to detect any potential *D. immitis* infestations that were prepatent at the time the initial heartworm screening was performed. All dogs were observed hourly for 4 hours after treatment then daily until necropsy on Day 125.

Results: The results of the worm counts at necropsy demonstrate that the control dogs were adequately infected by *D. immitis* (geometric mean 36.2). No heartworms were recovered from the PANACUR Plus Soft Chew group. The PANACUR Plus Soft Chew was 100% effective against induced infections of *D. immitis* in dogs.

Conclusions: The study demonstrated that the PANACUR Plus Soft Chews were effective against induced infections of *D. immitis* in dogs.

Adverse Reactions: There were no adverse reactions reported in this study.

8. Dose confirmation and non-interference-*Dirofilaria immitis*

Study Number 2045-011-01

Title: Dose confirmation, non-interference study to confirm the efficacy of a fenbendazole, ivermectin and praziquantel combination soft chew product when administered to dogs as a single treatment against induced *Dirofilaria immitis* infections.

Type of Study: Laboratory effectiveness and non-interference study

Purpose: The objectives of this study were to a) assess the effectiveness of a fenbendazole, ivermectin, and praziquantel combination soft chew product (PANACUR Plus) when administered as a single dose of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg bodyweight against experimentally induced heartworm infections (*D. immitis*) in dogs, b) demonstrate that 100 mg/kg fenbendazole alone is not effective against experimentally induced *D. immitis* infections in dogs, and c) demonstrate that 5 mg/kg praziquantel alone is not effective against experimentally induced *D. immitis* infections in dogs.

Clinical Investigator: Dr. John McCall
TRS Labs, Inc.
Athens, GA

Animals: A total of 40 purpose-bred Beagles (20 males and 20 females) approximately six to nine months of age and weighing 6.64 to 15.86 kg (14.6 to 34.9 pounds) at the time of treatment were used in this study.

Dosage Groups (10 dogs per group):
Group 1: (5 male, 5 female) PANACUR Plus Soft Chew (a minimum of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg bodyweight)

Group 2: (5 male, 5 female) Fenbendazole soft chews (a minimum of 100 mg fenbendazole per kg bodyweight)

Group 3: (5 male, 5 female) Praziquantel soft chews (a minimum of 5 mg praziquantel per kg bodyweight)

Group 4: (5 male, 5 female) Control (0 mg/kg delivered in the tablet formulation without active ingredients).

Route of Administration: Oral

Test Duration: 125 days

Study Design: Dogs were determined to be free from existing heartworm infections and healthy on physical exam, hematology and serum chemistry. Dogs were randomly allocated into either the combination soft chew treatment, fenbendazole soft chew treatment, praziquantel soft chew treatment or control groups. All dogs were inoculated subcutaneously with approximately 50 viable L3 *D. immitis* larvae 30 days prior to administration of either the combination soft chew, fenbendazole soft chew, praziquantel soft chew or control (Day 0). Antigen testing for *D. immitis* was performed again on Day 90 of the study to detect any potential *D. immitis* infestations that were prepatent at the time the initial heartworm screening was performed. All dogs were observed hourly for 4 hours after treatment then daily until necropsy on Day 125.

Results: The results of the worm counts at necropsy demonstrate that the placebo treated dogs were adequately infected by *D. immitis* (geometric mean 23.3). No heartworms were recovered from the PANACUR Plus Soft Chew group. The PANACUR Plus Soft Chew was 100% effective against induced infections of *D. immitis* in dogs.

The results of the worm counts at necropsy demonstrated that fenbendazole alone and praziquantel alone, were both less than 100% effective against induced infections of *D. immitis*. Thus, fenbendazole and praziquantel were not effective against *D. immitis*.

Conclusions: This study demonstrated that the PANACUR Plus Soft Chews were effective against induced infections of *D. immitis* in dogs. Fenbendazole and praziquantel did not demonstrate effectiveness against induced infections of *D. immitis* in dogs.

Adverse Reactions: One dog from the PANACUR Plus Soft Chew group vomited within the one-hour period after dosing. The dog was redosed in accordance to the protocol. No other adverse reactions occurred during the study.

9. Field Safety Study:

Study Number 2045-012-00

Title: Clinical study to evaluate the palatability and safety of fenbendazole, ivermectin, and praziquantel combination soft chews in dogs.

Type of Study: Field safety and palatability study.

Purpose: This study was performed to assess the palatability and safety of a fenbendazole, ivermectin, and praziquantel combination soft chew product administered at a monthly minimum dose of 100 mg fenbendazole, 6 mcg ivermectin, and 5 mg praziquantel per kg body weight in dogs.

Clinical Investigators:

Dr. Brett Berryhill
Baton Rouge, LA

Dr. Garry Cowan
Wichita, KS

Dr. Sam Geller
Quakertown, PA

Dr. Steve Hodes
Mine Hill, NJ

Dr. James Winsor
Inver Grove Heights, MN

Dr. Diane Cosko
Lebec, CA

Dr. Richard DeVries
Albany, NY

Dr. Donald Heagren
Durham, NC

Dr. Mark Lapierre
Greensboro, NC

Animals: A total of 106 healthy client-owned dogs (53 females and 53 males) were enrolled in the study. Dogs were between 7 months and 13 years of age and weighed 4.5 to 61.64 kg (9.9 to 135.6 pounds) in body weight at the time of enrollment.

Dosage Groups: All dogs were offered the investigational drug at the proposed label dose.

Route of Administration: Oral

Test Duration: Approximately 65 days

Study Design: Treatment was given to the dogs by the owners on Day 0 and then monthly until approximately Day 60. The dogs were offered the chews by hand or chews were placed in an empty bowl. If the dog did not accept the chews within 5 minutes, the chews were offered with a small amount of food. If the dog did not consume the chews by these methods, the dose was placed in dog's mouth either broken into pieces or whole and the dog was encouraged to chew. At each dosing, the owners assessed and recorded palatability. Owners observed their dogs for adverse reactions throughout the study. Dogs returned to the investigator between Days 65 and 72 for a final physical examination, serum chemistry, and hematology evaluation.

Palatability was calculated as follows:

The dog's voluntary acceptance percentage was determined with the following formula:

$$\frac{\text{The number of trials where the animal voluntarily consumed the entire dose within 5 minutes when offered by hand or from an empty food bowl}}{\text{Total number of trials per animal}} \times 100$$

The average across all dogs was determined with the following formula:

$$\frac{\text{The sum of all the dogs' voluntary acceptance percentages}}{\text{The total number of dogs}}$$

PANACUR Plus was considered palatable if the average of the dog voluntary acceptance percentages was greater than or equal to 70%.

Results: One hundred and six dogs were included in the field study analysis for palatability. By the third dose, the average percent voluntary acceptance for PANACUR Plus was calculated to be 59% when offered from the hand or from an empty food bowl and 68% when offered from the hand, from an empty food bowl, or with a small amount of food. Eighteen percent of dogs refused the third dose of PANACUR Plus.

Gastrointestinal disturbances such as diarrhea, change in stool color, soft stool and vomiting were adverse reactions experienced during the study. Table 9 lists the adverse reactions reported and the numbers of dogs experiencing them.

Table 9. Adverse reactions reported in the field study[1]

Adverse Reaction	No. of Dogs (%) N = 105
Diarrhea / soft stool	9 (8.6)
Light colored stool	9 (8.6)
Vomiting	7 (6.7)
Decreased appetite	2 (1.9)
Lethargy	2 (1.9)

Hypersalivation	1 (1.0)

[1] Dogs may have experienced more than one of the observations during the study.

Conclusions: Gastrointestinal disturbances such as diarrhea or soft stool, change in stool color, and vomiting represented the majority of adverse reactions experienced by dogs in this study. Most of these reactions were mild in nature and resolved with little or no medical intervention, indicating PANACUR Plus Soft Chews are safe for use in dogs. Palatability was not demonstrated in this study. In the event that the product is refused, the label recommends alternative treatment.

III. TARGET ANIMAL SAFETY:

A. Safety in Ivermectin-Sensitive Dogs - Study No. 2045-013-01

Title: Safety of a fenbendazole, ivermectin, and praziquantel chewable combination product administered orally to ivermectin-sensitive Collies at 1X, 3X, or 5X the maximum exposure dose for a Shetland Sheepdog.

Study Type: Laboratory safety study

Investigator: Amy Cada, Ph.D.
DeSoto Research Farm
DeSoto, Kansas

Purpose: This study was performed to determine whether Collies with a known sensitivity to ivermectin would develop signs of ivermectin toxicosis when administered PANACUR Plus Soft Chews at 1X, 3X, or 5X the maximum potential exposure dose. The maximum potential exposure dose was based upon the largest mg/kg exposure to the active ingredients that could be received by an average sized adult Shetland Sheepdog (7.6 kg), which is the smallest breed identified as having potential ivermectin sensitivity.

Test Animals: Sixteen ivermectin-sensitive Collies (9 males and 7 females), between 7 months and 7 years of age, weighing 16.5 to 33.5 kg (36.3 to 73.7 pounds) on Day -2 were enrolled. These dogs were selected on the basis of having previously exhibited clinical signs of ivermectin toxicity following oral administration of 120 mcg/kg ivermectin.

Dogs were ranked according to ivermectin sensitivity (mild, moderate, severe), followed by body weight within sex, beginning with the heaviest dog receiving a severe score. Dogs were then assigned sequentially into four blocks of 4 dogs each, three treatment groups and one control group. Within a block, dogs were randomly allocated to 1 of 4 treatment groups, with a minimum of one female per treatment group.

Table 10. Dosage groups in study number 2045-013-01

Treatment Group	No. and Gender of Dogs[b]	Fenbendazole (mg/kg)	Ivermectin (mcg/kg)	Praziquantel (mg/kg)
0X[a]	2 m, 2 f	0.0	0.0	0.0
1X	2 m, 2 f	149	8.9	7.5
3X	3 m, 1 f	447	26.7	22.5
5X	2 m, 2 f	745	44.5	37.5

[a] Control (0 mg/kg delivered in the tablet formulation without active ingredients).
[b] m=males, f=females

Route: Oral

Study Duration: 7 days

Study Schedule and Observations: Test article and control treatments were administered once on Day 0. Health observations were made at 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, and 24 hours post-dose for signs of ivermectin toxicosis. On Days 2 through 6 observations were made at least twice daily. Hematology and clinical chemistry analysis were performed on each animal on Day -4 and Day 6.

Results: A mild ivermectin toxicity reported as mydriasis was observed in one dog treated with the 5X dose as a single observation 8 hours post-treatment lasting 1 hour. Dogs treated with 0X and 5X experienced more soft stools and diarrhea than dogs in the other treatment groups, which was attributed to the laxative effect caused by the large number of chews administered to these dogs. There was no clinically relevant effect on hematology or clinical chemistry.

Conclusion: Oral administration of a 1X and 3X dose of PANACUR Plus Soft Chews to ivermectin-sensitive Collies was not associated with any signs of ivermectin toxicity. At 5X, a mild sign of ivermectin toxicity (mydriasis) was observed in one dog.

B. Target Animal Safety Study - Study No. 2045-003-01

Title: Target animal safety study in Beagle dogs administered a fenbendazole, ivermectin, and praziquantel combination soft chew at 1X, 3X and 5X the maximum adult toy breed dose rate bi-weekly for a total of 6 treatments.

Study Type: Laboratory safety study

Investigator: Mark Allan, BVSc
Intervet, Inc.
DeSoto, Kansas

Purpose: This study was performed to determine the safety of a fenbendazole, ivermectin, praziquantel soft chew product in Beagle dogs when administered at 1X, 3X,

or 5X the maximum potential exposure dose for an average size adult toy breed dog (3 lbs).

Test Animals: Twenty four 16 ± 1 week-old Beagles (12 males and 12 females), weighing 4.7 to 6.75 kg (10.34 to 14.85 pounds) on Day -1, were blocked by weight and randomized to one of four treatment groups.

Table 11. Dosage groups in study number 2045-003-01

Treatment Group	No. and Gender of Dogs	Fenbendazole (mg/kg)	Ivermectin (mcg/kg)	Praziquantel (mg/kg)
0X[a]	3 dogs/gender	0.0	0.0	0.0
1X	3 dogs/gender	324	19.3	16.4
3X	3 dogs/gender	972	57.9	49.2
5X	3 dogs/gender	1620	81.5	82.0

[a] Control (0 mg/kg delivered in the tablet formulation without active ingredients).

Route: Oral

Study Duration: 77 days

Study Schedule and Observations: Dogs were dosed once (by oral administration) every two weeks for a total of six treatments on Days 0, 14, 28, 42, 56, and 70 with either the test article or control. Physical exams were performed on Days -10, -2, 19, 40, 61, and 75. Body weight was measured on Days -10, -1, 6, 13, 20, 27, 34, 41, 48, 55, 62, 69, and day 76 or 77. Hematology, serum chemistry, and urinalysis samples were collected on Days -10, -3, 20, 41, 62, and Day 76 or 77. Necropsies were performed on Day 76 or 77.

Statistical Methods: For variables measured multiple days during the study, such as hematology, a repeated measures analysis of variance was used to test the effects of treatment, treatment by day, treatment by sex, and treatment by sex by day. For variables measured once, such as organ weights, an analysis was used to test the effects of treatment and treatment by sex. When present, pre-treatment measurements were included as covariates. Follow-up pairwise mean comparisons between the control group and the treated groups were performed, as necessary. For categorical variables, a Fisher's Exact Test was performed by day and treatment.

Results: All dogs remained healthy and gained weight throughout the study. There were no clinically relevant treatment related changes in food consumption, hematology, clinical chemistries, coagulation parameters, urinalyses, necropsies, or histopathology.

The primary clinical signs were gastrointestinal reactions, including soft feces, diarrhea and vomiting, observed within 24 hours of dosing in all groups. Abnormal feces were attributed to a laxative effect produced by the large quantity of chews ingested by dogs in the control and 5X groups.

A significant increase in vomiting ($p = 0.06$) was observed 4 hours post-dosing in the 5X group on 3 out of 6 dosing days. One dog in the 5X group displayed mild salivation associated with vomiting on Day 56 (treatment #5).

Conclusion: This study demonstrates the safety of PANACUR Plus in adult dogs at doses equivalent to the maximum exposure dose for an average adult toy breed dog (3 lbs). Adverse reactions were mild and included soft feces, diarrhea and vomiting.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to PANACUR Plus:

Human Warnings are provided on the product label as follows: "Not for human use. **Keep this and all drugs out of the reach of children.** If accidental ingestion occurs, contact a Poison Control Center or a physician immediately."

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514. The data demonstrate that PANACUR Plus, when used according to the label, is safe and effective for the treatment and control of adult *Toxocara canis* (roundworm), *Ancylostoma caninum* (hookworm), *Trichuris vulpis* (whipworm), and *Dipylidium caninum* (tapeworm) and for the prevention of heartworm disease caused by *Dirofilaria immitis* in adult dogs.

A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise and proper diagnosis are required to determine the existence of heartworm infections and to monitor safe use of the product.

B. Exclusivity:

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval.

C. Patent Information:

The sponsor did not submit any patent information with this application.

VII. ATTACHMENTS:

Facsimile Labeling:

- Package Insert
- Owner Information Bag (Front and Back)
- Blister Label – Small Size (2.16 g) Soft Chew
- Blister Label – Large Size (5.4 g) Soft Chew
- Small Carton Label
- Large Carton Label
- Finished Carton Diagram