

Date of Approval: November 14, 2019

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-518

BRAVECTO® PLUS

fluralaner and moxidectin topical solution

Cats

BRAVECTO® PLUS is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and for the treatment of infections with intestinal roundworm (*Toxocara cati*; 4th stage larvae, immature adults and adults) and hookworm (*Ancylostoma tubaeforme*; 4th stage larvae, immature adults and adults). BRAVECTO® PLUS 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) and *Dermacentor variabilis* (American dog tick)] for 2 months in cats and kittens 6 months of age and older and weighing 2.6 lb or greater.

Sponsored by:

Intervet, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-518

B. Sponsor

Intervet, Inc.,
2 Giralda Farms,
Madison, NJ 07940

Drug Labeler Code: 000061

C. Proprietary Name

BRAVECTO® PLUS

D. Drug Product Established Name

Fluralaner and moxidectin topical solution

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Solution

G. Amount of Active Ingredient

Each milliliter contains 280 mg of fluralaner and 14 mg of moxidectin

H. How Supplied

BRAVECTO® PLUS is available in three tube sizes to treat cats ranging in weight from 2.6 lb – 27.5 lb (1.2 kg to 12.5 kg). Each tube is packaged individually in a pouch. Product may be supplied in 1 or 2 tubes per carton.

I. Dispensing Status

Rx

J. Dosage Regimen

BRAVECTO® PLUS should be administered topically as a single dose every 2 months according to the Dosage Schedule below to provide a minimum dose of 18.2 mg/lb (40 mg/kg) fluralaner and 0.9 mg/lb moxidectin (2 mg/kg).

For prevention of heartworm disease, BRAVECTO® PLUS should be administered at 2-month intervals. BRAVECTO® PLUS may be administered year-round without interruption or at a minimum should be administered at 2-month intervals beginning at the cat's first seasonal exposure to mosquitoes and continuing until the cat's last seasonal exposure to mosquitoes. If a dose is missed and a 2-

month interval between doses is exceeded, administer BRAVECTO® PLUS immediately and resume the dosing every 2 months.

When replacing a monthly heartworm preventative product, the first dose of BRAVECTO® PLUS should be given within one month of the last dose of the former medication.

Dosage Schedule

Body Weight Ranges (lb)	Fluralaner content (mg/tube)	Moxidectin content (mg/tube)	Tubes Administered
2.6 – 6.2	112.5	5.6	One
>6.2 – 13.8	250	12.5	One
>13.8 - 27.5*	500	25	One

*Cats over 27.5 lb should be administered the appropriate combination of tubes.

K. Route of Administration

Topical

L. Species/Class

Cats

M. Indication

BRAVECTO® PLUS is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and for the treatment of infections with intestinal roundworm (*Toxocara cati*; 4th stage larvae, immature adults and adults) and hookworm (*Ancylostoma tubaeforme*; 4th stage larvae, immature adults and adults). BRAVECTO® PLUS 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) and *Dermacentor variabilis* (American dog tick)] for 2 months in cats and kittens 6 months of age and older and weighing 2.6 lb or greater.

II. EFFECTIVENESS

The effectiveness of BRAVECTO® PLUS was demonstrated in 14 well-controlled laboratory studies, described below. These studies demonstrate that BRAVECTO® PLUS is effective against a variety of both internal and external parasites. BRAVECTO® PLUS was administered to 376 laboratory cats. The most common adverse reactions from the laboratory studies were dermatological changes at the application site (alopecia, crusts, and irritation), hypersalivation, and diarrhea.

A. Dosage Characterization

Fluralaner:

For the flea and tick indications, the minimum effective fluralaner dose of 40 mg/kg, administered topically, every 8 - 12 weeks in cats and kittens 6 months of age and older, and weighing 2.6 pounds or greater, is supported by data contained in NADA 141-459 for BRAVECTO® (fluralaner topical solution).

Moxidectin:

A published study¹ and the results of a pilot study (S13343-00) support the topical administration of moxidectin at a dose of 1 mg/kg as effective against intestinal roundworm and hookworm infections as well as for the prevention of heartworm disease for one month in cats. Because the product profile for BRAVECTO® PLUS includes heartworm protection for greater than one month, the dose selection focused on determining the topical dose of moxidectin required to achieve this duration of effectiveness. A plasma concentration of 0.5 ng/mL was targeted as a conservative estimate for effectiveness against *Dirofilaria immitis* larvae.

Pharmacokinetic studies demonstrated that moxidectin plasma concentrations in cats administered a topical moxidectin dose of 1 mg/kg began to fall below the effectiveness threshold estimate of 0.5 ng/mL by Day 56 post-treatment. Plasma moxidectin concentrations from cats treated with topical doses of 2 or 4 mg moxidectin/kg bodyweight remained above this effectiveness threshold for at least 91 days following treatment. Therefore, a minimum effective moxidectin dose of 2 mg/kg, administered topically, was identified as an appropriate dose for a 2- to 3-month dosing regimen for the prevention of heartworm disease and for effectiveness against intestinal roundworms and hookworms in cats.

A 2-month dosing regimen was selected because in one study using a recent heartworm isolate (Study S15102-01), a single dose did not demonstrate adequate effectiveness to prevent adult *D. immitis* infections when administered 3 months before infection.

B. Substantial Evidence

Nematode Indications (heartworm and gastrointestinal):

Per 21 CFR 514.4(c), each active ingredient in a combination must make a contribution to the effectiveness of the combination new animal drug. In lieu of demonstrating the unique contribution of each active ingredient by adding additional treatment groups to the dose confirmation studies conducted with this combination product, information to support the contribution of each active ingredient was evaluated from *in vitro* and *in vivo* studies conducted to evaluate the potential anthelmintic activity of fluralaner against nematodes. These studies included nematodes that commonly infect poultry (*Ascaridia galli*), swine

¹ Lok, J.B. et al., "Six-month prophylactic efficacy of moxidectin sustained release (SR) injectable for dogs against experimental heartworm infection in growing puppies," *Veterinary Parasitology* 133, (2005): 233-241.

(*Oesophagostomum dentatum*), and ruminants (*Trichostrongylus axei* and *T. colubriformis*). Additionally, both *in vitro* and *in vivo* studies were conducted to evaluate the activity of fluralaner against *D. immitis* larvae. The conclusion from these evaluations was that fluralaner does not have effective anthelmintic activity at the doses included in this combination product, and therefore the inclusion of moxidectin in this combination is necessary for the product to be effective for the heartworm, roundworm, and hookworm indications. Furthermore, the conclusion that fluralaner does not interfere with the effectiveness of moxidectin is supported by the studies below that confirm the effectiveness of this combination.

1. Prevention of Heartworm Disease (*Dirofilaria immitis*):

- a. **Title:** Evaluation of the Effectiveness of Fluralaner 280 mg/mL plus Moxidectin 14 mg/mL Spot-on Solution for Cats for the Prevention of *Dirofilaria immitis* Infection (Heartworm Disease) in Cats. (Study No. S15102-01)

Study Dates: June 2015 to Sept 2016

Study Location: Athens, GA, USA

Study Design:

Objective: To confirm the effectiveness of fluralaner and moxidectin topical solution at the recommended minimum dose (40 mg/kg fluralaner and 2 mg/kg moxidectin) for the prevention of heartworm infection in cats when administered either two or three months prior to *D. immitis* infection. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Study Animals: 30 healthy cats (Domestic short-hair, 15 males and 15 females), approximately 7 months of age to 1.0 years of age, and 2.5 to 5.8 kg body weight.

Experimental Design: Cats were ranked and blocked by descending order of body weight within sex, and one cat from each block was randomly assigned to one of the following groups:

- Group 1: untreated control (10 cats)
- Group 2: fluralaner and moxidectin topical solution, treated on Day 0 to evaluate 90-day heartworm prevention (10 cats)
- Group 3: fluralaner and moxidectin topical solution, treated on Day 30 to evaluate 60-day heartworm prevention (10 cats)

Each cat was experimentally infected by subcutaneous inoculation with 100 third stage *D. immitis* larvae (L₃) on Day 90.

Drug Administration: Fluralaner and moxidectin topical solution was administered topically to the 10 cats in each of the fluralaner and moxidectin topical solution groups (Groups 2 and 3) on Days 0 or 30, respectively, at doses as close as possible to 40 mg/kg fluralaner and 2

mg/kg moxidectin. Hair at the administration site was parted and fluralaner and moxidectin topical solution was applied to the skin in one spot at the base of the skull. Fluralaner doses ranged from 39.7 to 40.3 mg/kg and moxidectin doses were administered at 2.0 mg/kg. Cats in the control group (Group 1) and the treated group not receiving the drug on either Day 0 or 30 were sham treated on those days.

Measurements and Observations: The primary variable for effectiveness was the heartworm counts collected from the cats.

Blood samples were collected on Day -8 prior to animal selection and allocation and on Day 89 before heartworm infection. These samples were tested for heartworm antibody, heartworm antigen (from heat-treated blood samples), and the presence of microfilariae to confirm that the cats had not previously been infected with heartworm. Blood samples were also collected and tested for heartworm antigen and the presence of microfilariae on Days 180, 210, 240, and 273. General health observations were conducted daily and at approximately 1, 3, 6, and 24 hours after drug administration. Treatment site observations were made at 1, 2, 3, 7, 14, 28, 31, 32, 33, 37, 44, 58, 88, 118, 148, 178, 208, 238, and 273 days following treatment. Cats were weighed on Day -2. At necropsy on Day 273, the heart, lungs and all associated blood vessels of each cat were opened and processed, and the numbers of *D. immitis* worms were recorded. The recovered worms were examined for viability and maturity and were sexed and counted. Heartworm counts and health observations were conducted by individuals masked to treatment.

Statistical Methods: No statistical comparisons were made among treatment groups. Geometric mean worm counts were calculated for each study group. The log (count + 1) transformation was used to calculate geometric means.

Results: A minimum of two worms in at least six control cats was considered an adequate infection for the study to be considered valid. Seven of the ten control cats satisfied the adequacy of infection requirement.

No cat tested positive for *D. immitis* microfilaria before or after infection.

Eight of 10 cats from the control group had positive *D. immitis* antigen test results as early as Day 210 (120 days after infection). One cat treated with fluralaner and moxidectin topical solution (Group 2) had a positive *D. immitis* antigen test result on Day 273 (183 days after infection). All other cats from the two fluralaner and moxidectin topical solution treated groups and the two remaining cats from the control group tested negative for *D. immitis* antigen at every pre- and post-infection time point.

One cat had a weak positive test result for *D. immitis* antibody on Day 89 of the study (one day before infection). All other samples from all cats, both before allocation and infection, tested negative for *D. immitis* antibodies.

Three of 10 cats treated 90 days before infection (Group 2) each had one heartworm recovered at necropsy. No heartworms were recovered from any of the cats treated 60 days before infection (Group 3).

Table II.1: Study S15102-01; *D. immitis* Worm Count Results

Group	Treatment Day	Infection Day	Number of cats with <i>D. immitis</i> recovered	Geometric Mean (range) of <i>D. immitis</i> recovered	Percent Effectiveness
1	none	90	7/10	3.0 (3-16)	NA
2	0	90	3/10	0.2 (1)	92.3
3	30	90	0/10	0.0	100

Adverse Reactions: One cat in Group 3 was observed to be drooling 3 minutes following drug administration; the drooling stopped by 5 minutes following drug administration. One cat in Group 2 had alopecia of the right ear beginning on Day 4 and continuing throughout the study. A second cat in Group 2 had crusts, irritation, and alopecia beginning on Day 25 and continuing until Day 27.

Conclusion: This study demonstrated the effectiveness of fluralaner and moxidectin topical solution against experimental infection with *D. immitis* when administered at the minimum label dose two months prior to infection. The study failed to demonstrate effectiveness when administered three months prior to infection. Drooling and dermatologic conditions (alopecia, crusts, irritation) should be considered possible drug-related adverse reactions.

- b. **Title:** Evaluation of the Effectiveness of Fluralaner 280 mg/mL plus Moxidectin 14 mg/mL Spot-on Solution for Cats for the Prevention of *Dirofilaria immitis* Infection (Heartworm Disease) in Cats. (Study No. S15102-03)

Study Dates: May 2017 to June 2018

Study Location: Auburn, AL, USA

Study Design:

Objective: To confirm the effectiveness of fluralaner and moxidectin topical solution at the recommended minimum dose (40 mg/kg fluralaner and 2 mg/kg moxidectin) for the prevention of heartworm infection in cats when administered either two or three months prior to *D. immitis* infection. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Study Animals: 30 healthy cats (Domestic short-hair, 16 males and 14 females), approximately 7 to 9 months of age, and 2.6 to 5.3 kg body weight.

Experimental Design: Cats were ranked and blocked by descending order of body weight within sex and one cat from each block was randomly assigned to one of the following groups:

- Group 1: untreated control (10 cats)
- Group 2: fluralaner and moxidectin topical solution, treated on Day 0 to evaluate 90-day heartworm prevention (10 cats)
- Group 3: fluralaner and moxidectin topical solution, treated on Day 30 to evaluate 60-day heartworm prevention (10 cats)

Each cat was experimentally infected by subcutaneous inoculation with 100 third stage *D. immitis* larvae (L₃) on Day 90.

Drug Administration: Fluralaner and moxidectin topical solution was administered topically to the ten cats in each of the fluralaner and moxidectin topical solution groups (Groups 2 and 3) on Days 0 or 30, respectively, at doses as close as possible to 40 mg/kg fluralaner and 2 mg/kg moxidectin. Hair at the administration site was parted and fluralaner and moxidectin topical solution was applied to the skin in one spot at the base of the skull. Fluralaner doses ranged from 39.6 to 40.4 mg/kg and moxidectin doses were administered at 2.0 mg/kg. Cats in the control group (Group 1) and the treated group not receiving the drug on either Day 0 or 30 were sham treated on those days.

Measurements and Observations: The primary variable for effectiveness was the heartworm counts collected from the cats.

Blood samples were collected on Day -8 or -7 prior to animal selection and allocation and on Day 89 before heartworm infection. These samples were tested for heartworm antibody, heartworm antigen (from heat-treated blood samples), and the presence of microfilariae to confirm that the cats had not previously been infected with heartworm. Blood samples were also collected and tested for heartworm antigen and the presence of microfilariae on Days 180, 210, 240, and 271. General health observations were conducted daily and at approximately 1, 3, 6, and 24 hours after drug administration. Treatment site observations were made at 1, 2, 3, 7, 14, 28, 31, 32, 33, 36, 43, 57, 88, 119, 148, 179, 209, 238, and 270 days following treatment. Cats were weighed on Days -2 and 28. At necropsy on Day 272 or 273, the heart, lungs and all associated blood vessels of each cat were opened and processed, and the numbers of *D. immitis* worms were recorded. The recovered worms were examined for viability and maturity and were sexed and counted. Heartworm counts and health observations were conducted by individuals masked to treatment.

Statistical Methods: No statistical comparisons were made among treatment groups. Geometric mean worm counts were calculated for each study group. The log (count + 1) transformation was used to calculate geometric means.

Results: A minimum of two worms in at least six control cats was considered an adequate infection for the study to be considered valid. Seven of the ten control cats satisfied the adequacy of infection requirement.

No cat tested positive for *D. immitis* microfilaria before or after infection.

All cats tested negative for *D. immitis* antibodies both before allocation (Day 0) and infection (Day 89).

Four of 10 cats from the control group had positive *D. immitis* antigen test results as early as Day 240 (150 days after infection) and 6 of 10 control cats had positive results by Day 271. All other cats from the two fluralaner and moxidectin topical solution treated groups and the four remaining cats from the control group tested negative for *D. immitis* antigen at every pre- and post-infection time point.

No heartworms were recovered from any of the cats administered fluralaner and moxidectin topical solution 90 days before infection (Group 2) or 60 days before infection (Group 3).

Table II.2: Study S15102-03; *D. immitis* Worm Count Results

Group	Treatment Day	Infection Day	Number of cats with <i>D. immitis</i> recovered	Geometric Mean (range) of <i>D. immitis</i> recovered	Percent Effectiveness
1	none	90	7/10	3.5 (2-16)	NA
2	0	90	0/10	0.0	100
3	30	90	0/9*	0.0	100

*One cat in the group treated 60 days before infection (Group 3) died prior to infection on Day 89. The cause of death was due to a pre-existing health problem (hypertrophic cardiomyopathy) unrelated to treatment.

Adverse Reactions: One cat in Group 2 was observed to have redness and alopecia at the application site starting on Day 3. The redness resolved by Day 5 and hair began to regrow at the site by Day 11. The same cat was observed to have intermittent mid-back pain starting on Day 2 and continuing through Day 195. The cat was monitored through Day 262 with no further back pain noted. No other treatment related adverse reactions were observed in this study.

Conclusion: This study demonstrated the effectiveness of fluralaner and moxidectin topical solution against experimental infection with *D. immitis* when administered at the minimum label dose two and three months prior to infection. Dermatologic conditions (alopecia, irritation) at the application site and intermittent back pain should be considered possible drug-related adverse reactions.

2. Treatment of Infections with Gastrointestinal Nematodes:

- a. **Title:** Evaluation of the Effectiveness of Fluralaner 280 mg/mL + Moxidectin 14 mg/mL Spot-on Solution for Cats against Natural Infections with *Toxocara cati* and/or *Ancylostoma tubaeforme* in Cats. (Study No. S15214-02)

Study Dates: April 2016 to September 2016

Study Location: Stanwood, MI, USA

Study Design:

Objective: To confirm the effectiveness of fluralaner and moxidectin topical solution at the recommended minimum dose (40 mg/kg fluralaner and 2 mg/kg moxidectin) against natural infections with *T. cati* and *A. tubaeforme* in cats. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Study Animals: 20 healthy cats (Domestic short-, medium- and long-hair, 13 males and 7 females), exact ages unknown but determined to be greater than 12 weeks of age, and 2.0 to 5.2 kg body weight.

Experimental Design: Twenty naturally-infected cats that were positive for *A. tubaeforme*, based on screening fecal egg counts, were ranked by ascending order of their identification number and randomly assigned to the untreated control group (10 cats) or the fluralaner and moxidectin topical solution (10 cats) treatment group. Eighteen of the 20 cats (9 cats/group) were also positive for *T. cati* eggs. Drug administration was on Day 0. One control cat was removed during the study because of an error with the worm count method, leaving nine cats in the control group.

Drug Administration: On Day 0, fluralaner and moxidectin topical solution was administered topically to the ten cats in the fluralaner and moxidectin topical solution group (Group 2) at doses as close as possible to 40 mg/kg fluralaner and 2 mg/kg moxidectin. Hair at the administration site was parted, and fluralaner and moxidectin topical solution was applied to the skin in one spot at the base of the skull. Fluralaner doses ranged from 39.7 to 40.4 mg/kg, and moxidectin doses were administered at 2.0 mg/kg. Cats in the control group (Group 1) were sham treated.

Measurements and Observations: The primary variable for effectiveness was the nematode count collected from the cats. General health observations were conducted daily and at 1, 3, 6, and 24 hours after drug administration. Treatment site observations were made on Days 1, 2, 3, 7, and 10. Cats were weighed on Day -2. At necropsy on Day 10, the gastrointestinal tract, including the stomach, small intestines and large intestines, from each cat was removed and processed, and all stages of worms were recovered, identified and counted. Nematode

counts and health observations were conducted by individuals masked to treatment.

Statistical Methods: Nematode counts of each species were log-transformed prior to analysis with a linear model that included treatment group as a fixed effect at a two-sided 5% significance level. Percent effectiveness against the control was calculated based on geometric means.

Results: A minimum of five worms in at least six control cats was considered an adequate infection for the study to be considered valid. Seven of the nine control cats satisfied the adequacy of infection requirement for *T. cati*, and eight of the nine control cats satisfied the adequacy of infection requirement for *A. tubaeforme*.

Fluralaner and moxidectin topical solution was 100% effective against adult *T. cati* and *A. tubaeforme* infections. The geometric means of adult *T. cati* and *A. tubaeforme* worms in the fluralaner and moxidectin topical solution group were significantly different from the control group ($p < 0.0001$).

Table II.3: Study S15214-02; Adult *T. cati* and *A. tubaeforme* Worm Count Results

Treatment	<i>T. Cati</i> Geometric Mean	<i>T. Cati</i> Percent Effectiveness	<i>A. tubaeforme</i> Geometric Mean	<i>A. tubaeforme</i> Percent Effectiveness
Control	9.6	NA	28.4	NA
Fluralaner and moxidectin topical solution	0.0	100	0.0	100

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

Conclusion: This study demonstrated the effectiveness of fluralaner and moxidectin topical solution for the treatment of adult *T. cati* and *A. tubaeforme* infections in naturally infected cats.

- b. **Title:** Evaluation of the Effectiveness of Fluralaner 280 mg/mL + Moxidectin 14 mg/mL Spot-on Solution for Cats against Mature Experimentally Induced *Toxocara cati* and *Ancylostoma tubaeforme* Infections in Cats. (Study No. S15313-00)

Study Dates: February 2016 to November 2017

Study Location: Rockwood, TN, USA

Study Design:

Objective: To confirm the effectiveness of fluralaner and moxidectin topical solution at the recommended minimum dose (40 mg/kg fluralaner

and 2 mg/kg moxidectin) against experimental infections with adult *T. cati* and *A. tubaeforme* in cats. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Study Animals: 18 healthy cats (Domestic short-hair, 9 males and 9 females), approximately 5 to 7 months of age, and 2.0 to 3.6 kg body weight.

Experimental Design: Each cat was experimentally infected with approximately 500 *T. cati* infective eggs and approximately 300 *A. tubaeforme* infective larvae (L₃) on Days -60 and -30, respectively. Eighteen cats that were positive for both *T. cati* and *A. tubaeforme* eggs during fecal examination were selected for the study and randomly assigned to either the untreated control group (9 cats) or fluralaner and moxidectin topical solution treatment group (9 cats). Drug administration was on Day 0.

Drug Administration: On Day 0, fluralaner and moxidectin topical solution was administered topically to the nine cats in the fluralaner and moxidectin topical solution group (Group 2), at doses as close as possible to 40 mg/kg fluralaner and 2 mg/kg moxidectin. Hair at the administration site was parted, and fluralaner and moxidectin topical solution was applied to the skin in one spot at the base of the skull. Fluralaner doses ranged from 39.5 to 40.5 mg/kg and moxidectin doses were administered at 2.0 mg/kg. Cats in the control group (Group 1) were sham treated.

Measurements and Observations: The primary variable for effectiveness was the nematode count collected from the cats. General health observations were conducted daily and at 1, 3, 6, and 24 hours after drug administration. Treatment site observations were made on Days 1, 2, 3, 7, and 10. Cats were weighed on Day -2. At necropsy on Day 10, the gastrointestinal tract, including the stomach, small intestines and large intestines, from each cat was removed and processed, and all stages of worms were recovered, identified and counted. Nematode counts and health observations were conducted by individuals masked to treatment.

Statistical Methods: Nematode counts of each species were log-transformed prior to analysis with a linear model that included treatment group as a fixed effect at a two-sided 5% significance level. Percent effectiveness against the control was calculated based on geometric means.

Results: A minimum of five worms in at least six control cats was considered an adequate infection for the study to be considered valid. Eight of the nine control cats satisfied the adequacy of infection requirement for *T. cati* and *A. tubaeforme*.

The fluralaner and moxidectin topical solution was 98.3% and 97.1% effective against adult *T. cati* and *A. tubaeforme*, respectively. The geometric means of adult *T. cati* and *A. tubaeforme* worms in the fluralaner and moxidectin topical solution group were significantly different from the control group ($p < 0.0001$).

Table II.4: Study S15313-00; Adult *T. cati* and *A. tubaeforme* Worm Count Results

Treatment	<i>T. Cati</i> Geometric Mean	<i>T. Cati</i> Percent Effectiveness	<i>A. tubaeforme</i> Geometric Mean	<i>A. tubaeforme</i> Percent Effectiveness
Control	24.9	NA	6.7	NA
Fluralaner and moxidectin topical solution	0.4	98.3	0.2	97.1

Adverse Reactions: Two cats in the fluralaner and moxidectin topical solution group had diarrhea three to five days after dosing. No treatment for the diarrhea was administered, and the cats were normal the following day.

Conclusion: This study demonstrated the effectiveness of fluralaner and moxidectin topical solution for the treatment of adult *T. cati* and *A. tubaeforme* infections in experimentally infected cats. Diarrhea should be considered a possible drug-related adverse reaction.

- c. **Title:** Determination of the Efficacy of Fluralaner 280 mg/mL + Moxidectin 14 mg/mL Spot-on Solution for Cats against Immature [fourth stage (L₄) and pre-adults (L₅)] *Ancylostoma tubaeforme* in Cats after Topical Administration. (Study No. S15355-00)

Study Dates: February 2016 to October 2016

Study Location: Athens, GA, USA

Study Design:

Objective: To confirm the effectiveness of fluralaner and moxidectin topical solution at the recommended minimum dose (40 mg/kg fluralaner and 2 mg/kg moxidectin) against experimental infections with fourth stage larvae (L₄) and immature adult (L₅) *A. tubaeforme* in cats. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Study Animals: 30 healthy cats (Domestic short-hair, 15 males and 15 females), approximately 4 months of age, and 1.4 to 2.0 kg body weight.

Experimental Design: Each cat was experimentally infected with approximately 200 *A. tubaeforme* infective larvae (L₃) on Day 0. Thirty cats were randomly assigned to three groups of ten cats each. Group 1

evaluated the effectiveness of fluralaner and moxidectin topical solution against fourth stage *A. tubaeforme* larvae (L₄), Group 2 evaluated the effectiveness of the same topical solution against immature adult (L₅) *A. tubaeforme*, and Group 3 was the negative control group. The control group was administered saline.

Cats assigned to the fluralaner and moxidectin topical solution groups were administered treatment once on either Day 7 (Group 1) or Day 11 (Group 2). To maintain masking, cats in the fluralaner and moxidectin topical solution groups (Groups 1 or 2) that were not scheduled to be treated that day were administered saline at the application site.

Drug Administration: Fluralaner and moxidectin topical solution was administered topically to the ten cats each in Groups 1 and 2 on Days 7 and 11, respectively, at doses as close as possible to 40 mg/kg fluralaner and 2 mg/kg moxidectin. Hair at the administration site was parted, and fluralaner and moxidectin topical solution was applied to the skin in one spot at the base of the skull. Fluralaner doses ranged from 39.2 to 42.7 mg/kg, and moxidectin doses were administered at 2.0 mg/kg. Cats in the control group (Group 3) were administered saline in one spot at the base of the skull.

Measurements and Observations: The primary variable for effectiveness was the nematode count collected from the cats. General health observations were conducted daily and at 1, 3, 6, and 24 hours after drug administration. Treatment site observations were made on Days 8, 9, and 10 (Group 1) and on Days 12, 13, and 14 (Group 2). At necropsy on Day 18, the gastrointestinal tract, including the stomach, small intestines and large intestines, from each cat was removed and processed, and all stages of worms were recovered, identified and counted. Cats were weighed on Day 6 (Group 1) and Day 10 (Group 2). Nematode counts and health observations were conducted by individuals masked to treatment.

Statistical Methods: A mixed model analysis was used to analyze log-transformed nematode counts, with treatment and sex as fixed factors and block as a random effect. Unadjusted pairwise comparisons of Groups 1 and 2 versus Group 3 were performed. All statistical tests were two-tailed with a level of significance of 5%. Percent effectiveness against the control was calculated based on geometric means.

Results: A minimum of five worms in at least six control cats was considered an adequate infection for the study to be considered valid. All ten control cats satisfied the adequacy of infection requirement for *A. tubaeforme*.

The fluralaner and moxidectin topical solution was 100% effective against the L₄ and immature adult (L₅) stages of *A. tubaeforme*. The geometric means of *A. tubaeforme* worms in the fluralaner and moxidectin topical solution groups were significantly different from the control group ($p < 0.0001$).

Table II.5: Study S15355-00; *A. tubaeforme* Worm Count Results

Group	Treatment	Stage Evaluated	Geometric Mean	Percent Effectiveness
1	Fluralaner and moxidectin topical solution (Day 14)	L ₄	0.0	100
2	Fluralaner and moxidectin topical solution (Day 28)	Immature adult (L ₅)	0.0	100
3	Control	NA	23.0	NA

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

Conclusion: This study demonstrated the effectiveness of fluralaner and moxidectin topical solution for the treatment of L₄ and immature adult (L₅) stages of *A. tubaeforme* infections in experimentally infected cats.

- d. **Title:** Determination of the Efficacy of Fluralaner 280 mg/mL + Moxidectin 14 mg/mL Spot-on Solution for Cats against Immature [fourth stage (L₄) and pre-adults (L₅)] *Ancylostoma tubaeforme* in Cats after Topical Administration. (Study No. S15138-00)

Study Dates: November 2015 to June 2016

Study Location: Bloemfontein, South Africa

Study Design:

Objective: To confirm the effectiveness of fluralaner and moxidectin topical solution at the recommended minimum dose (40 mg/kg fluralaner and 2 mg/kg moxidectin) against experimental infections with fourth stage larvae (L₄) and immature adult (L₅) *A. tubaeforme* in cats. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Study Animals: 24 healthy cats (European mixed breed short-hair, 10 males and 14 females), approximately 4 months to 1.3 years of age, and 1.5 to 3.3 kg body weight.

Experimental Design: Each cat was experimentally infected with approximately 150 *A. tubaeforme* infective larvae (L₃) on Day 0. Twenty-four cats were randomly assigned to three groups of eight cats each. Group 1 evaluated the effectiveness of fluralaner and moxidectin topical solution against fourth stage *A. tubaeforme* larvae (L₄), Group 2 evaluated effectiveness of the same topical solution against immature adult (L₅) *A. tubaeforme*, and Group 3 was the negative control group. The control group was administered saline.

Cats assigned to the fluralaner and moxidectin topical solution groups were administered treatment once on either Day 7 (Group 1) or Day 11 (Group 2). To maintain masking, cats in the fluralaner and moxidectin topical solution groups (Groups 1 or 2) that were not scheduled to be treated that day were administered saline at the application site.

Drug Administration: Fluralaner and moxidectin topical solution was administered topically to the eight cats each in Groups 1 and 2 on Days 7 and 11, respectively, at doses as close as possible to 40 mg/kg fluralaner and 2 mg/kg moxidectin. Hair at the administration site was parted, and fluralaner and moxidectin topical solution was applied to the skin in one spot at the base of the skull. Fluralaner doses ranged from 39.2 to 40.7 mg/kg and moxidectin doses were administered at 2.0 mg/kg. Cats in the control group (Group 3) were administered saline in two spots at the base of the skull.

Measurements and Observations: The primary variable for effectiveness was the nematode count collected from the cats. General health observations were conducted daily and at 1, 3, 6, and 24 hours after drug administration. Treatment site observations were made on Days 8, 9, and 10 (Group 1) and on Days 12, 13, and 14 (Group 2). At necropsy on Day 18, the gastrointestinal tract, including the stomach, small intestines and large intestines, from each cat was removed and processed, and all stages of worms were recovered, identified and counted. Cats were weighed on Day 6 (Group 1) and Day 10 (Group 2). Nematode counts and health observations were conducted by individuals masked to treatment.

Statistical Methods: A mixed model analysis was used to analyze log-transformed nematode counts, with treatment and sex as fixed factors and block as a random effect. Unadjusted pairwise comparisons of Groups 1 and 2 versus Group 3 were performed. All statistical tests were two-tailed with a level of significance of 5%. Percent effectiveness against the control was calculated based on geometric means.

Results: A minimum of five worms in at least six control cats was considered an adequate infection for the study to be considered valid. All eight control cats satisfied the adequacy of infection requirement for *A. tubaeforme*.

The fluralaner and moxidectin topical solution was 100% effective against the L₄ and immature adult (L₅) stages of *A. tubaeforme*. The geometric means of *A. tubaeforme* worms in the fluralaner and moxidectin topical solution groups were significantly different from the control group ($p < 0.0001$).

Table II.6: Study S15138-00; *A. tubaeforme* Worm Count Results

Group	Treatment	Stage Evaluated	Geometric Mean	Percent Effectiveness
1	Fluralaner and moxidectin topical solution (Day 14)	L ₄	0.0	100
2	Fluralaner and moxidectin topical solution (Day 28)	Immature adult (L ₅)	0.0	100
3	Control	NA	72.1	NA

Adverse Reactions: One cat in the fluralaner and moxidectin topical solution group had thinning of the hair at the application site on Day 10.

Conclusion: This study demonstrated the effectiveness of fluralaner and moxidectin topical solution for the treatment of L₄ and immature adult (L₅) stages of *A. tubaeforme* infections in experimentally infected cats. Thinning of the hair at the application site should be considered a possible drug-related adverse reaction.

- e. **Title:** Determination of the Efficacy of Fluralaner 280 mg/mL + Moxidectin 14 mg/mL Spot-on Solution for Cats against Immature [fourth stage (L₄) and pre-adults (L₅)] *Toxocara cati* in Cats after Topical Administration. (Study No. S15356-00)

Study Dates: June 2016 to February 2017

Study Location: Rockwood, TN, USA

Study Design:

Objective: To confirm the effectiveness of fluralaner and moxidectin topical solution at the recommended minimum dose (40 mg/kg fluralaner and 2 mg/kg moxidectin) against experimental infections with fourth stage larvae (L₄) and immature adult (L₅) *T. cati* in cats. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Study Animals: 30 healthy cats (Domestic short-hair, 15 males and 15 females), approximately 2.5 months of age, and 1.1 to 1.7 kg body weight.

Experimental Design: Each cat was experimentally infected with approximately 300 *T. cati* infective eggs on Day 0. Thirty cats were randomly assigned to three groups of ten cats each. Group 1 evaluated

the effectiveness of fluralaner and moxidectin topical solution against fourth stage *T. cati* larvae (L₄), Group 2 evaluated the effectiveness of the same topical solution against immature adult (L₅) *T. cati*, and Group 3 was the negative control group. The control group was administered saline.

Cats assigned to the fluralaner and moxidectin topical solution groups were administered treatment once on either Day 14 (Group 2) or Day 28 (Group 3). To maintain masking, cats in the fluralaner and moxidectin topical solution groups (Groups 1 or 2) that were not scheduled to be treated that day were administered saline at the application site.

Drug Administration: Fluralaner and moxidectin topical solution was administered topically to the ten cats in Groups 1 and 2 on Days 14 and 28, respectively, at doses as close as possible to 40 mg/kg fluralaner and 2 mg/kg moxidectin. Hair at the administration site was parted, and fluralaner and moxidectin topical solution was applied to the skin in one spot at the base of the skull. Fluralaner doses ranged from 39.0 to 40.9 mg/kg and moxidectin doses were administered at 2.0 mg/kg. Cats in the control group (Group 3) were administered saline in one spot at the base of the skull.

Measurements and Observations: The primary variable for effectiveness was the nematode count collected from the cats. General health observations were conducted daily and at 1, 3, 6, and 24 hours after drug administration. Treatment site observations were made on Days 15, 16, and 17 (Group 1) and on Days 29, 30, and 31 (Group 2). At necropsy on Day 38, the gastrointestinal tract, including the stomach, small intestines and large intestines, from each cat was removed and processed, and all stages of worms were recovered, identified and counted. Cats were weighed on Days -1, 4, 13 (Group 1), and Day 27 (Group 2). Nematode counts and health observations were conducted by individuals masked to treatment.

Statistical Methods: A mixed model analysis was used to analyze log-transformed nematode counts, with treatment and sex as fixed factors and block as a random effect. Unadjusted pairwise comparisons of Groups 1 and 2 versus Group 3 were performed. All statistical tests were two-tailed with a level of significance of 5%. Percent effectiveness against the control was calculated based on geometric means.

Results: A minimum of five worms in at least six control cats was considered an adequate infection for the study to be considered valid. All ten control cats satisfied the adequacy of infection requirement for *T. cati*.

The fluralaner and moxidectin topical solution was 98.6% and 100% effective against the L₄ and immature adult (L₅) stages of *T. cati*, respectively. The geometric means of *T. cati* worms in the fluralaner and moxidectin topical solution groups were significantly different from the control group ($p < 0.0001$).

Table II.7: Study S15356-00; *T. cati* Worm Count Results

Group	Treatment	Stage Evaluated	Geometric Mean	Percent Effectiveness
1	Fluralaner and moxidectin topical solution (Day 14)	L ₄	0.8	98.6
2	Fluralaner and moxidectin topical solution (Day28)	Immature adult (L ₅)	0.0	100
3	Control	NA	59.6	NA

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

Conclusion: This study demonstrated the effectiveness of fluralaner and moxidectin topical solution for the treatment of L₄ and immature adult (L₅) stages of *T. cati* infections in experimentally infected cats.

- f. **Title:** Determination of the Efficacy of Fluralaner 280 mg/mL + Moxidectin 14 mg/mL Spot-on Solution for Cats against Immature [fourth stage (L₄) and pre-adults (L₅)] *Toxocara cati* in Cats after Topical Administration (Study No. S15187-00)

Study Dates: December 2015 to October 2016

Study Location: Glenamoy, Co. Mayo, Ireland

Study Design:

Objective: To confirm the effectiveness of fluralaner and moxidectin topical solution at the recommended minimum dose (40 mg/kg fluralaner and 2 mg/kg moxidectin) against experimental infections with fourth stage larvae (L₄) and immature adult (L₅) *T. cati* in cats. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Study Animals: 24 healthy cats (European mixed breed short-hair, 12 males and 12 females), approximately 2.5 to 3.6 months of age, and 1.1 to 2.1 kg body weight.

Experimental Design: Each cat was experimentally infected with approximately 300 *T. cati* infective eggs on Day 0. Twenty-four cats were randomly assigned to three groups of eight cats each. Group 1 evaluated the effectiveness of fluralaner and moxidectin topical solution against fourth stage *T. cati* larvae (L₄), Group 2 evaluated the effectiveness of the same topical solution against immature adult (L₅) *T. cati*, and Group 3 was the negative control group. The control group was administered saline.

Cats assigned to the fluralaner and moxidectin topical solution groups were administered treatment once on either Day 14 (Group 1) or Day 28 (Group 2). To maintain masking, cats in the fluralaner and moxidectin topical solution groups (Groups 1 or 2) that were not scheduled to be treated that day were administered saline at the application site.

Drug Administration: Fluralaner and moxidectin topical solution was administered topically to the eight cats each in Groups 1 and 2 on Days 14 and 28, respectively, at doses as close as possible to 40 mg/kg fluralaner and 2 mg/kg moxidectin. Hair at the administration site was parted and fluralaner and moxidectin topical solution was applied to the skin in one spot at the base of the skull. Fluralaner doses ranged from 39.3 to 40.9 mg/kg and moxidectin doses were administered at 2.0 mg/kg. Cats in the control group (Group 3) were administered saline in one spot at the base of the skull.

Measurements and Observations: The primary variable for effectiveness was the nematode count collected from the cats. General health observations were conducted daily and at 1, 3, 6, and 24 hours after drug administration. Treatment site observations were made on Days 15, 16, and 17 (Group 1) and on Days 29, 30, and 31 (Group 2). At necropsy on Day 70, the gastrointestinal tract, including the stomach, small intestines and large intestines, from each cat was removed, processed and all stages of worms were recovered, identified and counted. Cats were weighed on Days -1, 4, and 13 (Group 1), 23 and 27 (Group 2). Nematode counts and health observations were conducted by individuals masked to treatment.

Statistical Methods: A mixed model analysis was used to analyze log-transformed nematode counts, with treatment and sex as fixed factors and block as a random effect. Unadjusted pairwise comparisons of Groups 1 and 2 versus Group 3 were performed. All statistical tests were two-tailed with a level of significance of 5%. Percent effectiveness against the control was calculated based on geometric means.

Results: A minimum of five worms in at least six control cats was considered an adequate infection for the study to be considered valid. Seven of the eight control cats satisfied the adequacy of infection requirement for *T. cati*.

The fluralaner and moxidectin topical solution was 93.5% and 98.0% effective against the L₄ and immature adult (L₅) stages of *T. cati*, respectively. The geometric means of *T. cati* worms in the fluralaner and moxidectin topical solution groups were significantly different from the control group ($p < 0.0001$).

Table II.8: Study S15187-00; *T. cati* Worm Count Results

Group	Treatment	Stage Evaluated	Geometric Mean	Percent Effectiveness
1	Fluralaner and moxidectin topical solution (Day 14)	L ₄	0.6	93.5
2	Fluralaner and moxidectin topical solution (Day 28)	Immature adult (L ₅)	0.2	98.0
3	Control	NA	9.6	NA

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

Conclusion: This study demonstrated the effectiveness of fluralaner and moxidectin topical solution for the treatment of L₄ and immature adult (L₅) stages of *T. cati* infections in experimentally infected cats.

Ectoparasite Indications (Fleas and Ticks):

1. Flea indications (*Ctenocephalides felis*):

Title: Evaluation of the Effectiveness and Speed of Kill of Fluralaner 280 mg/mL plus Moxidectin 14 mg/mL Spot-on Solution for Cats against Experimental Infestations of *Ctenocephalides felis* in Cats. (Study No. S15318-00)

Study Dates: June 2016 to November 2016

Study Location: Turlock, CA, USA

Study Design:

Objective: To confirm the effectiveness and speed of kill of fluralaner and moxidectin topical solution at the recommended minimum dose (40 mg/kg fluralaner and 2 mg/kg moxidectin) for the treatment of flea infestations. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Study Animals: 50 healthy cats (Domestic short-haired, 22 males and 28 females), 6 months to 10.9 years of age, and 2.3 to 7.6 kg body weight.

Experimental Design: Prior to allocation to treatment groups on Day -5, an initial flea infestation and count was conducted to evaluate the susceptibility of each cat to experimental infestation (host suitability). Cats were ranked and blocked by live flea count, and one cat from each block was randomly assigned to one of two untreated control groups (10 cats/group), one of two fluralaner and moxidectin topical solution groups (10 cats/group), or a moxidectin topical solution group (10 cats).

Drug administration was on Day 0. Flea infestations were conducted on Days -1, 30, 60, and 90. At each infestation, each cat was infested with approximately 100 unfed adult fleas.

For Groups 1 and 2 (one control and one fluralaner and moxidectin topical solution group), flea counts were conducted at 12 hours following drug administration or infestation. For Groups 3, 4, and 5 (one control, one fluralaner and moxidectin topical solution group, and one moxidectin topical solution group), flea counts were conducted at 24 hours following drug administration or infestation. Fleas were not returned to the cat after counting.

Drug Administration: On Day 0, fluralaner and moxidectin topical solution was applied to 20 cats at doses as close as possible to 40 mg/kg fluralaner and 2 mg/kg moxidectin. Fluralaner doses ranged from 39.4 to 40.9 mg/kg, and moxidectin doses ranged from 2.0-2.1 mg/kg. The moxidectin topical solution was administered topically to 10 cats at a dose of 2.0 mg/kg. For both solutions, hair at the administration site was parted, and the topical solution was applied to the skin in one or two spots at the base of the skull. Cats in the control group were sham treated.

Measurements and Observations: The primary variable for effectiveness was live flea counts collected from the cats. At flea counts on Days 0, 30, 60, and 90, and Days 1, 31, 61, and 91 for the 12-hour and 24-hour groups, respectively, fleas were removed, and the numbers of live fleas were recorded. General health observations were conducted daily for 3 minutes and at approximately 1, 3, 6, and 24 hours following drug administration. Treatment site observations were made on Days 1, 2, 3, 7, 14, 30, 60, and 90. Cats were weighed on Day -1 for dose calculations. Flea counts and health observations were conducted by individuals masked to treatment.

Statistical Methods: A 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 treated group with its paired control group were tested using a two-sided 5% significance level. Percent effectiveness of each treated group with respect to its paired control group was calculated based on geometric means.

Results: At each flea count, at least 9 of the 10 cats in the 12-hour control group and at least 8 of the 10 cats in the 24-hour control group had an adequate infestation, defined as at least 50 live fleas (50% of the infestations of 100 fleas per cat).

The 12-hour fluralaner and moxidectin topical solution group had a greater than 90% reduction in live flea counts at 12 hours following drug administration or infestation for 3 months. On all count days following drug administration, live flea counts between the fluralaner and moxidectin topical solution treated group and the control group were significantly different ($p \leq 0.0004$).

Table II.9: Study S15318-00; Live Flea Count Results, 12-hour Counts

Day for 12-hour Counts	Control Group Flea Counts*	Fluralaner and Moxidectin Topical Solution Group Flea Counts*	Percent Effectiveness
0	75.4	0.0	100
30	68.9	0.0	100
60	68.4	0.7	99.0
90	72.2	5.3	92.6

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

The 24-hour fluralaner and moxidectin topical solution group had a greater than 90% reduction in live flea counts at 24 hours following administration or infestation for 3 months. On all count days following drug administration, live flea counts between the fluralaner and moxidectin topical solution group and the control group were significantly different ($p < 0.0001$).

The moxidectin topical solution group did not demonstrate 90% effectiveness against fleas at 24 hours following drug administration or infestation at any time during the study.

Table II.10: Study S15318-00; Live Flea Count Results, 24-hour Counts

Day for 24-hour Counts	Control Group	Fluralaner and Moxidectin Topical Solution Group		Moxidectin Topical Solution Group	
	Flea Counts*	Flea Counts*	Percent Effectiveness	Flea Counts*	Percent Effectiveness
0	65.0	0.0	100	74.1	0.0
31	66.4	0.0	100	62.7	5.5
61	72.6	0.2	99.7	57.9	20.2
91	62.3	4.0	93.6	50.2	19.4

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

Adverse Reactions: At approximately 4 hours following administration, a cat in the 12-hour fluralaner and moxidectin topical solution group was panting and had an elevated body temperature and dilated pupils. Cold packs were placed with the cat, and the cat returned to normal within 3 to 4 hours. One

cat that received the moxidectin topical solution had hypersalivation immediately after application of the product. The cat returned to normal without treatment for the hypersalivation.

Conclusion: This study demonstrated the effectiveness of fluralaner and moxidectin topical solution for the treatment of existing flea infestations for three months when assessed 12 and 24 hours after drug administration or infestation. Moxidectin alone was not effective against flea infestations, thus justifying the inclusion of fluralaner in this combination. The panting, pyrexia, and mydriasis in the cat treated with fluralaner and moxidectin topical solution, and the hypersalivation in the cat treated with the moxidectin topical solution, should be considered possible drug-related adverse reactions.

Additional Study: In a second well-controlled laboratory study, fluralaner and moxidectin topical solution had a greater than 90% reduction in live flea counts at 24 hours following administration or infestation for 61 days. Fluralaner and moxidectin topical solution was less than 90% effective (75%) at 91 days.

2. Treatment and Control of Tick Infestations:

- a. **Title:** Evaluation of the Effectiveness of Fluralaner 280 mg/mL + Moxidectin 14 mg/mL Spot-on Solution for Cats against Experimental Infestations of *Dermacentor variabilis* in Cats. (Study No. 15311-01)

Study Dates: February 2016 to March 2017

Study Location: Stanwood, MI, USA

Study Design:

Objective: To confirm the effectiveness of fluralaner and moxidectin topical solution at the recommended minimum dose (40 mg/kg fluralaner and 2 mg/kg moxidectin) for the treatment and control of infestations of *D. variabilis* in cats. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Study Animals: 30 healthy cats (Domestic short-hair; 6 males and 24 females), approximately 8.5 to 9.5 months of age, and 2.1 to 4.8 kg body weight.

Experimental Design: Prior to allocation to treatment groups on Day -5, an initial tick infestation and count was conducted to evaluate the susceptibility of each cat to experimental infestation (host suitability). Cats were ranked and blocked by live tick count, and one cat from each block was randomly assigned to an untreated control group (10 cats), a fluralaner and moxidectin topical solution treatment group (10 cats), or a moxidectin topical solution treatment group (10 cats).

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 30, 60, and 90. At each infestation, each cat was infested with

approximately 50 adult, newly emerged, unfed *D. variabilis* ticks (approximate 50:50 ratio of male to female ticks).

Tick counts were performed on Day 2, 48 hours after drug administration, and on Days 32, 62, and 92, 48 hours after tick infestations. Ticks were not returned to the cat after counting.

Drug Administration: On Day 0, fluralaner and moxidectin topical solution was applied to 10 cats at doses as close as possible to 40 mg/kg fluralaner and 2 mg/kg moxidectin. Fluralaner doses ranged from 39.6 to 40.4 mg/kg, and moxidectin was administered at 2.0 mg/kg. The moxidectin topical solution was administered topically to 10 cats at 2.0 mg/kg. For both solutions, hair at the administration site was parted, and the topical solution was applied to the skin in one or two spots at the base of the skull. Cats in the control group were sham treated.

Measurements and Observations: The primary variable for effectiveness was the counts of live ticks collected from the cats. At tick counts on Days 2, 32, 62, and 92, ticks were removed, and the numbers of live and dead ticks were recorded. General health observations were conducted daily. In addition, each cat was observed for 3 minutes and at approximately 1, 3, 6, and 24 hours following drug administration. Treatment site observations were made on Days 1, 2, 3, 7, 14, 30, 60, and 92. Cats were weighed on Day -2 for dose calculations. Tick counts and health observations were conducted by individuals masked to treatment.

Statistical Methods: A 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. The comparisons of each treated group with its paired control group were tested using a two-sided 5% significance level. Percent effectiveness of each treated group with respect to its paired control group was calculated based on geometric means.

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

The fluralaner and moxidectin topical solution group had a greater than 90% reduction in live tick counts at 48 hours following drug administration or infestation for 2 months (infestation on Day 60). On all count days following drug administration, live tick counts for the fluralaner and moxidectin topical solution group were significantly different from the control group ($p < 0.0001$).

The moxidectin topical solution group did not demonstrate 90% effectiveness against *D. variabilis* ticks at 48 hours following drug administration or infestation at any time during the study. Live tick counts in the moxidectin topical solution group were different ($p = 0.0160$) from the control group on Day 2 but not at any other point in the study ($p \geq 0.1305$).

Table II.11: Study S15311-01; *D. variabilis* Live Tick Count Results

Day for Tick Counts	Control Group	Fluralaner and Moxidectin Topical Solution Group		Moxidectin Topical Solution Group	
	Live Tick Counts*	Live Tick Counts*	Percent Effectiveness	Live Tick Counts*	Percent Effectiveness
2	22.8	0.0	100	14.6	35.9
32	31.2	0.0	100	26.8	14.1
62	38.9	0.4	99.0	37.5	3.6
92	22.8	3.2	86.0	20.4	10.5

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

On all count days following drug administration, dead tick counts for the fluralaner and moxidectin topical solution group were significantly different from the control group ($p \leq 0.0013$). On Day 2, dead tick counts for the moxidectin topical group were significantly different from the control group ($p = 0.0269$) but were not significantly different at any of the other count days ($p \geq 0.1247$).

Table II.12: Study S15311-01; *D. variabilis* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts*	Fluralaner and Moxidectin Topical Solution Group Dead Tick Counts*	Moxidectin Topical Solution Group Dead Tick Counts*
2	0.1	3.2	1.6
32	0.0	8.8	0.5
62	0.0	11.4	0.0
92	0.0	2.0	0.0

*Tick counts are geometric means.

Adverse Reactions: On Day 1, two cats from the fluralaner and moxidectin topical solution group and one cat from the control group were observed with mild crusts/scabs on the dorsal midline. These crusts/scabs resolved within five days.

Conclusion: This study demonstrated the effectiveness of fluralaner and moxidectin topical solution for the control (reduced live ticks) and treatment (increased dead ticks) of *D. variabilis* ticks for two months when assessed at 48 hours after drug administration or infestation. Fluralaner and moxidectin topical solution did not demonstrate adequate (> 90%) effectiveness against *D. variabilis* when assessed 48 hours after treatment or infestation for three months. Moxidectin alone was not effective for the control and treatment of *D. variabilis* ticks, thus justifying the inclusion of fluralaner in this combination. The crusts and scabs on the two treated cats should be considered possible drug-related adverse reactions.

- b. **Title:** Evaluation of the Effectiveness of Fluralaner 280 mg/ml + Moxidectin 14 mg/ml Spot-on Solution for Cats against Experimental Infestations of *Dermacentor variabilis* in Cats. (Study No. 15311-02)

Study Dates: February 2016 to February 2017

Study Location: Nowata, OK, USA

Study Design:

Objective: To confirm the effectiveness of fluralaner and moxidectin topical solution at the recommended minimum dose (40 mg/kg fluralaner and 2 mg/kg moxidectin) for the treatment and control of infestations of *D. variabilis* in cats. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Study Animals: 20 healthy cats (Domestic short- and long-hair; 9 males and 11 females), approximately 1.1 to 6.7 years of age, and 1.9 to 4.8 kg body weight.

Experimental Design: Prior to allocation to treatment groups on Day -3, an initial tick infestation and count was conducted to evaluate the susceptibility of each cat to experimental infestation (host suitability). Cats were ranked and blocked by live tick count, and one cat from each block was randomly assigned to the untreated control group (10 cats) or the fluralaner and moxidectin topical solution treatment group (10 cats).

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 30, 60, and 90. At each infestation, each cat was infested with approximately 50 adult, newly emerged, unfed *D. variabilis* ticks (approximate 50:50 ratio of male to female ticks).

Tick counts were performed on Day 2, 48 hours after drug administration, and on Days 32, 62, and 92, 48 hours after tick infestations. Ticks were not returned to the cat after counting.

Drug Administration: On Day 0, fluralaner and moxidectin topical solution was applied to 10 cats at doses as close as possible to 40 mg/kg fluralaner and 2 mg/kg moxidectin. Hair at the administration site was parted, and the topical solution was applied to the skin in one spot at the base of the skull. Fluralaner doses ranged from 39.6 to 40.4 mg/kg, and moxidectin was administered at 2.0 mg/kg. Cats in the control group were sham treated.

Measurements and Observations: The primary variable for effectiveness was the counts of live ticks collected from the cats. At tick counts on Days 2, 32, 62, and 92, ticks were removed, and the numbers of live and dead ticks were recorded. General health observations were conducted daily. In addition, each cat was observed for 3 minutes and at approximately 1, 3, 6, and 24 hours following drug administration. Treatment site observations were made on Days 1, 2, 3, 7, 14, 30, 60, and 92. Cats were weighed on Day -2 for dose calculations. Tick counts

and health observations were conducted by individuals masked to treatment.

Statistical Methods: A 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 was calculated based on geometric means.

Results: At each tick count day, at least 7 of the 10 cats in the control group had an adequate infestation, defined as at least 13 live *D. variabilis* ticks (25% of the infestations of 50 ticks per cat).

The fluralaner and moxidectin topical solution group had a greater than 90% reduction in live tick counts at 48 hours following drug administration or infestation for 1 month (infestation on Day 30).

On Days 2, 32, and 62 following drug administration, live tick counts for the fluralaner and moxidectin topical solution group were significantly different from the control group ($p \leq 0.0020$). On Day 92, live tick counts for the fluralaner and moxidectin topical solution group were not significantly different from the control group ($p=0.8157$).

Table II.13: Study S15311-02; *D. variabilis* Live Tick Count Results

Day for Tick Counts	Control Group Live Tick Counts *	Fluralaner and Moxidectin Topical Solution Group Live Tick Counts *	Percent Effectiveness
2	15.4	0.1	99.4
32	25.5	0.1	99.6
62	27.4	4.0	85.4
92	20.9	21.7	0.0

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

On all count days following drug administration, dead tick counts for the fluralaner and moxidectin topical solution group were significantly different from the control group ($p \leq 0.0024$).

Table II.14: Study S15311-02; *D. variabilis* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts *	Fluralaner and Moxidectin Topical Solution Group Dead Tick Counts *
2	0.1	2.8
32	0.1	16.9
62	0.0	7.7
92	0.1	2.3

*Tick counts are geometric means.

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

Conclusion: This study demonstrated the effectiveness of fluralaner and moxidectin topical solution for the control (reduced live ticks) and treatment (increased dead ticks) of *D. variabilis* ticks for one month when assessed at 48 hours after drug administration or infestation. Fluralaner and moxidectin topical solution did not demonstrate adequate (> 90%) effectiveness against *D. variabilis* when assessed 48 hours after treatment or infestation for both two and three months.

- c. **Title:** Evaluation of the Effectiveness of Fluralaner 280 mg/mL + Moxidectin 14 mg/mL Spot-on Solution for Cats against Experimental Infestations of *Dermacentor variabilis* in Cats. (Study No. S15311-03)

Study Dates: February 2017 to June 2018

Study Location: Nowata, OK, USA

Study Design:

Objectives: To confirm the effectiveness of fluralaner and moxidectin topical solution at the recommended minimum dose (40 mg/kg fluralaner and 2 mg/kg moxidectin) for the treatment and control of infestations of *D. variabilis* in cats. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Study Animals: 20 healthy cats (Domestic short- and long-hair; 7 males and 13 females), approximately 1.1 to 1.8 years of age, and 2.9 to 4.8 kg body weight.

Experimental Design: Prior to allocation to treatment groups on Day -4, an initial tick infestation and count was conducted to evaluate the susceptibility of each cat to experimental infestation (host suitability). Cats were ranked and blocked by live tick count, and one cat from each block was randomly assigned to the untreated control group (10 cats) or the fluralaner and moxidectin topical solution treatment group (10 cats).

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 30, 60, and 90. At each infestation, each cat was infested with approximately 50 adult, newly emerged, unfed *D. variabilis* ticks (approximate 50:50 ratio of male to female ticks).

Tick counts were performed on Day 2, 48 hours after drug administration, and on Days 32, 62, and 92, 48 hours after tick infestations. Ticks were not returned to the cat after counting.

Drug Administration: On Day 0, fluralaner and moxidectin topical solution was applied to 10 cats at doses as close as possible to 40 mg/kg fluralaner and 2 mg/kg moxidectin. Hair at the administration site was parted, and the topical solution was applied to the skin in one spot at the base of the skull. Fluralaner doses ranged from 39.6 to 40.3 mg/kg, and moxidectin was administered at 2.0 mg/kg. Cats in the control group were sham treated.

Measurements and Observations: The primary variable for effectiveness was the counts of live ticks collected from the cats. At tick counts on Days 2, 32, 62, and 92, ticks were removed, and the numbers of live and dead ticks were recorded. General health observations were conducted daily. In addition, each cat was observed for 3 minutes and at approximately 1, 3, 6, and 24 hours following drug administration. Treatment site observations were made on Days 1, 2, 3, 7, 14, 30, 60, and 92. Cats were weighed on Day -2 for dose calculations. Tick counts and health observations were conducted by individuals masked to treatment.

Statistical Methods: A 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 was calculated based on geometric means.

Results: At each tick count day, all 10 cats in the control group had an adequate infestation, defined as at least 13 live *D. variabilis* ticks (25% of the infestations of 50 ticks per cat).

The fluralaner and moxidectin topical solution group had a greater than 90% reduction in live tick counts at 48 hours following drug administration or infestation for 2 months (infestation on Day 60).

On Days 2, 32, 62, and 92 following drug administration, live tick counts for the fluralaner and moxidectin topical solution group were significantly different from the control group ($p < 0.0001$).

Table II.15: Study S15311-03; *D. variabilis* Live Tick Count Results

Day for Tick Counts	Control Group Live Tick Counts *	Fluralaner and Moxidectin Topical Solution Group Live Tick Counts *	Percent Effectiveness
2	30.0	0.0	100
32	35.6	0.0	100
62	29.3	1.9	93.5
92	28.6	9.1	68.3

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

On all count days following drug administration, dead tick counts for the fluralaner and moxidectin topical solution group were significantly different from the control group ($p < 0.0059$).

Table II.16: Study S15311-03; *D. variabilis* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts *	Fluralaner and Moxidectin Topical Solution Group Dead Tick Counts *
2	0.1	6.5
32	0.0	21.8
62	0.1	2.8
92	0.0	0.8

*Tick counts are geometric means.

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

Conclusion: This study demonstrated the effectiveness of fluralaner and moxidectin topical solution for the control (reduced live ticks) and treatment (increased dead ticks) of *D. variabilis* ticks for two months when assessed at 48 hours after drug administration or infestation. Fluralaner and moxidectin topical solution did not demonstrate adequate (> 90%) effectiveness against *D. variabilis* when assessed 48 hours after treatment or infestation for three months.

Overall Conclusions for D. variabilis:

Although Study S15311-02 failed to demonstrate > 90% effectiveness at 2 months, when combined with Studies S15311-01 and S15311-03, the average effectiveness through 2 months is > 90%. Therefore, the combined data demonstrate that fluralaner and moxidectin topical solution is effective for the treatment and control of *D. variabilis* infestations for 2 months when assessed at 48 hours after drug administration or infestation.

- d. **Title:** Evaluation of Effectiveness of Fluralaner 280 mg/ml + Moxidectin 14 mg/ml Spot-on Solution for Cats against Experimental Infestations of *Ixodes scapularis* in Cats. (Study No. 15312-01)

Study Dates: February 2016 to October 2016

Study Location: Turlock, CA, USA

Study Design:

Objective: To confirm the effectiveness of fluralaner and moxidectin topical solution at the recommended minimum dose (40 mg/kg fluralaner and 2 mg/kg moxidectin) for the treatment and control of infestations of *I. scapularis* in cats. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Study Animals: 30 healthy cats (Domestic short- and long-hair; 12 males and 18 females), 2.1 to 12.1 years of age, and 2.4 to 6.9 kg body weight.

Experimental Design: Prior to allocation to treatment groups on Day -5, an initial tick infestation and count was conducted to evaluate the susceptibility of each cat to experimental infestation (host suitability). Cats were ranked and blocked by live tick count, and one cat from each block was randomly assigned to an untreated control group (10 cats), a fluralaner and moxidectin topical solution treatment group (10 cats) or a moxidectin topical solution treatment group (10 cats).

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 30, 60, and 90. At each infestation, each cat was infested with approximately 75 adult, newly emerged, unfed *I. scapularis* ticks (approximate 50:50 ratio of male to female ticks).

Tick counts were performed on Day 2, 48 hours after drug administration, and on Days 32, 62, and 92, 48 hours after tick infestations. Ticks were not returned to the cat after counting.

Drug Administration: On Day 0, fluralaner and moxidectin topical solution was applied to 10 cats at doses as close as possible to 40 mg/kg fluralaner and 2 mg/kg moxidectin. Fluralaner doses ranged from 39.7 to 40.2 mg/kg, and moxidectin was administered at 2.0 mg/kg. The moxidectin topical solution was administered topically to 10 cats at 2.0 mg/kg. For both solutions, hair at the administration site was parted, and the topical solution was applied to the skin in one or two spots at the base of the skull. Cats in the control group were sham treated.

Measurements and Observations: The primary variable for effectiveness was the counts of live ticks collected from the cats. At tick counts on Days 2, 32, 62, and 92, ticks were removed, and the numbers of live and dead ticks were recorded. General health observations were conducted daily. In addition, each cat was observed for 3 minutes and at approximately 1, 3, 6, and 24 hours following drug administration.

Treatment site observations were made on Days 1, 2, 3, 7, 14, 30, 60, and 92. Cats were weighed on Day -2 for dose calculations. Tick counts and health observations were conducted by individuals masked to treatment.

Statistical Methods: A 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. The comparisons of each treated group with its paired control group were tested using a two-sided 5% significance level. Percent effectiveness of each treated group with respect to its paired control group was calculated based on geometric means.

Results: At each tick count day, all 10 cats in the control group had an adequate infestation, defined as at least 19 live *I. scapularis* ticks (25% of the infestations of 75 ticks per cat).

The fluralaner and moxidectin topical solution group had a greater than 90% reduction in live tick counts at 48 hours following drug administration or infestation for 3 months (infestation on Day 90). On all count days following drug administration, live tick counts for the fluralaner and moxidectin topical solution group were significantly different from the control group ($p < 0.0001$).

The moxidectin topical solution group did not demonstrate 90% effectiveness against *I. scapularis* ticks at 48 hours following drug administration or infestation at any time during the study. Live tick counts in the moxidectin topical solution group were different ($p = 0.0010$) from the control group on Day 2 but not at any other point in the study ($p \geq 0.0661$).

Table II.17: Study S15312-01; *I. scapularis* Live Tick Count Results

Day for Tick Counts	Control Group	Fluralaner and Moxidectin Topical Solution Group		Moxidectin Topical Solution Group	
	Live Tick Counts *	Live Tick Counts *	Percent Effectiveness	Live Tick Counts *	Percent Effectiveness
2	48.6	0.1	99.7	27.4	43.6
32	63.1	0.6	99.0	41.4	34.4
62	54.1	0.3	99.4	48.7	10.0
92	52.9	0.7	98.7	52.1	1.5

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

On all count days following drug administration, dead tick counts for the fluralaner and moxidectin topical solution group were significantly different from the control group ($p < 0.0001$). On Day 2, dead tick counts for the moxidectin topical solution group were significantly different from the control group ($p < 0.0001$) but were not significantly different at any of the other count days ($p \geq 0.3866$).

Table II.18: Study S15312-01; *I. scapularis* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts *	Fluralaner and Moxidectin Topical Solution Group Dead Tick Counts *	Moxidectin Topical Solution Group Dead Tick Counts *
2	0.0	18.2	9.6
32	0.0	15.4	0.1
62	0.0	13.9	0.0
92	0.0	15.5	0.0

*Tick counts are geometric means.

Adverse Reactions: Four cats in the fluralaner and moxidectin topical solution or moxidectin topical solution group developed, at various days throughout the study, excoriations behind their ears from scratching. All four cats were administered medication and returned to normal.

Conclusion: This study demonstrated the effectiveness of fluralaner and moxidectin topical solution for the control (reduced live ticks) and treatment (increased dead ticks) of *I. scapularis* ticks for three months when assessed at 48 hours after drug administration or infestation. Moxidectin alone was not effective for the control and treatment of *I. scapularis* ticks, thus justifying the inclusion of fluralaner in this combination. The pruritus and secondary excoriations in the four treated cats should be considered possible drug-related adverse reactions.

- e. **Title:** Evaluation of the Effectiveness of Fluralaner 280 mg/mL + Moxidectin 14 mg/mL Spot-on Solution for Cats against Experimental Infestations of *Ixodes scapularis* in Cats. (Study No. 15312-03)

Study Dates: June 2018 to November 2018

Study Location: Bloemfontein, South Africa

Study Design:

Objective: To confirm the effectiveness of fluralaner and moxidectin topical solution at the recommended minimum dose (40 mg/kg fluralaner and 2 mg/kg moxidectin) for the treatment and control of infestations of *I. scapularis* in cats. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Study Animals: 20 healthy cats (Domestic short-, medium- and long-hair; 9 males and 11 females), approximately 0.7 to 8.2 years of age, and 2.0 to 4.4 kg body weight.

Experimental Design: Prior to allocation to treatment groups on Day -5, an initial tick infestation and count was conducted to evaluate the susceptibility of each cat to experimental infestation (host suitability). Cats were ranked and blocked by live tick count, and one cat from each block was randomly assigned to the untreated control group (10 cats) or the fluralaner and moxidectin topical solution treatment group (10 cats).

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 30, 60, and 90. At each infestation, each cat was infested with approximately 50 adult, unfed *I. scapularis* (U.S. source) ticks (approximate 40:10 ratio of female to male ticks).

Tick counts were performed on Day 2, 48 hours after drug administration, and on Days 32, 62, and 92, 48 hours after tick infestations. Ticks were not returned to the cat after counting.

Drug Administration: On Day 0, fluralaner and moxidectin topical solution was applied to 10 cats, at doses as close as possible to 40 mg/kg fluralaner and 2 mg/kg moxidectin. Hair at the administration site was parted, and the topical solution was applied to the skin in one or two spots at the base of the skull. Fluralaner doses ranged from 39.6 to 40.6 mg/kg, and moxidectin was administered at 2.0 mg/kg. Cats in the control group were sham treated.

Measurements and Observations: The primary variable for effectiveness was the counts of live ticks collected from the cats. At tick counts on Days 2, 32, 62, and 92, ticks were removed, and the numbers of live and dead ticks were recorded. General health observations were conducted daily. In addition, each cat was observed for 3 minutes and at approximately 1, 3, 6, and 24 hours following drug administration. Treatment site observations were made on Days 1, 2, 3, 7, 14, 30, 60, and 92. Cats were weighed on Day -2 for dose calculations. Tick counts and health observations were conducted by individuals masked to treatment.

Statistical Methods: A 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 was calculated based on geometric means.

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

The fluralaner and moxidectin topical solution group had a greater than 90% reduction in live tick counts at 48 hours following drug administration or infestation for 3 months (infestation on Day 90).

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

Table II.19: Study S15312-03; *I. scapularis* Live Tick Count Results

Day for Tick Counts	Control Group Live Tick Counts *	Fluralaner and Moxidectin Topical Solution Group Live Tick Counts *	Percent Effectiveness
2	17.4	0.0	100
32	26.8	0.0	100
62	35.1	0.0	100
92	26.6	0.5	98.1

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

On all count days following drug administration, dead tick counts for the fluralaner and moxidectin topical solution group were significantly different from the control group ($p \leq 0.0003$).

Table II.20: Study S15312-03; *I. scapularis* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts *	Fluralaner and Moxidectin Topical Solution Group Dead Tick Counts *
2	0.8	6.0
32	0.1	11.1
62	0.3	12.9
92	0.0	7.4

*Tick counts are geometric means.

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

Conclusion: This study demonstrated the effectiveness of fluralaner and moxidectin topical solution for the control (reduced live ticks) and treatment (increased dead ticks) of *I. scapularis* ticks for three months when assessed at 48 hours after drug administration or infestation.

III. TARGET ANIMAL SAFETY

The safety of BRAVECTO® PLUS was demonstrated in three well-controlled laboratory studies and in one well-controlled field study described below. The purpose of these studies was to provide information on the safety of BRAVECTO® PLUS when used according to the label in cats. In the margin of safety study, which included groups of cats administered elevated doses of the drug, adverse reactions included hypersalivation, pruritus at the administration site, and loose feces. Oral tolerance was evaluated to assess the effects of accidental oral ingestion in cats, including from licking or grooming the application site. Oral administration resulted in hypersalivation in five cats immediately following administration, as well as vomiting in two cats at 2 and 8 hours post-oral administration, respectively. Cats also had reduced food consumption on the day of administration. In the heartworm-positive safety study, self-limiting hypersalivation was observed on the day of treatment in both groups administered fluralaner and moxidectin topical solution (6/8 cats in the 1X group and 7/8 cats in the 3X group). Three treated cats (2/8 cats in the 1X group

and 1/8 cats in the 3X group) had neurologic signs during the study, including ataxia, paresis, and muscle tremors, and were euthanized due to quality-of-life concerns. Therefore, BRAVECTO® PLUS should be used with caution in cats that are heartworm positive. In a well-controlled field study, BRAVECTO® PLUS was used concurrently with other medications, such as vaccines, anthelmintics, antibiotics, and steroids. No adverse reactions were observed from the concurrent use of BRAVECTO® PLUS with other medications. These safety studies, in combination with the safety information collected in the effectiveness studies, demonstrate the safety of BRAVECTO® PLUS when used according to the label.

A. Margin of Safety Study

Title: Target Animal Safety Study in Kittens when Administered Fluralaner 280 mg/mL plus Moxidectin 14 mg/mL Spot-on Solution for Cats Topically on Three Occasions 56 Days Apart (Study D0009\15-002).

Study Dates: May 2015 to October 2016

Study Location: Mayo, Ireland

Study Design:

Objective: To assess the safety of fluralaner and moxidectin topical solution administered at doses of 1X, 3X, and 5X the maximum labeled dose (93.0 mg fluralaner/kg and 4.7 mg moxidectin/kg, 279.0 mg fluralaner/kg and 14.0 mg moxidectin/kg, and 465.0 mg fluralaner/kg and 23.3 mg moxidectin/kg, respectively) to kittens three times at eight-week intervals. The study was conducted in accordance with the Good Laboratory Practice (GLP) principles of the Organization for Economic Co-Operation and Development (OECD).

Study Animals: 40 healthy weaned kittens (mixed-breed, 20 male and 20 female), 61 to 92 days of age, and 0.9 to 1.9 kg body weight.

Experimental design: Cats were randomized to one of four treatment groups of ten kittens per group (five per sex) within sex by body weight. The study was run in three sets as kittens became available. Cats were administered fluralaner and moxidectin topical solution at 1X, 3X, and 5X the maximum labeled dose (93.0 mg fluralaner/kg and 4.7 mg moxidectin/kg) three times at eight-week intervals (Days 0, 56, and 112) or were administered mineral oil (control group).

Drug administration: Hair at the administration site was parted, and the fluralaner and moxidectin topical solution or mineral oil was applied to the skin along the cat's top-line, starting at the shoulder blades and moving toward the tail.

Measurements and Observations: Clinical observations were made twice daily, five times during the first hour after dosing, and at 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, and 84 hours after dosing on Days 0, 56, and 112. Body weight was recorded weekly. Individual food consumption was recorded daily. Physical examinations were performed on Days -14, -7, -1, 14, 55 or 56, 70, 111, 126, and 167. Blood samples were collected for clinical pathology (hematology, coagulation profile, clinical chemistry, and serum amyloid A) on Days -13 (no coagulation), -6

(coagulation only), 21, 50, 106, and 162; and for plasma fluralaner and moxidectin concentrations on Days -1, 3, 7, 14, 28, 42, 55, 59, 63, 70, 84, 98, 111, 115, 119, 126, 140, 154, and 167. Urine samples were collected overnight for urinalysis on Days -7/-6, 20/21, 49/50, 105/106, and 161/162. All cats were euthanized on Day 168 and underwent full gross necropsy, organ weight determination, and histopathological evaluation.

Statistical Methods: Hematology, clinical chemistry, coagulation, serum amyloid A, numerical urinalysis variables, heart rate, rectal temperature, and food consumption were analyzed using repeated measures mixed model analysis of covariance. Pre-treatment measurement was included as a covariate. Body weight was analyzed using a repeated measures mixed model. Organ weights were analyzed using a mixed model analysis of variance.

Results: There were no clinically-relevant, treatment-related effects on physical examinations, body weights, food consumption, clinical pathology (hematology, clinical chemistries, serum amyloid A, coagulation profile, and urinalysis), gross pathology, or organ weights. Single incidences of self-limiting hypersalivation in three kittens (one kitten in the 1X group and two kittens in the 3X group) and pruritus at the administration site in one kitten in the 3X group were observed on the day of administration. Transient loose feces were noted in four kittens (one in each dose group) during the first 4 to 48 hours after dosing. Cosmetic changes at the application site included matting/clumping/spiking of hair, wetness, or a greasy appearance. Minimally increased numbers of globular leukocytes in the duodenum, jejunum, and ileum were noted during histopathologic examination in all of the dose groups (five kittens in the control group, four in the 1X group, nine in the 3X group, and six in the 5X group). None of the kittens had abnormal clinical pathology results or clinical signs associated with the microscopic findings.

Plasma concentrations of fluralaner confirmed systemic exposure in all kittens administered fluralaner and moxidectin topical solution. Fluralaner and moxidectin concentrations did not reach steady state during the study. There was a less than dose proportional increase and approximately 3X accumulation in both fluralaner and moxidectin plasma concentrations after administration of the 3X and 5X doses.

Conclusion: This study supports the safe use of fluralaner and moxidectin topical solution in cats when used at the labeled dose and duration. Treatment-related effects included hypersalivation, pruritus at the administration site, and loose feces.

B. Oral Safety Study

Title: Target Animal Safety Study in Cats when Administered Fluralaner 280 mg/mL plus Moxidectin 14 mg/mL Spot-on Solution for Cats Orally on One Occasion (Study D009\15-001).

Study Dates: May 2015 to May 2016

Study Location: Mayo, Ireland

Study Design:

Objective: To assess the effects of fluralaner and moxidectin topical solution in juvenile cats following oral administration at a dose of 1X of the maximum labeled dose (93.0 mg fluralaner/kg and 4.7 mg moxidectin/kg). The study was conducted in accordance with the Good Laboratory Practice (GLP) principles of the Organization for Economic Co-Operation and Development (OECD).

Study Animals: 12 healthy cats (mixed-breed, 6 male and 6 female), 4 to 9 months of age, and 1.9 to 5.2 kg body weight.

Experimental Design: Cats were randomized to two treatment groups of six cats per group (three per sex) within sex by age on Day -1. Cats were orally administered fluralaner and moxidectin topical solution at 93.0 and 4.7 mg/kg, respectively (the maximum labeled dose), once or were administered saline (control group).

Drug Administration: The cats were fed prior to oral administration of fluralaner and moxidectin topical solution.

Measurements and Observations: Clinical observations were made twice daily, for 10 minutes immediately after dosing, and at 15 and 30 minutes, and 1, 2, 3, 4, 8, 12, 24, 36, 48, 60, 72, and 84 hours after dosing on Day 0. Body weight was recorded weekly. Individual food consumption was recorded daily. Physical examinations were performed on Days -14, -7, -1, and 28. Blood samples were collected for clinical pathology (hematology, coagulation profile, clinical chemistry, and serum amyloid A) on Days -13 and 8 and for plasma fluralaner and moxidectin concentrations on Days -5, 2, 7, 14, and 28. Urine samples were collected overnight for urinalysis on Days -14/-13 and 7/8.

Statistical Methods: Weekly food consumption was analyzed using a repeated measures mixed model analysis of covariance. Bodyweight was analyzed by mixed model analysis of covariance for a repeated measures design. The pre-treatment bodyweight values were averaged to provide baseline as a covariate in the model. Hematology, clinical chemistry, coagulation, serum amyloid A, numerical urinalysis variables, heart rate, and rectal temperature were analyzed by mixed model analysis of covariance with the pre-treatment measurement included as a covariate.

Results: There were no clinically-relevant, treatment-related effects on physical examinations, body weights, or clinical pathology (hematology, clinical chemistries, coagulation profiles, serum amyloid A, and urinalysis). Hypersalivation was observed in five of six cats orally administered fluralaner and moxidectin topical solution. One treated cat vomited 2 hours after dosing and another vomited 8 hours after dosing. Food consumption was reduced in treated cats on the day of dosing.

The systemic fluralaner and moxidectin exposures after a single oral dose were approximately the same and twice the exposure, respectively, as after the first topical 1X dose in the margin of safety study. The systemic fluralaner and moxidectin exposures after a single oral dose were approximately one third and less than half of the exposure, respectively, as after the third topical 5X dose in the margin of safety study.

Conclusion: The oral administration of fluralaner and moxidectin topical solution at 93.0 and 4.7 mg/kg, respectively, was well tolerated in cats. Treatment-related effects include hypersalivation immediately after treatment and vomiting and reduced food consumption on the day of treatment.

C. Field Safety Study

Title: Clinical Field Safety Evaluation of Fluralaner 280 mg/mL and Moxidectin 14 mg/mL Spot-on Solution for Cats (Study S15088-00)

Study Dates: September 2015 to June 2017

Study Locations:

Largo, FL
Starke, FL
Augusta, ME
Springfield, MO

Study Design:

Objective: To assess the safety and tolerability of fluralaner 280 mg/mL and moxidectin 14 mg/mL topical solution for cats when administered by cat owners under field use conditions. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Study Animals: The study included 176 client-owned cats from 87 households; 135 cats (65 households) were treated with fluralaner and moxidectin topical solution and 41 cats (22 households) were treated with a topical solution containing imidacloprid plus moxidectin (active control). The study enrolled 95 females and 81 males, 10 weeks to 19.7 years of age, and 3.4 to 22.8 lb body weight. The study included purebred and mixed breed cats.

Enrollment eligibility included households with no more than 5 cats. There were no breed or sex restrictions, but pregnant or lactating cats were not eligible for enrollment. There were restrictions on the use of medications or products with flea treatment or control activity in any household cat or household premises prior to or during the study period. Products labeled for use against ear mite infestations, roundworm or hookworm infections, or prevention of heartworm infections were also not permitted.

Experimental Design: Households were randomly assigned to treatment with fluralaner and moxidectin topical solution or the active control in a ratio of three treated to one control household. Owners treated all cats in the fluralaner and moxidectin topical solution group after Visit 1 on Day 0 and again after Visit 4 on approximately Day 90. Control cats were treated after Visit 1 on Day 0 and again

after Visits 2, 3, and 4 on approximately Days 30, 60, and 90 for a total of four treatments. All cats within a household received the same treatment at the same time points. All cats completed the study following Visit 5 on approximately Day 120.

Investigators who performed safety assessments (physical examinations, clinical pathology result assessments, and adverse event assessments) and personnel that participated in collection or recording of outcomes were masked to treatment. Treatment administrators at each study location and owners were not masked.

Drug Administration: In the treated group, owners administered the fluralaner and moxidectin topical solution, at labeled doses, on Days 0 and 90. In the control group, owners administered the imidacloprid plus moxidectin topical solution at labeled doses on Days 0, 30, 60, and 90.

Measurements and Observations: The primary variables were physical examinations performed at each visit (Days 0, 30, 60, 90, and 120) and clinical pathology performed for all cats on Days 0, 90, and 120. Adverse reactions (AR) were recorded throughout the study.

Statistical Methods: No statistical analyses were conducted.

Results: There were no serious adverse reactions in any of the cats associated with treatment with fluralaner and moxidectin topical solution or the control.

Table III.1: Field Study S15088-00; Adverse Reactions

Adverse Reaction	Fluralaner and Moxidectin Topical Solution Group: Percent of Cats with the AR During the 120-Day Study (n=135 cats)	Active Control Group: Percent of Cats with the AR During the 120-Day Study (n=41 cats)
Vomiting	5.9%	12.2%
Alopecia (not at application site)	5.2%	2.4%
Pruritus	4.4%	12.2%
Application site pruritus	4.4%	4.9%
Diarrhea	3.7%	7.3%
Lethargy	3.7%	9.8%
Dry skin	3.0%	0.0%
Elevated alanine aminotransferase (ALT)*	3.0%	0.0%
Hypersalivation	1.5%	1.5%
Application site alopecia	0.7%	0.0%

*ALT was greater than twice the upper reference range of 100 IU/L. These cats also had mild elevations of aspartate aminotransferase (AST) (less than twice the upper reference range of 100 IU/L). No clinical signs associated with liver disease were noted in these cats.

Conclusion: This study demonstrated that fluralaner and moxidectin topical solution was safe when applied at the labeled dose to client-owned cats representing a range of breeds and sizes from across the United States.

D. Safety Study in Cats Infected with Adult *Dirofilaria immitis*

Title: Target Animal Safety Study in Cats Infected with Adult Heartworm following the Topical Administration of Fluralaner 280 mg/ml + Moxidectin 14 mg/ml Spot-on Solution for Cats (Study S14342-00)

Study Dates: January 2016 to May 2018

Study Location: Waverly, NY

Study Design:

Objective: To assess the safety of fluralaner and moxidectin topical solution following topical administration at doses of 1X (93.0 mg/kg fluralaner and 4.7 mg/kg moxidectin) or 3X (279.0 mg/kg fluralaner and 14.0 mg/kg moxidectin) the maximum label dose to cats infected with adult heartworm (*D. immitis*). The study was conducted in accordance with Good Laboratory Practice (GLP) regulations.

Study Animals: Twenty-four cats (domestic short hair, 12 male and 12 female), 14 to 15 months of age, and 2.7 to 6.2 kg body weight. Cats were each infected with approximately 100 *D. immitis* third stage larvae by subcutaneous injection approximately 8 months prior to test article administration. All cats tested positive for adult heartworm infection by antigen test and/or microfilaria test and/or echocardiography prior to treatment.

Experimental design: The study was a masked, controlled, laboratory study. Cats were ranked by Study Day -1 body weights regardless of sex and randomly assigned, in blocks of three, to one of three treatment groups (control, 1X, or 3X group). There were eight cats per group. Personnel performing body weight determination, clinical observations, physical examinations, clinical pathology analyses, and necropsies were masked to the treatment.

Drug administration: Cats were administered fluralaner and moxidectin topical solution at 93.0 mg/kg fluralaner and 4.7 mg/kg moxidectin or 279.0 mg/kg fluralaner and 14.0 mg/kg moxidectin (1X or 3X the maximum label dose, respectively) or were administered mineral oil (control group) on Day 0. The fluralaner and moxidectin topical solution or mineral oil was applied to the skin as a line from the base of the head along the back of the cats.

Measurements and Observations: Cage-side observations were conducted twice daily and clinical observations once daily. Physical examinations were performed on Days -14, -1, and 0, at 4 hours post-dose, and on Days 1, 9, 16, 22, 30, 58, and 90. Immediate post-dose observations were conducted one hour post-dosing. Body weight was recorded weekly. Blood samples were collected for clinical pathology (hematology, coagulation profile, and clinical chemistry) on Days -13, 28, 56, and 84 and for plasma fluralaner and moxidectin concentrations on Days -13, 7, 28, 56, and 84. All cats underwent macroscopic

examination at necropsy with histopathological examination of gross lesions. Adult heartworms were harvested at necropsy, measured, sexed, and assessed for vitality.

Statistical Methods: All continuous variables were analyzed using repeated measures analysis of variance using the best fitted covariance structure, with time, treatment, time-by-treatment interaction as fixed effects, pre-treatment values as a covariate (where applicable), and block and animal ID included as random effects. All statistical tests and pairwise comparisons between treatment groups were based on a significance level of 0.10. The Kenward-Roger approximation for denominator degrees of freedom was used. No adjustment was made for multiple comparisons.

Results: There were no clinically-relevant, treatment-related effects on body weights, clinical pathology (hematology, clinical chemistry, and coagulation profile), gross pathology, or histopathology. Self-limiting hypersalivation due to grooming was observed on the day of treatment in both groups administered fluralaner and moxidectin topical solution (6/8 cats in the 1X group and 7/8 cats in the 3X group). No cats in the control group exhibited hypersalivation.

Two cats were found dead prior to dosing. Premature deaths after dosing consisted of two cats in the 1X group and one cat in the 3X group. All 3 of these cats exhibited neurologic clinical signs during the study and were euthanized due to quality-of-life concerns. Two of these cats (one 1X and one 3X) had aberrant heartworm migration into the epidural space discovered on necropsy. Clinical signs in the one cat in the 1X group included ataxia, paresis, and muscle tremors 25 days after dosing. Clinical signs in the one cat in the 3X group included depression, dehydration, a hunched position, and an inability to stand 22 days after dosing. Clinical signs in the other cat in the 1X group that did not have any aberrant heartworm migration included ataxia, depression, lethargy, vomiting, and vocalization 38 days after dosing. None of the cats in the control group exhibited neurologic clinical signs throughout the study.

Table III.2: Study S14342-00; Adult Heartworms Recovered at Necropsy after Treatment

Treatment Group	# of cats per group	# of cats with worms	Live worm range (Min, Max)	Dead worm range (Min, Max)	Average # of live worms
0X	7*	7	2, 17	0, 1	6
1X	8	8	0, 17	0, 3	5
3X	8	8	0, 10	0, 9	5

*One cat was found dead prior to dose administration on Day 0.

Conclusion: The administration of fluralaner and moxidectin topical solution to cats infected with adult *D. immitis* was associated with adverse reactions. Post-dosing hypersalivation is a drug-related adverse reaction. Additionally, because neurologic signs occurred in one treated cat with no aberrant heartworm migration to the epidural space, neurologic signs (ataxia), depression, lethargy, vomiting, and vocalization are considered possibly drug-related. Similar signs did not occur in any control cats. BRAVECTO® PLUS should be used with caution in cats that are heartworm positive.

E. Additional Experience

(Study numbers: S15329-00, S14357-00, FCF501, S15214-01, S15101-00)

In a well-controlled laboratory effectiveness study with cats infected with gastrointestinal (GI) nematodes, one cat experienced bloody stool, beginning 7 days after BRAVECTO® PLUS administration. The condition was ongoing through the end of the study, ten days after BRAVECTO® PLUS administration. In addition, four cats, three cats treated with BRAVECTO® PLUS and one cat treated with Bravecto® (fluralaner topical solution), infested with ear mites (*Otodectes cynotis*) experienced neurologic signs characterized by disorientation, ataxia, head tilt, horizontal nystagmus, and protrusion of the left third eyelid that began 28 days after Bravecto® or BRAVECTO® PLUS administration. In all four cats, clinical signs began after ear flushing, either during recovery from sedation, or the next day, and lasted from 11 to 89 days.

In a pilot oral safety study, adult cats orally administered 0.5X or 1X the maximum labeled dose of BRAVECTO® PLUS had foaming hypersalivation for up to five minutes and reduced food consumption on the day of dosing. One cat exhibited transient lacrimation from one eye during the first 15 minutes after dosing.

In a European field study, one cat experienced hypersalivation and one cat experienced dyspnea and licking at the application site on the same day as receiving BRAVECTO® PLUS. One cat experienced bloody vomiting within 5 days of BRAVECTO® PLUS administration. Three cats experienced pruritus at the application site on the same day or 14 days after BRAVECTO® PLUS administration. Ten cats experienced alopecia at or near the application site within 27 days of BRAVECTO® PLUS administration.

From foreign market experience, the following adverse events were reported voluntarily: polydipsia, swelling of the chin and lips, periorbital swelling, blepharospasm, pruritus, erythema, aggression, agitation, pyrexia, mydriasis, hypersalivation, hyperactivity, alopecia, and excessive grooming. These adverse events occurred within 48 hours of administration. In addition, one veterinarian experienced tingling and numbness of the fingers, hand, and arm, and swelling of the hand and arm after getting BRAVECTO® PLUS on her fingers. Additional signs, including blurred vision, and disorientation, occurred after taking an antihistamine.

IV. HUMAN FOOD SAFETY

This drug is intended for use in cats. 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® PLUS:

Human Warnings:

Not for human use. Keep this and all drugs out of the reach of children.

Do not contact or allow children to contact the application site until 2 hours post application.

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. Avoid contact with skin and eyes. If contact with eyes occurs, then flush eyes slowly and gently with water. **If wearing contact lenses, eyes should be rinsed first, then remove contact lenses and continue rinsing, then seek medical advice immediately. Wash hands and contacted skin thoroughly with soap and water immediately after use of the product. If the product accidentally contacts skin and a sticky residue persists after washing, rubbing alcohol (70% isopropyl alcohol) can be applied to the area to remove the residue.**

The product is highly flammable. Keep away from heat, sparks, open flame or other sources of ignition.

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® PLUS, when used according to the label, is safe and effective for the prevention of heartworm disease caused by *Dirofilaria immitis* and for the treatment of infections with intestinal roundworm (*Toxocara cati*; 4th stage larvae, immature adults and adults) and hookworm (*Ancylostoma tubaeforme*; 4th stage larvae, immature adults and adults). BRAVECTO® PLUS 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) and *Dermacentor variabilis* (American dog tick)] for 2 months in cats and kittens 6 months of age and older and weighing 2.6 lb 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 and proper diagnosis are required to determine the existence of heartworm infections and to monitor the safe use of the product.

B. Exclusivity

BRAVECTO® PLUS, 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® PLUS.

C. Patent Information

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