Date of Approval: July 9, 2020

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-532

BRAVECTO® 1-MONTH

Fluralaner

Chewable Tablet

Dogs

BRAVECTO® 1-MONTH kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*) and the treatment and control of tick infestations [*Ixodes scapularis* (black-legged tick), *Dermacentor variabilis* (American dog tick) and *Rhipicephalus sanguineus* (brown dog tick)] for one month in dogs and puppies 8 weeks of age and older, and weighing 4.4 pounds or greater.

BRAVECTO® 1-MONTH is also indicated for the treatment and control of *Amblyomma americanum* (lone star tick) infestations for one month in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater.

Sponsored by:

Intervet, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-532

B. Sponsor

Intervet, Inc.
2 Giralda Farms
Madison, NJ 07940

Drug Labeler Code: 000061

C. Proprietary Name

BRAVECTO® 1-MONTH

D. Drug Product Established Name

Fluralaner

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Chewable tablet

G. Amount of Active Ingredient

Each chewable tablet ("chew") contains 45, 100, 200, 400, or 560 mg of fluralaner

H. How Supplied

BRAVECTO® 1-MONTH is available in five strengths (45, 100, 200, 400, and 560 mg fluralaner per chew). Each chew is packaged individually into aluminum foil blister packs sealed with a peelable paper backed foil lid stock. Product may be packaged in 1, 3, or 4 chews per package.

I. Dispensing Status

Rx

J. Dosage Regimen

BRAVECTO® 1-MONTH should be administered orally as a single dose monthly according to the Dosage Schedule below to provide a minimum dose of 4.5 mg/lb (10 mg/kg) fluralaner.

BRAVECTO® 1-MONTH should be administered with food.

Dosage Schedule

Body Weight Ranges (lb)	Fluralaner content (mg)	Chews Administered
4.4 – 9.9	45	One
>9.9 – 22.0	100	One
>22.0 – 44.0	200	One
>44.0 – 88.0	400	One
>88.0 – 123.0*	560	One

*Dogs over 123.0 lb should be administered the appropriate combination of chews

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

BRAVECTO® 1-MONTH kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*) and the treatment and control of tick infestations [*Ixodes scapularis* (black-legged tick), *Dermacentor variabilis* (American dog tick) and *Rhipicephalus sanguineus* (brown dog tick)] for one month in dogs and puppies 8 weeks of age and older, and weighing 4.4 pounds or greater.

BRAVECTO® 1-MONTH is also indicated for the treatment and control of *Amblyomma americanum* (lone star tick) infestations for one month in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater.

II. EFFECTIVENESS

The effectiveness of BRAVECTO® 1-MONTH was demonstrated in one field and nine laboratory studies described below. These studies demonstrated that BRAVECTO® 1-

MONTH is effective against *Ixodes scapularis*, *Rhipicephalus sanguineus*, and *Dermacentor variabilis* tick infestations, and *Ctenocephalides felis* flea infestations, for one month in 8-week-old puppies. These studies also demonstrate that BRAVECTO® 1-MONTH is effective against *Amblyomma americanum* for one month in 6-month-old dogs, but not in 8- or 12-week-old puppies.

The studies conducted to demonstrate the effectiveness of BRAVECTO® chewable tablet for dogs (NADA 141-426, approved May 25, 2014) and BRAVECTO® topical solution for dogs (NADA 141-459, approved July 20, 2016) against *Ixodes scapularis, Dermacentor variabilis,* and *Rhipicephalus sanguineus,* at 48 hours after treatment or infestation, identified *R. sanguineus* as the least susceptible of these three tick species to fluralaner at the 48 hours timepoint. Therefore, the two laboratory studies conducted against *R. sanguineus* in 8-week-old puppies demonstrate the effectiveness of BRAVECTO® 1-MONTH against *R. sanguineus*, as well as *I. scapularis* and *D. variabilis,* 48 hours after treatment or infestation.

A. Dosage Characterization

Studies conducted to demonstrate the effectiveness of BRAVECTO® chewable tablets for dogs (NADA 141-426) and BRAVECTO® topical solution for dogs (NADA 141-459) demonstrated that, for both products, *Amblyomma americanum* was the least susceptible tick species at all timepoints (48 or 72 hours). Additionally, fleas were more susceptible to fluralaner than ticks. Therefore, to determine the oral fluralaner dose required for a one-month treatment interval for fleas and ticks, three studies were conducted against adult *A. americanum* with doses ranging from 2.5 to 10.0 mg/kg. The results of these studies demonstrated consistent effectiveness at the 10 mg/kg dose, but not at doses of 2.5, 5.0, and 7.5 mg/kg, for one month against *A. americanum.* Therefore, a minimum oral dose of 10 mg/kg was selected for BRAVECTO® 1-MONTH.

B. Substantial Evidence

1. Treatment and prevention of flea infestations, dogs 8 weeks and older:

   a. **Title:** Clinical Effectiveness of 5.46% w/w Fluralaner Flavored Chewable Tablets for Dogs against Fleas: A Multi-center Pivotal Field Trial. (Study No. S16367-00)

      Study Dates: April 24, 2017 to January 29, 2019

      Study Locations:
      Cropwell, AL
      Middletown, CT
      Starke, FL
      Springfield, MO
      Quakertown, PA
      Seguin, TX
      Decatur, IL

      Of the seven sites, one (Middletown, CT) did not enroll any cases.

Study Design:
Objective: The field study assessed safety and effectiveness against fleas, signs of flea allergy dermatitis (FAD), and palatability of fluralaner chewable tablets at the recommended minimum dose (10 mg/kg). The study was conducted in accordance with good clinical practice (GCP) guidelines.

Study Animals: 271 client-owned dogs from 149 households; 201 dogs (112 households) treated with fluralaner chewable tablets and 70 dogs (37 households) treated with afoxolaner chewable tablets (active control). The fluralaner group enrolled 100 females and 101 males, 8 weeks to 18.0 years of age, and 4.4 to 145.2 lbs. body weight. The study included purebred and mixed breed dogs.

Enrollment eligibility included: Households with no more than 5 dogs, at least one dog with a minimum of 10 live fleas, and no other pets that could harbor fleas. There were no breed or gender restrictions, but households with pregnant or lactating dogs were not eligible for enrollment. There were restrictions on the use of medications or products with flea treatment to control activity in any household dogs or household premises prior to or during the study period.

Experimental Design: Households were randomly assigned to treatment with fluralaner chewable tablets or the active control in a ratio of three fluralaner households to one control household. Owners treated all dogs in the fluralaner and control groups after Visit 1 on Day 0 and again after Visit 2 and Visit 3 on approximately Days 30 and 60. All dogs were removed from study following Visit 4 on approximately Day 90. A primary dog from each household was randomly selected from dogs with 10 or more live fleas. Only the primary dog was assessed for effectiveness against fleas. Owners administered the treatments and all dogs received the same treatments at the same time.

Investigators who performed flea allergy dermatitis and safety assessments (physical exams, clinical pathology result assessments, and adverse event assessments), and personnel that performed flea counts were masked to treatment. Treatment administrators at each study location and owners were not masked.

Drug Administration: In the fluralaner group, owners administered a fluralaner chewable tablet, at labeled doses, on Days 0, 30, and 60. The fluralaner chewable tablet was administered at mealtime, immediately before the dog was offered its food. Owners were asked to record palatability. If a dog was assigned to receive more than one fluralaner chewable tablet for a single dose, the Palatability Scoring was performed for the entire multi-tablet dose. In the active control group, owners administered an afoxolaner chewable tablet, at labeled doses, on Days 0, 30, and 60.

Measurements and Observations: The primary variable was the difference in live flea counts on the primary dogs on Days 30 (Visit 2), 60 (Visit 3),

and 90 (Visit 4) versus pre-treatment (Visit 1). Additional variables included progression of signs of FAD, recovery of ticks, clinical pathology, and palatability. Statistical analyses were not performed for these additional variables.

Statistical Methods: Log transformed live flea counts {loge(x+1)} from each treatment group were analyzed separately, at each post-treatment time point, using a repeated measures linear mixed model with time as a fixed effect and site and time-by-site interaction as random effects. A significant time effect at a two-sided significance level alpha = 0.05 would indicate a significant difference between the baseline and the post-treatment flea counts. Least squares means from the model analysis were back transformed to obtain the estimates for geometric mean flea counts to calculate percent effectiveness.

Results: For each Visit 2, 3, and 4, the effectiveness of fluralaner chewable tablets, based on geometric means, was greater than 99%.

Tablet II.1: Field Study S16367-00 Effectiveness Against Fleas

Visit	Fluralaner Group	Active Control Group
Visit 1 Number of Primary Dogs	110	37
Visit 1 Geometric Mean Flea Count	50.9	48.8
Visit 2 Number of Primary Dogs	104	34
Visit 2 Geometric Mean Flea Count	0.2	0.5
Visit 2 Percent Effectiveness	99.6%	99.0%
Visit 3 Number of Primary Dogs	102	34
Visit 3 Geometric Mean Flea Count	0.0	0.2
Visit 3 Percent Effectiveness	99.9%	99.5%
Visit 4 Number of Primary Dogs	98	34
Visit 4 Geometric Mean Flea Count	0.0	0.0
Visit 4 Percent Effectiveness	99.9%	100.0%

Note: The geometric means of the live flea counts were obtained by back transforming the least squares means from the mixed models.

Within each treatment group, geometric mean flea counts were significantly different ($P < 0.001$) from Visit 1 at Visits 2, 3, and 4.

At least 90% of the dogs treated with fluralaner chewable tablets with signs attributed to FAD at Visit 1, and not on medications that could affect the assessment of FAD, had resolution of the signs by Visit 4 at Week 12 (Day 90).

Table II.2: Field Study S16367-00 Resolution of Signs of Flea Allergy Dermatitis (FAD)

FAD sign	Percent of Fluralaner Group Dogs with the FAD sign at Visit 1 that was resolved at Visit 4	Percent of Active Control Group Dogs with The FAD sign at Visit 1 that was resolved at Visit 4
Erythema	100% (71/71)	100% (32/32)
Alopecia	93.6% (44/47)	100% (23/23)
Papules	100% (14/14)	100% (6/6)
Scales	100% (20/20)	100% (12/12)
Crusts	90.5% (19/21)	100% (11/11)
Excoriation	100% (29/29)	100% (18/18)

Dogs with signs of FAD showed improvement in erythema, alopecia, papules, scales, crusts, and excoriation as direct result of eliminating flea infestations.

Owners recorded palatability information for 579 doses of fluralaner chewable tablets administered. Owners first offered the fluralaner chewable tablets by hand. If not consumed, they offered the fluralaner chewable tablets in food, and if not consumed they placed the fluralaner chewable tablet in the back of dogs' mouths. Dogs voluntarily consumed 81.5% of the doses offered within five minutes of offering. Four dogs coughed within one hour of dosing with fluralaner.

Table II.3: Field Study S16367-00 Palatability of Fluralaner Chewable Tablets

Stage of Uptake	Number of Doses	Percent of Doses
Free Choice – Within 1 minute of offering	427	73.7%
Free Choice – Within 1 – 5 minutes of offering	45	7.8%
With food or other treat	52	9.0%
Pilled or forced	55	9.5%
Owner unable to dose	0	0.0%
Total	579	100.0%

Adverse Reactions: There were no serious adverse reactions associated with treatment in any of the dogs administered fluralaner chewable tablets or the active control product. Potential adverse reactions are provided in Table II.4. The most frequently reported finding in dogs in both groups was pruritus.

Table II.4: Field Study S16367-00 Adverse Reactions

Adverse Reaction (AR)	Fluralaner Group: Percentage of Dogs with the AR during the 90-Day Study (n= 201 dogs)	Active Control Group: Percentage of Dogs with the AR during the 90-Day Study (n= 70 dogs)
Pruritus	7.0%	10.0%
Diarrhea	3.0%	4.3%
Vomiting	3.0%	4.3%
Decreased Appetite	3.0%	0.0%
Liver enzymes (serum ALT or ALP) greater than twice the upper reference range*	1.0%	1.4%
Lethargy	1.0%	1.4%
Weight loss (>15%)	0.5%	0.0%

*Alanine aminotransferase (ALT); alkaline phosphatase (ALP)

One dog in the BRAVECTO® 1-Month group with a history of seizures managed with anticonvulsant medication had seizure activity 28 days after its first dose; the dog received its second dose later the same day. No additional seizures occurred during the study. One dog in the control group with no history of seizures had seizure activity 12 days after its second dose. The dog was started on anticonvulsant medication and no additional seizures occurred during the study.

Conclusion: This study demonstrated that fluralaner chewable tablets were safe and effective for the treatment and prevention of flea infestations when administered monthly to client-owned dogs and puppies at labeled doses.

2. Treatment and prevention of flea infestations, dogs 6 months of age and older:

   a. **Title:** Efficacy, Prevention of Infestation, and Speed of Kill of 5.46% w/w Fluralaner Chewable Tablets for Dogs against Infestations of *Ctenocephalides felis* in Dogs. (Study No. S16375-00)

   Study Dates: April 2017 to March 2018

   Study Location: Turlock, CA, USA

   Study Design:

   Objective: To confirm the effectiveness and speed of kill of fluralaner chewable tablets at the recommended minimum dose (10 mg/kg) to kill adult fleas (*C. felis*) and prevent and treat flea infestations in dogs. The

study was conducted in accordance with Good Clinical Practice (GCP) guidelines.
Study Animals: 40 healthy dogs (pure and mixed breed, 22 males and 18 females), 3.2 to 11.1 years of age, and 8.4 to 16.9 kg body weight.

Experimental Design: Prior to allocation to treatment groups on Day -8, an initial flea infestation and count was conducted to evaluate susceptibility of each dog to experimental infestation (host suitability). Dogs were ranked and blocked by live flea count, and one dog from each block was randomly assigned to one of two untreated control groups (10 dogs/group) or one of two fluralaner (10 dogs/group) treatment groups.

Drug administration was on Day 0. Flea infestations were conducted on Days -1, 7, 14, 21, 28, 35, 42, and 49. At each infestation, each dog was infested with approximately 100 unfed adult fleas. Flea counts were conducted on Days 0, 7, 14, 21, 28, 35, 42, and 49 and Days 1, 8, 15, 22, 29, 36, 43, and 50 for the 12-hour and 24-hour groups, respectively. Fleas were not returned to the dog after counting.

Table II.5: Study S16375-00 Treatment Groups

Treatment Group	Treatment (Minimum Dose)	Number and Gender of Animals	Time of Post-Treatment or Infestation Flea Count
1	**Control (0 mg/kg)**	**10 (4 M, 6 F)**	**12 hours**
2	**Fluralaner (10 mg/kg)**	**10 (5 M, 5 F)**	**12 hours**
3	**Control (0 mg/kg)**	**10 (5 M, 5 F)**	**24 hours***
4	**Fluralaner (10 mg/kg)**	**10 (8 M, 2 F)**	**24 hours***

*Egg counts were also conducted.

Drug Administration: On Day 0, the 20 dogs in the fluralaner groups were administered one to three whole fluralaner chewable tablets, at doses as close as possible to 10 mg/kg without under-dosing. Doses ranged from 9.9 to 12.8 mg/kg per dog. The chewable tablets were administered by placement on the back of the dog's tongue (pilling) within 20 minutes after food had been offered. Dogs in the control group were sham-dosed.

Measurements and Observations: The primary variable for effectiveness was the counts of live fleas collected from the dogs. The secondary variable for effectiveness was the flea egg counts. At flea counts on Days 0, 7, 14, 21, 28, 35, 42, and 49 and Days 1, 8, 15, 22, 29, 36, 43, and 50 for the 12-hour and 24-hour groups, respectively, fleas were removed, and the numbers of live fleas recorded. Additionally, for the Group 3 and 4 dogs assessed at the 24-hour time points, flea eggs were collected for

approximately 24 hours post-treatment or infestation (Days 1, 8, 15, 22, 29, and 36). Following collection, eggs were counted, placed in a petri dish containing flea media, incubated for 35 days and the number of adult fleas which emerged was determined. General health observations were conducted daily and at approximately 1, 3, 6, and 24 hours following drug administration. Dogs were weighed on Day -1 for dose calculations. Flea counts, egg counts, and health observations were conducted masked to treatment.

Statistical Methods: A linear mixed model analysis was used to analyze log-transformed flea counts at each evaluation time point, with treatment group as a fixed effect and the allocation blocks as a random effect. The comparisons of each fluralaner group with its paired control group were tested using a two-sided 5% significance level. Percent effectiveness against the control group was calculated based on arithmetic means. Effectiveness for the prevention indication was concluded if egg counts from the fluralaner group dogs were essentially zero on Day 8 and later (eggs present on Day 1 were not deemed as a lack of effectiveness) in the face of robust egg production from the control dogs.

Results: At each flea count day, all 20 dogs in the 12-hour control group and the 24-hour control group had an adequate infestation, defined as at least 50 live fleas (50% of the infestations of 100 fleas per dog).

The 12-hour fluralaner group had greater than 90% reduction in live flea counts at 12 hours following treatment or infestation for 49 days (infestation on Day 49) compared to the corresponding control group. On all count days following drug administration, live flea counts between the two groups were significantly different ($p < 0.0001$).

Table II.6: Speed of Kill S16375-00 Live Flea Count and Percent Effectiveness, 12-hour Counts

Day for 12-hour Counts	Control Group Flea Counts*	Fluralaner Group Flea Counts*	Percent Effectiveness
0	78.2	0.0	100
7	86.8	0.0	100
14	78.0	0.2	99.7
21	81.7	0.6	99.3
28	77.3	0.6	99.2
35	84.8	0.7	99.2
42	80.8	1.2	98.5
49	85.5	3.6	95.8

*Flea counts are arithmetic means and percent effectiveness is based on arithmetic means.

The 24-hour fluralaner group had greater than 90% reduction in live flea counts at 24 hours following treatment or infestation for 50 days (infestation on Day 49) compared to the corresponding control group. On all count days following drug administration, live flea counts between the

fluralaner treated group and the control group were significantly different ($p < 0.0001$). Flea egg counts demonstrated a significant difference ($p < 0.0001$) between the two groups and was numerically reduced in the fluralaner group.

Table II.7: Speed of Kill S16375-00 Live Flea Count and Percent Effectiveness, 24-hour Counts

Day for 24-hour Counts	Control Group Flea Counts*	Fluralaner Group Flea Counts*	Percent Effectiveness
1	72.6	0.0	100
8	80.2	0.0	100
15	72.7	0.0	100
22	73.2	0.0	100
29	71.4	0.0	100
36	75.7	0.0	100
43	73.9	0.0	100
50	80.9	0.0	100

*Flea counts are arithmetic means and percent effectiveness is based on arithmetic means.

Table II.8: Speed of Kill S16375-00 Flea Egg Counts, 24-hour Counts

Day of Egg Collection	Control Group Flea Egg Counts (Range)*	Fluralaner Group Flea Egg Counts (Range)*
1	44.1 (6 – 104)	5.0 (0 – 18)
8	19.5 (0 – 63)	0.0
15	36.5 (0 – 90)	0.0
22	33.1 (1 – 81)	0.0
29	48.2 (0 – 138)	0.0
36	40.2 (1 – 91)	0.0

*Flea counts are arithmetic means.

Adverse Reactions: At approximately 1 hour following administration, a dog in the 24-hour fluralaner group was observed to have diarrhea. No treatment to address the diarrhea was administered and the dog returned to normal without treatment.

Conclusion: This study demonstrated the effectiveness of fluralaner chewable tablets for the treatment of existing flea infestations for 50 days when assessed 12 and 24 hours after drug administration or infestation. The study also demonstrated that fluralaner chewable tablets prevent flea infestations by killing fleas before they can lay eggs. Diarrhea should be considered a drug-related adverse reaction.

b. **Title:** Determination of the Onset of Activity of 5.46% w/w Fluralaner Chewable Tablets for Dogs against Fleas (*Ctenocephalides felis*) on Dogs 4

Hours After Oral Treatment, at a Dose of 10 mg/kg Body Weight. (Study No. S17177-00)

Study Dates: September 2017 to January 2018

Study Location: Bloemfontein, South Africa

Study Design:

Objective: To confirm the onset of activity of fluralaner chewable tablets at the recommended minimum dose (10 mg/kg) to kill adult fleas (*C. felis*) in dogs. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Study Animals: 20 healthy dogs (pure and mixed breed, 10 males and 10 females), 1.0 to 7.0 years of age, and 11.0 to 20.6 kg body weight.

Experimental Design: Prior to allocation to treatment groups on Day -5, an initial flea infestation and count was conducted to evaluate susceptibility of each dog to experimental infestation (host suitability). Dogs were randomly assigned to the untreated control group (10 dogs) or the fluralaner group (10 dogs), stratified by sex. Dogs were randomly allocated to two study rooms.

Drug administration was on Day 0. Flea infestations were conducted on Day -1. Each dog was infested with approximately 100 unfed adult fleas. Flea counts were conducted at 4 hours following drug administration. Fleas were not returned to the dog after counting.

Drug Administration: On Day 0, the ten dogs in the fluralaner group were administered one to three whole fluralaner chewable tablets, at doses as close as possible to 10 mg/kg without under-dosing. Doses ranged from 10.9 to 13.2 mg/kg per dog. The chewable tablets were administered by placement on the back of the dog's tongue (pilling) within 20 minutes after food had been offered. Dogs in the control group were sham-dosed.

Measurements and Observations: The primary variable for effectiveness was the counts of live fleas collected from the dogs. At the flea count on Day 0, fleas were removed, and the numbers of live fleas recorded. General health observations were conducted daily. Dogs were weighed on Day -2 for dose calculations. Flea counts and health observations were conducted by individuals masked to treatment.

Statistical Methods: A linear mixed model analysis was used to analyze the live flea counts, with treatment, sex, sex-by-treatment as fixed factors; room as a random factor; and pre-treatment flea counts as a covariate. The comparison of the fluralaner group with the control group was tested using a two-sided 5% significance level. Percent effectiveness against the control group was calculated based on arithmetic means.

Results: All 10 dogs in the control group had an adequate infestation, defined as at least 50 live fleas (50% of the infestations of 100 fleas per dog). At four hours after drug administration, the live flea count in the fluralaner group was significantly different from the control group ($p < 0.0001$).

Table II.9: Speed of Kill S17177-00 Live Flea Count and Percent Effectiveness

Time of Flea Count after Dosing	Control Group Flea Counts*	Fluralaner Group Flea Counts*	Percent Effectiveness
4 hours	70.2	11.7	83.3

*Flea counts are arithmetic means and percent effectiveness is based on arithmetic means.

Adverse Reactions: No adverse reactions were reported in this study.

Conclusion: This study demonstrated the onset of activity of fluralaner chewable tablets to kill adult fleas in 4 hours after drug administration.

3. Treatment and prevention of flea infestations, dogs and puppies 8 weeks of age and older:

   a. **Title:** Efficacy of 5.46% w/w Fluralaner Chewable Tablets for Dogs against Infestations of *Rhipicephalus sanguineus* and *Ctenocephalides felis* in Growing Puppies. (Study No. S17215-00)

   Study Dates: December 2017 to January 2019

   Study Location: Turlock, CA, USA

   Study Design:

   Objective: To confirm the effectiveness of fluralaner chewable tablets at the recommended minimum dose (10 mg/kg) to kill adult fleas (*C. felis*) and for the treatment and control of infestations of *R. sanguineus* in growing puppies, starting at 8 or 12 weeks of age. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

   Study Animals: 40 healthy puppies (mixed breed, 19 males and 21 females). The puppies in the 8-week-old group ranged from 7.9 to 8.9 weeks of age, and 3.9 to 5.9 kg body weight. The puppies in the 12-week-old group ranged from 11.3 to 12.9 weeks of age, and 6.5 to 10.1 kg body weight.

   Experimental Design: Prior to allocation to treatment groups by age category (8- and 12-week-old) on Day -5, puppies were randomly assigned to one of two untreated control groups (10 puppies/group) or one of two fluralaner (10 puppies/group) treatment groups.

Drug administration was on Day 0. Flea infestations were conducted on Days -1 and 28. At each infestation, each puppy was infested with approximately 100 unfed adult fleas. Flea counts were conducted on all puppies on Day 2 (48 hours post-treatment) and on Day 30

Tick infestations were conducted on Days -2, 7, 14, 21, and 28. At each infestation, each puppy was infested with approximately 50 adult, unfed *R. sanguineus* ticks. Tick counts were performed on Day 2, 48 hours after drug administration, and on Days 9, 16, 23, and 30, 48 hours after tick infestations.

Fleas and ticks were not returned to the puppy after counting.

Drug Administration: On Day 0, the 20 puppies in the fluralaner groups were administered one or two whole fluralaner chewable tablets, at doses as close as possible to 10 mg/kg without under-dosing. Doses ranged from 10.2 to 19.8 mg/kg and 10.2 to 14.4 mg/kg for 8- and 12-week old puppies, respectively. The chewable tablets were administered by placement on the back of the puppy's tongue (pilling) within 20 minutes after food had been offered. Puppies in the control groups were sham-dosed.

Measurements and Observations: The primary variables for effectiveness were the counts of live fleas and ticks collected from the puppies. At flea counts on Days 2 and 30, and tick counts on Days 2, 9, 16, 23, and 30, fleas and ticks were removed, and the numbers of live fleas and live and dead ticks were recorded. General health observations were conducted daily, and at approximately 1, 3, and 6 hours following drug administration. Puppies were weighed on Day -5 for dose calculations. Flea and tick counts and health observations were conducted masked to treatment.

Statistical Methods: A linear mixed model analysis was used to analyze log-transformed flea and tick counts at each evaluation time point, with treatment group as a fixed effect, at a two-sided 5% significance level. Percent effectiveness against the control group was calculated based on arithmetic means.

Results: At each flea count day, at least 9 of the 10 puppies in each control group had an adequate infestation, defined as at least 50 live fleas (50% of the infestations of 100 fleas per puppy). At each tick count day, all 20 puppies in both control groups had an adequate infestation, defined as at least 13 live *R. sanguineus* ticks (25% of the infestations of 50 ticks per puppy).

The 8- and 12-week-old fluralaner groups had greater than 90% reduction in live flea counts at 48 hours following treatment or infestation for 30 days (infestation on Day 28) and greater than 90% reduction in live tick counts at 48 hours following treatment or infestation for 30 days (infestation on Day 28) compared to the corresponding control groups.

On all count days following drug administration, live flea and tick counts for the 8- and 12-week-old fluralaner groups were significantly different ($p < 0.0001$) from the corresponding control groups.

Table II.10: *C. felis* S17215-00 Live Flea Count and Percent Effectiveness, 8-week-old Puppies

Day for Flea Counts	Control Group Live Flea Counts*	Fluralaner Group Live Flea Counts*	Percent Effectiveness
2	82.7	0.0	100
30	83.8	0.0	100

*Flea counts are arithmetic means and percent effectiveness is based on arithmetic means.

Table II.11: *C. felis* S17215-00 Live Flea Count and Percent Effectiveness, 12-week-old Puppies

Day for Flea Counts	Control Group Live Flea Counts*	Fluralaner Group Live Flea Counts*	Percent Effectiveness
2	81.4	0.0	100
30	75.8	0.0	100

*Flea counts are arithmetic means and percent effectiveness is based on arithmetic means.

Table II.12: *R. sanguineus* S17215-00 Live Tick Count and Percent Effectiveness, 8-week-old Puppies

Day for Tick Counts	Control Group Live Tick Counts*	Fluralaner Group Live Tick Counts*	Percent Effectiveness
2	40.5	0.0	100
9	40.3	0.0	100
16	46.8	0.2	99.6
23	43.4	0.2	99.5
30	47.0	1.1	97.7

*Tick counts are arithmetic means and percent effectiveness is based on arithmetic means.

Table II.13: *R. sanguineus* S17215-00 Live Tick Count and Percent Effectiveness, 12-week-old Puppies

Day for Tick Counts	Control Group Live Tick Counts*	Fluralaner Group Live Tick Counts*	Percent Effectiveness
2	39.7	0.0	100
9	29.6	0.0	100
16	37.5	0.0	100
23	33.7	0.0	100
30	41.5	0.1	99.8

*Tick counts are arithmetic means and percent effectiveness is based on arithmetic means.

On all count days following drug administration, dead tick counts for the 8- and 12-week-old fluralaner groups were significantly different from the corresponding control groups ($p \leq 0.0103$).

Table II.14: *R. sanguineus* S17215-00 Dead Tick Count Results, 8-week-old Puppies

Day for Tick Counts	Control Group Dead Tick Counts*	Fluralaner Group Dead Tick Counts*
2	0.0	6.0
9	0.0	0.8
16	0.0	1.9
23	0.0	1.0
30	0.0	1.3

*Tick counts are arithmetic means.

Table II.15: *R. sanguineus* S17215-00 Dead Tick Count Results, 12-week-old Puppies

Day for Tick Counts	Control Group Dead Tick Counts*	Fluralaner Group Dead
2	0.0	6.8
9	0.0	3.1
16	0.0	2.1
23	0.0	4.1
30	0.0	3.6

*Tick counts are arithmetic means.

Adverse Reactions: No adverse reactions were reported in this study.

Conclusion: This study demonstrated the effectiveness of fluralaner for the treatment of existing flea infestations for 30 days when assessed 48 hours after drug administration or infestation in both 8- and 12- week-old growing puppies. This study also demonstrated that fluralaner killed 100% of adult fleas at each time point, thus contributing to the prevention of flea infestations. This study demonstrated the effectiveness of fluralaner for the control (reduced live ticks) and treatment (increased dead ticks) of *R. sanguineus* for 30 days when assessed at 48 hours after drug administration or infestation in both 8- and 12- week-old growing puppies.

b. Prevention of flea infestations in dogs and puppies 8 weeks of age and older:

In the laboratory dose confirmation study (Study No. S16375-00), all dogs were infested with fleas on Day -1, 7, 14, 21, 28, 35, 42, and 49. Treatment with fluralaner was administered on Day 0. During this initial onset of effectiveness, fleas from dogs in both the fluralaner and control groups generated eggs (0-18 eggs, and 6–104 eggs at 24 hours post-treatment, respectively). At subsequent evaluations, fleas from dogs in

the fluralaner group produced no eggs, while fleas from dogs in the control group continued to produce eggs (0-138 eggs). Therefore, any adult fleas that hatched from the eggs generated immediately post-treatment and infested a treated dog would be killed, thus inhibiting the perpetuation of the flea infestation. Because female fleas initiate egg laying 24 to 36 hours after their initial blood meal (Dryden, 1989[1]), any subsequent generations of adult fleas that infested a treated dog would be killed before they are able to lay eggs, thus inhibiting the perpetuation of the flea infestation.

In the laboratory dose confirmation study (Study No. S17215-00), 8- and 12-week-old puppies were infested with fleas on Day -1 and Day 28, and treatment with fluralaner was administered on Day 0. During this time, the fleas had the ability to initiate feeding, mate, and start laying eggs. At all-time points, 100% of the fleas from puppies in both groups administered fluralaner were killed. Therefore, any adult fleas that hatched from the eggs generated immediately post-treatment and infested a treated dog would be killed, thus preventing flea infestations. Because fluralaner killed 100% of the fleas at all time points, fluralaner has prevented an infestation.

Additionally, the field study supporting substantial evidence of effectiveness for the flea indication (Study No. S16367-00) was conducted in households with existing flea infestations of varying severity. After fluralaner was initially administered, dogs were likely re-infested with adult fleas generated from the pre-adult stages already present in the environment or from adult fleas in different environments. At that point, the study evaluated the perpetuation of flea infestations. Because the field study demonstrated continued effectiveness of fluralaner against fleas, this study confirmed that fluralaner inhibited flea infestations on dogs and puppies.

Collectively, data from the laboratory dose confirmation studies (Study No. S17215-00 and S16375-00) and the field effectiveness study (Study No. S16367-00) support the effectiveness of BRAVECTO® 1-Month (fluralaner) for the prevention of flea (*C. felis*) infestations on puppies 8 weeks of age and older.

4. Treatment and control of tick infestations, dogs and puppies 6 months of age and older:

   a. **Title:** Efficacy of 5.46% w/w Fluralaner Chewable Tablets for Dogs against Infestations of *Amblyomma americanum* in dogs. (Study No. S16373-00)

      Study Dates: April 2017 to March 2018

      Study Location: Greenbrier, AR, USA

[1] Dryden, M.W. 1989. Biology of the cat flea, *Ctenocephalides felis felis*. Companion Anim. Prac. 19:23-27

Study Design:

Objective: To confirm the effectiveness of fluralaner chewable tablets at the recommended minimum dose (10 mg/kg) for the treatment and control of infestations of *A. americanum* in dogs. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Study Animals: 20 healthy dogs (pure and mixed breed; 10 males and 10 females), 3.8 to 5.4 years of age, and 6.7 to 13.7 kg body weight.

Experimental Design: Prior to allocation to treatment groups on Day -6, an initial tick infestation and count was conducted to evaluate susceptibility of each dog to experimental infestation (host suitability). Dogs were ranked and blocked by live tick count, and one dog from each block was randomly assigned to the untreated control (10 dogs) or the fluralaner (10 dogs) treatment group.

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 7, 14, 21, 28, 35, 42, and 49. At each infestation, each dog was infested with approximately 50 adult, unfed *A. americanum* ticks. Tick counts were conducted on Day 3, 72 hours following drug administration, and on Days 10, 17, 24, 31, 38, 45, and 52, 72 hours after tick infestations. Ticks were not returned to the dog after counting.

Drug Administration: On Day 0, the ten dogs in the fluralaner group were administered one or two whole fluralaner chewable tablets, at doses as close as possible to 10 mg/kg without under-dosing. Doses ranged from 10.0 to 13.4 mg/kg per dog. The chewable tablets were administered by placement on the back of the dog's tongue (pilling) within 20 minutes after food had been offered. Dogs in the control group were sham-dosed.

Measurements and Observations: The primary variable for effectiveness was the counts of live ticks collected from the dogs. At tick counts on Days 3, 10, 17, 24, 31, 38, 45, and 52, ticks were removed, and the numbers of live and dead ticks were recorded. General health observations were conducted daily, and at approximately 1, 3, 6, and 24 hours following drug administration. Dogs were weighed on Day -6 for dose calculations. Tick counts and health observations were conducted masked to treatment.

Statistical Methods: A linear mixed model analysis was used to analyze log-transformed tick counts at each evaluation time point, with treatment group as a fixed effect and the allocation blocks as a random effect, at a two-sided 5% significance level. Percent effectiveness against the control group was calculated based on arithmetic means.

Results: At each tick count day, at least 9 of the 10 dogs in the control group each had an adequate infestation, defined as at least 13 live *A. americanum* ticks (25% of the infestations of 50 ticks per dog).

The fluralaner group had greater than 90% reduction in live tick counts at 72 hours following treatment or infestation for 31 days (infestation on Day 28) compared to the control group. On all count days following drug administration, live tick counts for the fluralaner group were significantly different ($p < 0.0001$) from the control group.

Table II.16: *A. americanum* S16373-00 Live Tick Count and Percent Effectiveness

Day for Tick Counts	Control Group Live Tick Counts*	Fluralaner Group Live Tick Counts*	Percent Effectiveness
3	30.5	0.0	100
10	28.6	0.1	99.7
17	22.5	0.0	100
24	22.8	0.5	97.8
31	28.1	0.6	97.9
38	30.0	4.3	85.7
45	30.4	7.0	77.0
52	24.2	4.3	86.2

*Tick counts are arithmetic means and percent effectiveness is based on arithmetic means.

On all count days following drug administration, dead tick counts for the fluralaner group were significantly different from the control group ($p < 0.0001$).

Table II.17: *A. americanum* S16373-00 Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts*	Fluralaner Group Dead Tick Counts*
3	0.0	11.6
10	0.0	8.7
17	0.0	6.5
24	0.0	15.2
31	0.0	13.4
38	0.0	14.3
45	0.0	11.3
52	0.0	11.2

*Tick counts are arithmetic means.

Adverse Reactions: No adverse reactions were reported in this study.

Conclusion: This study demonstrated the effectiveness of fluralaner chewable tablets for the control (reduced live ticks) and treatment (increased dead ticks) of *A. americanum* ticks for 31 days when assessed at 72 hours after drug administration or infestation.

b. **Title:** Efficacy of 5.46% w/w Fluralaner Chewable Tablets for Dogs against Infestations of *Amblyomma americanum* in Dogs. (Study No. S16374-00)

Study Dates: April 2017 to March 2018

Study Location: Canyon, TX, USA

Study Design:

Objective: To confirm the effectiveness of fluralaner chewable tablets at the recommended minimum dose (10 mg/kg) for the treatment and control of infestations of *A. americanum* in dogs. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Study Animals: 20 healthy dogs (Beagles; 10 males and 10 females), 1.7 to 7.1 years of age, and 6.1 to 13.1 kg body weight.

Experimental Design: Prior to allocation to treatment groups on Day -8, an initial tick infestation and count was conducted to evaluate susceptibility of each dog to experimental infestation (host suitability). Dogs were ranked and blocked by live tick count, and one dog from each block was randomly assigned to the untreated control group (10 dogs) or the fluralaner (10 dogs) treatment group.

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 7, 14, 21, 28, 35, 42, and 49. At each infestation, each dog was infested with approximately 50 adult, unfed *A. americanum* ticks. Tick counts were conducted on Day 3, 72 hours following drug administration, and on Days 10, 17, 24, 31, 38, 45, and 52, 72 hours after tick infestations. Ticks were not returned to the dog after counting.

Drug Administration: On Day 0, the ten dogs in the fluralaner group were administered one or two whole fluralaner chewable tablets, at doses as close as possible to 10 mg/kg without under-dosing. Doses ranged from 10.0 to 13.9 mg/kg per dog. The chewable tablets were administered by placement on the back of the dog's tongue (pilling) within 20 minutes after food had been offered. Dogs in the control group were sham-dosed.

Measurements and Observations: The primary variable for effectiveness was the counts of live ticks collected from the dogs. At tick counts on Days 3, 10, 17, 24, 31, 38, 45, and 52, ticks were removed, and the numbers of live and dead ticks were recorded. General health observations were conducted daily, and at approximately 1, 3, 6, and 24 hours following drug administration. Dogs were weighed on Day -8 for dose calculations. Tick counts and health observations were conducted masked to treatment.

Statistical Methods: A linear mixed model analysis was used to analyze log-transformed tick counts at each evaluation time point, with treatment group as a fixed effect and the allocation blocks as a random effect, at a two-sided 5% significance level. Percent effectiveness against the control group was calculated based on arithmetic means.

Results: At each tick count day, at least 6 of the 10 dogs in the control group each had an adequate infestation, defined as at least 13 live *A. americanum* ticks (25% of the infestations of 50 ticks per dog).

The fluralaner group had greater than 90% reduction in live tick counts at 72 hours following treatment or infestation for 31 days (infestation on Day 28) compared to the control group. On all count days following drug administration, live tick counts for the fluralaner group were significantly different ($p < 0.0040$) from the control group.

Table II.18: *A. americanum* S16374-00 Live Tick Count and Percent Effectiveness

Day for Tick Counts	Control Group Live Tick Counts*	Fluralaner Group Live Tick Counts*	Percent Effectiveness
3	16.7	0.0	100
10	16.0	0.0	100
17	13.8	0.0	100
24	13.5	0.7	94.8
31	16.6	0.6	96.4
38	16.3	2.3	85.9
45	20.0	4.4	78.0
52	14.6	6.0	58.9

*Tick counts are arithmetic means and percent effectiveness is based on arithmetic means.

On all count days following drug administration, dead tick counts for the fluralaner group were significantly different from the control group ($p < 0.0102$).

Table II.19: *A. americanum* S16374-00 Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts*	Fluralaner Group Dead
3	0.4	8.8
10	0.2	4.1
17	0.1	4.1
24	0.3	5.0
31	0.6	5.8
38	0.3	7.5
45	0.3	4.9
52	0.7	2.8

*Tick counts are arithmetic means.

Adverse Reactions: No adverse reactions were reported in this study.

Conclusion: This study demonstrated the effectiveness of fluralaner chewable tablets for the control (reduced live ticks) and treatment (increased dead ticks) of *A. americanum* ticks for 31 days when assessed at 72 hours after drug administration or infestation.

5. Treatment and Control of Tick Infestations, dogs and puppies 8 weeks of age and older:

   a. Refer to Study S17215-00 (Section II.B.3.a) entitled Efficacy of 5.46% w/w Fluralaner Chewable Tablets for Dogs against Infestations of *Rhipicephalus sanguineus* and *Ctenocephalides felis* in Growing Puppies.

   b. **Title:** Efficacy of 5.46% w/w Fluralaner Chewable Tablets for Dogs against Infestations of *Rhipicephalus sanguineus* in Growing Puppies. (Study No. S17233-00)

      Study Dates: October 2017 to August 2018

      Study Location: Bloemfontein, South Africa

      Study Design:

      Objective: To confirm the effectiveness of fluralaner chewable tablets at the recommended minimum dose (10 mg/kg) for the treatment and control of infestations of *R. sanguineus* in growing puppies, starting at 8 or 12 weeks of age. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

      Study Animals: 40 healthy puppies (pure and mixed breed; 16 males and 24 females). The puppies in the 8-week-old group ranged from 7.6 to 9.0 weeks of age, and 2.0 to 4.1 kg body weight. The puppies in the 12-week-old group ranged from 11.7 to 12.7 weeks of age, and 2.9 to 6.9 kg body weight.

      Experimental Design: Prior to allocation to treatment groups by age category (8- and 12-week-old) on Day -6, -5, or -4, puppies were ranked and blocked by weight within sex and randomly assigned to one of two untreated control groups or one of two fluralaner groups. Each group contained 10 puppies.

      Drug administration was on Day 0. Tick infestations were conducted on Days -2, 7, 14, 21, and 28. At each infestation, each puppy was infested with approximately 50 adult, unfed *R. sanguineus* ticks. Tick counts were performed on Day 2, 48 hours after drug administration, and on Days 9, 16, 23, and 30, 48 hours after tick infestations. Ticks were not returned to the puppy after counting.

      Drug Administration: On Day 0, the 20 puppies in the fluralaner groups were administered one to two whole fluralaner chewable tablets, at doses as close as possible to 10 mg without under-dosing. Doses ranged from 11.2 to 21.4 mg/kg and 11.2 to 18.6 mg/kg for 8- and 12-week old puppies, respectively. The chewable tablets were administered by placement on the back of the puppy’s tongue (pilling) within 20 minutes after food had been offered. Puppies in the control groups were sham-dosed.

Measurements and Observations: The primary variable for effectiveness was the counts of live ticks collected from the puppies. At tick counts on Days 2, 9, 16, 23, and 30, ticks were removed, and the numbers of live and dead ticks were recorded. General health observations were conducted daily, and at approximately 1, 3, and 6 hours following drug administration. Puppies were weighed on either Day -2 or Day -1 for dose calculations. Tick counts and health observations were conducted masked to treatment.

Statistical Methods: For each age category, a linear mixed model analysis was used to analyze log-transformed tick counts at each evaluation time point, with treatment group, sex, and sex by treatment as fixed effects and phase and block within phase by sex interaction as random effects, at a two-sided 5% significance level. Percent effectiveness against the control group was calculated based on arithmetic means.

Results: At each tick count day, at least 8 of the 10 puppies in each control group had an adequate infestation, defined as at least 13 live *R. sanguineus* ticks (25% of the infestations of 50 ticks per puppy).

The 8- and 12-week-old fluralaner groups had greater than 90% reduction in live tick counts at 48 hours following treatment or infestation for 30 days (infestation on Day 28) compared to the corresponding control groups. On all count days following drug administration, live tick counts for the 8- and 12-week-old fluralaner groups were significantly different ($p < 0.0001$) from the corresponding control groups.

Table II.20: *R. sanguineus* S17233-00 Live Tick Count and Percent Effectiveness, 8-week-old Puppies

Day for Tick Counts	Control Group Live Tick Counts*	Fluralaner Group Live Tick Counts*	Percent Effectiveness
2	35.2	0.0	100
9	23.7	0.0	100
16	29.7	0.1	99.6
23	38.0	0.4	98.8
30	32.1	0.0	100

*Tick counts are arithmetic means and percent effectiveness is based on arithmetic means.

Table II.21: *R. sanguineus* S17233-00 Live Tick Count and Percent Effectiveness, 12-week-old Puppies

Day for Tick Counts	Control Group Live Tick Counts*	Fluralaner Group Live Tick Counts*	Percent Effectiveness
2	34.9	0.0	100
9	33.4	0.0	100
16	33.2	0.0	100
23	22.8	0.1	99.5
30	26.2	0.0	100

*Tick counts are arithmetic means and percent effectiveness is based on arithmetic means.

On Days 2, 9, and 16 following drug administration, dead tick counts for the 8-week-old fluralaner groups were significantly different from the control group ($p \leq 0.0010$). On all count days following drug administration, dead tick counts for the 12-week-old fluralaner groups were significantly different from the control group ($p \leq 0.0174$).

Table II.22: *R. sanguineus* S17233-00 Dead Tick Count Results, 8-week-old Puppies

Day for Tick Counts	Control Group Dead Tick Counts*	Fluralaner Group Dead Tick Counts*
2	0.0	2.7
9	0.1	3.9
16	0.2	1.1
23	0.4	0.7
30	0.0	0.1

*Tick counts are arithmetic means

Table II.23: *R. sanguineus* S17233-00 Dead Tick Count Results, 12-week-old Puppies

Day for Tick Counts	Control Group Dead Tick Counts*	Fluralaner Group Dead
2	0.6	4.0
9	0.2	4.8
16	0.0	1.7
23	0.0	1.1
30	0.0	0.8

*Tick counts are arithmetic means

Adverse Reactions: No adverse reactions were reported in this study.

Conclusion: This study demonstrated the effectiveness of fluralaner for the control (reduced live ticks) and treatment (increased dead ticks) of *R. sanguineus* ticks for 30 days when assessed at 48 hours after drug administration or infestation in 8- and 12-week-old growing puppies.

c. ***Amblyomma americanum* studies (S17214-00, S19023-00, S17232-00):**

In two well-controlled laboratory studies, fluralaner was 30% and 56% effective against *A. americanum* in 8- and 12-week-old puppies, respectively, and 46% effective in 8-week-old puppies at 31 days. In another well-controlled laboratory study, fluralaner was ≥ 93.2% effective against *A. americanum* in 8- and 12-week-old puppies for 31 days. In one study, with 20 treated 8- and 12-week-old puppies, two 8-week-old and one 12-week-old puppy had bloody diarrhea on Days 2-3 and Day 1, respectively.

III. TARGET ANIMAL SAFETY

The safety of BRAVECTO® 1-MONTH was demonstrated in one three-month laboratory margin of safety study, described below, and the laboratory and field effectiveness studies, described above. The purpose of the margin of safety study was to evaluate the safety of fluralaner chewable tablets when administered at a maximum dose of 22.5 mg/kg to 8-week-old puppies. Observations possibly related to BRAVECTO® 1-MONTH (fluralaner) chewable tablets include vomiting, diarrhea, mucoid or discolored stool, trembling, tremors, splayed hind limbs, mandibular lymphadenopathy, abdominal distention, increased serum alanine aminotransferase (ALT), increased blood urea nitrogen (BUN) and serum creatinine values, and pituitary cysts. Mild, self-limiting gastrointestinal adverse reactions were reported in 4 dogs and puppies administered a minimum dose of 10 mg/kg in the laboratory effectiveness studies. In the field study, the most common adverse reactions were pruritus, diarrhea, vomiting, decreased appetite, lethargy, weight loss and elevated serum alanine aminotransferase (ALT) and alkaline phosphatase (ALP) enzymes.

These studies support the safe use of BRAVECTO® 1-MONTH (fluralaner) chewable tablets in dogs when used at the labeled dose and duration.

A. Margin of Safety Study

Title: 92-Day Oral Target Animal Safety Study of 5.46% w/w Fluralaner Chewable Tablets for Dogs. (Study Number: S16278-00-IMO-TAS-CN)

Study Dates: May 2017 to December 2018

Study Location: Mattawan, Michigan, USA

Study Design:

Objective: To assess the safety of fluralaner chewable tablets following oral administration at doses of 1X, 3X, and 5X the maximum labeled dose of 22.5 mg/kg to 8-week-old Beagles three times at one-month intervals. The study was conducted in accordance with Good Laboratory Practice (GLP) Regulations.

Study Animals: 32 healthy, weaned puppies (Beagles; 16 male and 16 female), 57-59 days of age, and 1.6 to 2.9 kg body weight.

Experimental Design: Dogs were randomized to one of four treatment groups of eight dogs per group (four per sex) stratified by sex, room and litter. Dogs were either administered fluralaner chewable tablets at 1X, 3X, and 5X the maximum labeled dose of 22.5 mg/kg, three times at one-month intervals (Days 1, 31, and 61) or were sham dosed (control group).

Drug Administration: Dogs were fed prior to drug administration. An appropriate number of fluralaner chewable tablets were placed on the back of each dog's tongue, after which dogs were administered approximately 5 mL of tap water using a syringe to facilitate swallowing.

Measurements and Observations: Cage side observations were conducted twice daily; detailed clinical examination were conducted weekly; post-dose cage side clinical examination were conducted during one hour after dosing; clinical assessments were conducted on Days -10, -1, and at approximately 1, 2, 4, and 8 hours post-dose on Days 1, 31, and 61; physical examinations were conducted on Days -13, -7, -1, 2, 16, 32, 45, 62, 75, and 90. Body weight was recorded weekly. Individual food consumption was recorded daily. Blood samples were collected for clinical pathology (hematology, coagulation profile, clinical chemistry, and C-reactive protein) pre-treatment and on Days 8, 55, and 85/86; and for plasma fluralaner concentrations pre-dose on Day 1 and at 48, 168, 336, and 696 hours following dosing on Days 1, 31, and 61. The plasma concentrations of fluralaner were measured using a validated Liquid chromatography–mass spectrometry (LC-MS/MS) method. All dogs were euthanized on Day 92 and underwent full gross necropsy, organ weight determination, and histopathological evaluation.

Statistical Methods: Statistical summaries were generated for clinical assessments, veterinary examinations, body weight, diet consumption, hematology, clinical chemistry, coagulation, C-reactive protein, urinalysis, and organ weights.

Results: There were no clinically-relevant, treatment-related effects on body weights, food consumption, organ weights, hematology, C-reactive protein, coagulation profile, and urinalysis.

Diarrhea and mucoid or discolored feces were the most common observations in this study, occurring at a similar incidence in the fluralaner and control groups. Although vomiting was seen in dogs in all dose groups throughout the study, one dog in the 5X group and one dog in the control group vomited the day after dosing on study day 2. One dog in the 1X group had self-limiting abdominal distention post-dosing on Day 61. One dog in the 1X group had splayed hind limbs on Day 61 at 1, 2, 4, and 8 hours post-dose. One dog in the 1X group demonstrated trembling on Day 2. One dog each in the 1X, 3X, and 5X groups had tremors on Day 1 at 4 hours post-dose. Mandibular lymphadenopathy was noted in one dog from the control group, one 1X dog, one 3X dog, and three 5X dogs on a treatment day (Day 31), and one control dog on Day 32. Mandibular lymphadenopathy was also noted in one dog from the control group, two 1X dogs, and three 5X dogs on Day 45.

One dog in the 3X group had elevated BUN (21.6 mg/dL; reference range: 9-19 mg/dL) on Day 8. One dog in the 5X group had elevated BUN (23.6 mg/dL) and serum creatinine (1.0 mg/dL; reference range: 0.4-0.7 mg/dL) on Day 85. Two dogs each from the 1X and 5X groups had serum ALT elevations (49-105 U/L; reference range: 10-48 U/L).

Pituitary cysts were noted macroscopically in two dogs from the 1X group and microscopically in three dogs from the 1X group, one dog from the 3X group, and two dogs in the 5X group.

Plasma concentrations of fluralaner showed that steady-state is achieved with three treatments administered at 30-day intervals. There was a less than dose

proportional increase in fluralaner plasma concentrations after administration of the 1X, 3X and 5X doses every 30 days for 3 doses. The accumulation of the 1X, 3X, and 5X doses between the first and third dose ranged from 1.1X to 5.0X , 0.7X to 1.7X, 0.6X to 2.5X, respectively (based on maximum plasma concentration: C_{max}) and 1.0X to 4.6X, 0.8X to 1.7X, 0.8X to 2.7X, respectively (based on the area under the plasma concentration-time curve from 0 to the last quantifiable concentration: AUC_{last}).

Conclusion: This study supports the safe use of fluralaner chewable tablets in dogs when used at the labeled dose and duration. Potential treatment-related effects include vomiting, diarrhea, mucoid or discolored stool**,** trembling, tremors, splayed hind limbs, mandibular lymphadenopathy, abdominal distention**,** increased serum alanine aminotransferase (ALT) values, increased blood urea nitrogen (BUN) and serum creatinine values, and pituitary cysts.

B. Reproductive Safety

Refer to Reproductive Safety Study 671596 in the FOI summary for BRAVECTO® Chewable Tablets (NADA 141-426).

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. 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 BRAVECTO® 1-MONTH:

Human Warnings:

Not for human use. Keep this and all drugs out of the reach of children. Keep the product in the original packaging until use, in order to prevent children from getting direct access to the product. Do not eat, drink or smoke while handling the product. Wash hands thoroughly with soap and water immediately after use of the product.

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 (FD&C Act) and 21 CFR part 514. The data demonstrate that BRAVECTO® 1-MONTH, when used according to the label, is safe and effective to kill adult fleas and for the treatment and prevention of flea infestations (*Ctenocephalides felis*) and the treatment and control of tick infestations [*Ixodes scapularis* (black-legged tick), *Dermacentor variabilis* (American dog tick) and *Rhipicephalus sanguineus* (brown dog tick)] for one month in dogs and puppies 8 weeks of age and older, and weighing 4.4 pounds or greater.

BRAVECTO® 1-MONTH is also indicated for the treatment and control of *Amblyomma americanum* (lone star tick) infestations for one month in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater.

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 is required to advise dog owners regarding use in breeding dogs and to monitor for and respond to adverse reactions.

B. Exclusivity

BRAVECTO® 1-MONTH, as approved in our approval letter, qualifies for THREE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the FD&C Act because the sponsor submitted an original NADA that contains new studies that demonstrate the safety and effectiveness of BRAVECTO® 1-MONTH.

C. Patent Information

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA website.