Date of Approval: July 20, 2016

CORRECTED FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-459

BRAVECTO

fluralaner topical solution

Dogs and Cats

BRAVECTO kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*) and the treatment and control of tick infestations [*Ixodes scapularis* (black-legged tick), *Dermacentor variabilis* (American dog tick), and *Rhipicephalus sanguineus* (brown dog tick)] for 12 weeks in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater.

BRAVECTO is also indicated for the treatment and control of *Amblyomma americanum* (lone star tick) infestations for 8 weeks in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater.

BRAVECTO kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*) and the treatment and control of *Ixodes scapularis* (black-legged tick) infestations for 12 weeks in cats and kittens 6 months of age and older, and weighing 2.6 pounds or greater.

BRAVECTO is also indicated for the treatment and control of *Dermacentor variabilis* (American dog tick) infestations for 8 weeks in cats and kittens 6 months of age and older, and weighing 2.6 pounds or greater.

Sponsored by:

Intervet, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-459

B. Sponsor

Intervet, Inc.
2 Giralda Farms
Madison, NJ 07940

Drug Labeler Code: 000061

C. Proprietary Name

BRAVECTO

D. Product Established Name

Fluralaner topical solution

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Solution

G. Amount of Active Ingredient

Each milliliter contains 280 mg fluralaner

H. How Supplied

BRAVECTO is available in five strengths (112.5, 250, and 500 mg fluralaner per tube for dogs and cats, and 1000 and 1400 mg fluralaner per tube for dogs). 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

Dogs
BRAVECTO should be administered topically as a single dose every 12 weeks according to the Dosage Schedule below to provide a minimum dose of 11.4 mg/lb (25 mg/kg) body weight.

BRAVECTO may be administered every 8 weeks in case of potential exposure to *Amblyomma americanum* ticks.

Dosage Schedule

Body Weight Ranges (lb)	Fluralaner content (mg)	Tube Administered
4.4 – 9.9	112.5	One
>9.9 – 22.0	250	One
>22.0 – 44.0	500	One
>44.0 – 88.0	1000	One
>88.0 – 123.0*	1400	One

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

Cats
BRAVECTO should be administered topically as a single dose every 12 weeks according to the Dosage Schedule below to provide a minimum dose of 18.2 mg/lb (40 mg/kg) body weight.

BRAVECTO may be administered every 8 weeks in case of potential exposure to *Dermacentor variabilis* ticks.

Dosage Schedule

Body Weight Ranges (lb)	Fluralaner content (mg)	Tube Administered
2.6 – 6.2	112.5	One
>6.2 – 13.8	250	One
>13.8 – 27.5*	500	One

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

K. Route of Administration

Topical

L. Species/Class

Dogs and cats

M. Indication

Dogs
BRAVECTO kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*) and the treatment and control of tick infestations [*Ixodes scapularis* (black-legged tick), *Dermacentor variabilis* (American dog tick), and *Rhipicephalus sanguineus* (brown dog tick)] for 12 weeks

in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater.

BRAVECTO is also indicated for the treatment and control of *Amblyomma americanum* (lone star tick) infestations for 8 weeks in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater.

Cats
BRAVECTO kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*) and the treatment and control of *Ixodes scapularis* (black-legged tick) infestations for 12 weeks in cats and kittens 6 months of age and older, and weighing 2.6 pounds or greater.

BRAVECTO is also indicated for the treatment and control of *Dermacentor variabilis* (American dog tick) infestations for 8 weeks in cats and kittens 6 months of age and older, and weighing 2.6 pounds or greater.

II. EFFECTIVENESS

A. Dosage Characterization

Dogs
Dose Selection:
Various studies conducted with orally and topically administered fluralaner demonstrate a direct relationship between fluralaner dose and duration of effectiveness against fleas and ticks. These studies also indicate that fleas are more susceptible to lower doses of fluralaner than ticks. A 12-week study in dogs that used a topical formulation of fluralaner at a dose of 10 mg/kg demonstrated 100% effectiveness against fleas versus 51% effectiveness against *Ixodes ricinus* ticks. The minimum effective dose was established based on the dose required for a 12-week duration of effectiveness against ticks.

A dose determination study with topical fluralaner at doses ranging from 10 to 40 mg/kg demonstrated that 25 mg/kg provided greater than 90% effectiveness for 12 weeks duration for fleas and *Rhipicephalus sanguineus* ticks. A dose of 25 mg/kg was selected for BRAVECTO topical solution for dogs.

Minimum age:
Laboratory studies conducted to demonstrate substantial evidence of effectiveness for flea and tick indications were conducted with dogs 6 months of age and older. However, in studies using the oral formulation in 8 and 9 week-old puppies, effectiveness against some tick species was not demonstrated past 30 to 58 days.

Pharmacokinetic studies demonstrate that oral administration of fluralaner results in a substantially lower peak plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC), and a shorter plasma elimination half-life (T½), in young puppies (8-9 weeks of age) compared to dogs aged 6 months and older, at approximately the same oral dose. Age related changes in pharmacokinetics following topical administration have not been evaluated.

Therefore, although the margin of safety study supports the safety of BRAVECTO in 8-week old puppies, substantial evidence to support the 12-week duration of effectiveness in dogs less than 6 months of age has not been demonstrated.

Cats
Studies conducted with topically administered fluralaner demonstrate a direct relationship between fluralaner dose and duration of effectiveness against fleas and ticks. Three laboratory effectiveness studies evaluating fluralaner demonstrated that a dose of 40 mg/kg administered once topically was sufficient to achieve >90% effectiveness against fleas and *Ixodes ricinus* ticks in cats for 12 weeks. The dose of 30 mg/kg did not provide sufficient effectiveness against fleas and *I. ricinus* ticks for 12 weeks. A dose of 50 mg/kg did not provide an additional beneficial effect over 40 mg/kg with respect to the target 12-week duration of effectiveness against ticks and fleas in cats. Therefore, a dose of 40 mg/kg was selected for BRAVECTO topical solution for cats.

B. Substantial Evidence

1. Dogs

   a. Laboratory Dose Confirmation Study S11139-03: Effectiveness for Fleas

   Title:
   Efficacy of 28% w/v fluralaner spot-on solution for dogs at the proposed recommended dose against Ctenocephalides felis infestations of dogs

   Study Location and Dates:
   Turlock, CA
   January 12, 2013 to May 16, 2013

   Study Design:
   The study was conducted in compliance with good clinical practice (GCP) guidelines.

   Study Animals:
   20 healthy dogs (pure- and mixed-bred, 8 males and 12 females), 2 to 13.6 years of age, and 8.6 to 33.3 kg body weight

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

   Drug administration was on Day 0. Flea infestations were conducted on Days -2, 28, 56, 84, and 112. At each infestation, each dog was infested with approximately 100 unfed adult fleas.

Drug Administration:
On Day 0, fluralaner topical solution was administered topically to the ten dogs in the fluralaner group, at doses as close as possible to 25 mg/kg. Doses ranged from 24 to 25 mg/kg. Hair at the administration site(s) was parted and fluralaner topical solution was applied to the skin in one or more spots along the dog's top-line, starting at the shoulder blades and moving toward the tail.

Measurements and Observations:
The primary variable for effectiveness was the counts of live fleas collected from the dogs. At flea counts on Days 2, 30, 58, 86, and 114, fleas were removed and the numbers of live fleas recorded. General health observations were conducted daily and at 1, 3, and 6 hours after drug administration. Treatment site observations were made at 24 and 48 hours post-treatment, on Day 7, and then weekly until completion of the study. Dogs were weighed on Day -2. Flea counts and health observations were conducted masked to treatment.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed flea counts, with 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:
At each flea count, there were a minimum of six dogs in the control group that had an adequate infestation, defined as at least 50 live fleas (50% of the infestations of 100 fleas per dog). On all count days following drug administration, live flea counts between the two groups were significantly different ($p < 0.001$).

Table II.1: Study S11139-03 Effectiveness Against Fleas

Day for Flea Counts	Control Group Flea Counts[a]	Fluralaner Group Flea Counts[a]	Percent Effectiveness
2	74.1	0.0	100
30	49.0	0.0	100
58	67.4	0.0	100
86	69.7	0.0	100
114	70.4	0.0	100

[a] Flea counts are geometric means and percent effectiveness is based on geometric means.

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

Conclusion:
This study demonstrated the effectiveness of fluralaner topical solution for the treatment of existing flea infestations for at least 12 weeks when assessed 48 hours after drug administration or infestation.

b. Field Study S11157-00: Effectiveness for Fleas

Title:
Clinical effectiveness of 28% w/v fluralaner spot-on solution for dogs against fleas: a multi-center pivotal field study in client-owned dogs

Study Locations and Dates:
Cropwell, AL
Starke, FL
Decatur, IL
Mishawaka, IN
Shawnee Mission, KS
Lake Charles, LA
Augusta, ME
Philadelphia, PA
Quakertown, PA
Germantown, TN
Austin, TX
Seguin, TX

May 6, 2013, to March 5, 2014

Study Design:
The study was conducted in compliance with good clinical practice (GCP) guidelines.

Objective:
The field study assessed safety, effectiveness against fleas, and signs of flea allergy dermatitis.

Study Animals:
The study included 321 client-owned dogs from 165 households; 221 dogs (121 households) treated with fluralaner topical solution and 100 dogs (44 households) treated with a topical solution containing fipronil and (s)-methoprene (control). The study enrolled 161 females and 160 males, 13 weeks to 17 years of age, and 4.4 to 136 lb body weight. The study included purebred and mixed breed dogs.

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

Experimental Design:
Households were randomly assigned to treatment with fluralaner or control in a ratio of three fluralaner households to one control household. Owners treated all dogs in the fluralaner group with fluralaner topical solution after Visit 1 on Day 0 and again after Visit 4 on Day 84 for a total of two

treatments. The fluralaner group finished the study at Visit 5 on Day 105. Owners treated all dogs in the control group with a fipronil + (s)-methoprene topical solution after Visit 1 on Day 0 and again after Visits 2 and 3 on Days 28 and 56 for a total of three treatments. The control group finished the study at Visit 4 on Day 84. All dogs within a household were in the same treatment group. A primary dog from each household was randomly selected from dogs with 10 or more live fleas at Visit 1. Only the primary dog was assessed for effectiveness against fleas. Owners administered the treatments and they treated all dogs in the household at the same times.

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

Drug Administration:
In the fluralaner group, Owners administered fluralaner topical solution, at labeled doses, on Days 0 and 84. In the control group, Owners applied the fipronil + (s)-methoprene topical solution at labeled doses on Days 0, 28, and 56.

Measurements and Observations:
The primary variable was the difference in live flea counts on the primary dogs on Days 28 (Visit 2), 56 (Visit 3), and 84 (Visit 4) versus pretreatment (Visit 1). Additional variables included progression of signs of flea allergy dermatitis, physical examinations, and clinical pathology. Statistical analyses were not performed for these additional variables.

Statistical Methods:
Log-transformed flea counts were analyzed using a mixed model at two-sided 5% significance level. Percent effectiveness against the pretreatment flea counts was calculated based on geometric means.

Results:
For each of Visits 2, 3, and 4, the effectiveness of fluralaner, based on geometric means, was greater than 90%.

Table II.2: Field Study S11157-00 Effectiveness against Fleas

Visit	Fluralaner Group	Control Group
Visit 1 Number of Dogs	120	44
Visit 1 Geometric Mean Flea Count	68.9	66.6
Visit 2 Number of Dogs	110	36
Visit 2 Geometric Mean Flea Count	0.1	12.5
Visit 2 Percent Effectiveness	99.8%	81.2%
Visit 3 Number of Dogs	105	36
Visit 3 Geometric Mean Flea Count	0.1	6.4
Visit 3 Percent Effectiveness	99.9%	90.3%
Visit 4 Number of Dogs	104	33
Visit 4 Geometric Mean Flea Count	0.1	4.7
Visit 4 Percent Effectiveness	99.9%	93.0%

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

At least 86% of the dogs treated with fluralaner topical solution with signs attributed to Flea Allergy Dermatitis (FAD) at Visit 1, and not administered other medications that could affect the assessment of FAD, had resolution of the signs by Visit 4 at Week 12.

Table II.3: Field Study S11157-00 Resolution of Signs of Flea Allergy Dermatitis

FAD Sign	Percent of Fluralaner Group Dogs with the FAD Sign at Visit1 that was Resolved at Week 12	Percent of Control Group Dogs with the FAD Sign at Visit 1 that was Resolved at Week 12
Erythema	91% (53/58 dogs)	60% (15/25 dogs)
Alopecia	86% (37/43 dogs)	79% (15/19 dogs)
Papules	97% (31/32 dogs)	100% (6/6 dogs)
Scales	93% (25/27 dogs)	73% (8/11 dogs)
Crusts	100% (28/28 dogs)	80% (8/10 dogs)
Excoriation	100% (25/25 dogs)	83% (5/6 dogs)

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

Adverse Reactions:
There were no serious adverse reactions in any of the dogs associated with treatment with fluralaner topical solution or the control.

Table II.4: Field Study S11157-00 Adverse Reactions

Adverse Reaction (AR)	Fluralaner Group: Percent of Dogs with the AR During the 105-Day Study (n= 221 dogs)	Active Control Group: Percent of Dogs with the AR During the 84-Day Study (n= 100 dogs)
Vomiting	6.3%	6.0%
Alopecia	4.1%	2.0%
Diarrhea	2.7%	11.0%
Lethargy	2.7%	2.0%
Decreased Appetite	1.4%	0.0%
Moist Dermatitis/Rash	0.9%	0.0%

In the field study, two dogs treated with fluralaner topical solution with no prior history of seizures each experienced a seizure. One dog had two seizures a day apart about 18 days after its first dose. The dog was started on antiepileptic medication and had no additional seizures during the study. A second dog had a seizure 76 days after its first dose and 3 days after starting fluoxetine for separation anxiety. The fluoxetine was discontinued and the dog experienced no additional seizures during the study.

One dog treated with fluralaner topical solution was observed by the owner to be off balance for about 30 minutes five days after its first dose and had no similar observations after the second dose. One dog with a history of seizures had a seizure the day after the second dose of the active control.

Conclusion:
This study demonstrated that fluralaner topical solution was safe and effective for the treatment of flea infestations when administered to client-owned dogs.

c. Laboratory Dose Confirmation Study S13299-00: Simulated Home Environment for Fleas

Title: Effectiveness of 28% w/v fluralaner spot-on solution for dogs at the proposed recommended dose for the control of *Ctenocephalides felis* in a simulated home environment for dogs

Study Location and Dates:
Turlock, CA
November 18, 2013, to April 21, 2014

Study Design:
The study was conducted in compliance with good clinical practice (GCP) guidelines.

Study Animals:
20 healthy dogs (Beagles, 11 males and 9 females), 1.2 to 7.6 years of age, and 8.1 to 13.1 kg body weight

Experimental Design:
Prior to allocation to treatment groups on Day -59, an initial flea infestation and count was conducted to evaluate susceptibility of each dog to experimental infestation (host suitability). Dogs were ranked and blocked by live flea count, and one dog from each block was randomly assigned to the untreated control (10 dogs) or the fluralaner (10 dogs) treatment group.

Beginning on Day -56, dogs were housed in individual pens that contained a carpet area. To establish a self-perpetuating flea life cycle in each pen, all dogs were infested weekly with approximately 100 newly emerged, unfed adult *C. felis* fleas starting on Day -56 through Day -21. To simulate introductions of new fleas into a home environment, each dog was infested with 50 newly emerged unfed adult fleas on Days 22, 50, and 78.

All live fleas counted on dogs on Day -1 were recovered and recorded but not replaced on the dogs. After the flea counts were completed, the dogs were held overnight in clean pens to prevent re-infestation prior to drug administration on Day 0. Flea counts were performed on all dogs on Day 1 (24 ± 4 hours post-treatment) and on Days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, and 77. Live fleas recovered during these flea counts were used to re-infest dogs. The final flea count was on Day 84.

Drug Administration:
On Day 0, fluralaner topical solution was administered topically to the ten dogs in the fluralaner group, at doses as close as possible to 25 mg/kg. Doses ranged from 24.1 to 26.0 mg/kg. Hair at the administration site was parted and fluralaner topical solution was applied to the skin in one spot along the dog's top-line between the shoulder blades.

Measurements and Observations:
The primary variable for effectiveness was the counts of live fleas collected from the dogs. Flea counts were conducted on all dogs on Days -1, 1, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, and 84. General health observations were conducted daily and at 1, 3, 6 hours after drug administration. Treatment site observations were made at 24 and 48 hours after drug administration on Day 7 and then weekly until completion of the study. Dogs were weighed on Days -1, 28, and 56. Flea counts and health observations were conducted masked to treatment group.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed flea counts, with 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:
On Day -1, the geometric mean flea counts on control and fluralaner group dogs were 24.2 and 10.4, respectively. The Day -1 live flea counts were not significantly different ($p = 0.168$) between the two groups. On all count days following drug administration, live flea counts between the two groups were significantly different ($p \leq 0.002$).

Table II.5: Simulated Home Environment S13299-00 Effectiveness

Day	Control Group Flea Counts[a]	Fluralaner Group Flea Counts[a]	Percent Effectiveness
-1	24.2	10.4	Not applicable
1	2.9	0.1	96.0
7	4.0	0.0	100
14	2.5	0.1	94.1
21	12.6	0.0	100
28	19.9	0.0	100
35	30.3	0.0	100
42	15.0	0.0	100
49	32.8	0.0	100
56	40.2	0.0	100
63	15.4	0.0	100
70	8.9	0.0	100
77	37.7	0.0	100
84	52.8	0.0	100

[a] Flea counts are geometric means and percent effectiveness is based on geometric means.

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

Conclusion:
This study demonstrated that fluralaner topical solution was effective for the prevention of flea infestations on dogs in a simulated home environment for 12 weeks.

d. Laboratory Dose Confirmation Study S10036-00: Speed of Kill for *Ctenocephalides felis* Fleas and *Rhipicephalus sanguineus* Ticks

Title:
Determination of the speed of kill of fluralaner administered once topically at a dose of 25 mg/kg body weight against brown dog tick infestations (*Rhipicephalus sanguineus*) and flea infestations (*Ctenocephalides felis*) on dogs

Study Location and Dates:
Auburn, AL
October 25, 2010, to March 11, 2011

Study Design:

Study Animals:
24 healthy dogs (Beagles, 18 males and 6 females), 1 year of age, and 9.2 to 17.6 kg body weight

Experimental Design:
Prior to allocation to treatment groups, an initial tick infestation and count was conducted to evaluate susceptibility of each dog to experimental infestation (host suitability). Dogs were ranked and blocked by live tick count into four blocks of six dogs each. Two blocks were randomly assigned to Phase A and two blocks to Phase B. Within each block, one dog was randomly assigned to one of three sham-treated control groups or one of three fluralaner treatment groups for Phase A or B. Day 0 (treatment day) of the two phases was separated by 35 days. Each phase included two of the four dogs in each treatment group.

Table II.6: Study S10036-00 Treatment Groups

Group	Treatment	Timing of Flea and Tick Counts	Number of Dogs
1	Control	8-hours	4 (2 in Phase A and 2 in Phase B)
2	Fluralaner	8-hours	4 (2 in Phase A and 2 in Phase B)
3	Control	12-hours	4 (2 in Phase A and 2 in Phase B)
4	Fluralaner	12-hours	4 (2 in Phase A and 2 in Phase B)
5	Control	24-hours	4 (2 in Phase A and 2 in Phase B)
6	Fluralaner	24-hours	4 (2 in Phase A and 2 in Phase B)

Drug administration was on Day 0 for each of the phases. Flea infestations were conducted on Days -2, 9, 30, 58, and 86. At each infestation, each dog was infested with approximately 100 unfed adult fleas. Tick infestations were conducted on Days -2, 7, 28, 56, and 84. At each infestation, each dog was infested with approximately 50 unfed adult *R. sanguineus* ticks.

Flea and tick counts were performed at 8, 12, and 24 hours after drug administration. Flea counts were also performed on at 8, 12, and 24 hours following flea infestations on Days 9, 30, 58, and 86. Tick counts were also performed at 8, 12, and 24 hours following tick infestations on Days 7, 28, 56, and 84. Fleas and ticks were not returned to the dog after counting.

Drug Administration:
On Day 0, fluralaner topical solution was administered topically to the twelve dogs in the fluralaner group, at doses as close as possible to 25 mg/kg. Doses ranged from 24.0 to 25.8 mg/kg. Hair at the administration site(s) was parted and fluralaner topical solution was applied directly to the

skin in one or more spots along the dog's top-line, starting at the shoulder blades and moving toward the tail. On Day 0, dogs in the control groups were sham-treated to maintain masking.

Measurements and Observations:
The primary variables for effectiveness were the counts of live fleas and ticks collected from the dogs. At flea and tick counts, fleas and ticks were removed and the numbers of live fleas and ticks were recorded. General health observations were conducted daily and at 15 and 30 minutes, 4, 8, and 24 hours after drug administration. Dogs were weighed on Day -3. Flea and tick counts and health observations were conducted masked to treatment.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed flea and tick counts, with treatment group as a fixed effect at a two-sided 5% significance level and phase, block and phase-by-block interaction as random effects. Percent effectiveness against the control was calculated based on geometric means.

Results:
At each flea count, the four dogs in each control group each had an adequate infestation, defined as at least 50 live fleas (50% of the infestations of approximately 100 fleas per dog).

The fluralaner group had greater than 90% reduction in live flea counts at 24 hours following treatment or infestation for 12 weeks (final flea infestation on Day 86). The 8-hour and 12-hour fluralaner groups did not demonstrate $\geq$ 90% effectiveness for 12 weeks (final infestation on Day 86).

On all count days following drug administration, live flea counts for the 24-hour fluralaner group were significantly different from the control group ($p < 0.001$).

Table II.7: Study S10036-00 8-Hour Live Flea Count Effectiveness

Day for 8-Hour Flea Counts	8-hour Control Group Flea Counts[a]	8-hour Fluralaner Group Flea Counts*	Percent Effectiveness
0	71.5	34.7	51.4
9	87.7	0.4	99.5
30	82.7	1.1	98.7
58	79.0	14.9	81.2
86	84.2	57.2	32.0

[a] Flea counts are geometric means and percent effectiveness is based on geometric means.

Table II.8: Study S10036-00 12-Hour Live Flea Count Effectiveness

Day for 12-Hour Flea Counts	12-hour Control Group Flea Counts[a]	12-hour Fluralaner Group Flea Counts[a]	Percent Effectiveness
0	78.3	10.6	86.5
9	84.4	0.0	100
30	82.9	0.0	100
58	78.9	0.4	99.5
86	82.4	21.9	73.4

[a] Flea counts are geometric means and percent effectiveness is based on geometric means.

Table II.9: Study S10036-00 24-Hour Live Flea Count Effectiveness

Day for 24-Hour Flea Counts	24-hour Control Group Flea Counts[a]	24-hour Fluralaner Group Flea Counts[a]	Percent Effectiveness
1	73.2	0.0	100
10	80.8	0.0	100
31	79.6	0.0	100
59	82.3	0.2	99.8
87	81.4	0.7	99.2

[a] Flea counts are geometric means and percent effectiveness is based on geometric means.

At each tick count, the four dogs (with the exception of one dog in the 24-hour control group that had 12 live ticks after the Day 84 tick infestation) in each control group each had an adequate infestation, defined as at least 13 live *R. sanguineus* ticks (25% of the infestations of 50 ticks per dog).

The 8-hour, 12-hour, and 24-hour fluralaner groups did not demonstrate ≥ 90% effectiveness on all count days following drug administration for 12 weeks (final infestation on Day 84).

Table II.10: *R. sanguineus* Study S10036-00 8-Hour Live Tick Count Effectiveness

Day for 8-Hour Tick Counts	8-hour Control Group Tick Counts[a]	8-hour Fluralaner Group Tick Counts[a]	Percent Effectiveness
0	38.1	45.2	0.0
7	28.3	1.5	94.6
28	34.2	7.9	77.0
56	29.4	14.2	51.6
84	29.1	26.9	7.5

[a] Tick counts are geometric means and percent effectiveness is based on geometric means.

Table II.11: *R. sanguineus* Study S10036-00 12-Hour Live Tick Count Effectiveness

Day for 12-Hour Tick Counts	12-hour Control Group Tick Counts[a]	12-hour Fluralaner Group Tick Counts[a]	Percent Effectiveness
0	29.9	28.8	3.5
7	29.3	0.0	100
28	25.8	0.4	98.4
56	36.4	6.8	81.3
84	29.9	18.6	37.6

[a] Tick counts are geometric means and percent effectiveness is based on geometric means.

Table II.12: *R. sanguineus* Study S10036-00 24-Hour Live Tick Count Effectiveness

Day for 24-Hour Tick Counts	24-hour Control Group Tick Counts[a]	24-hour Fluralaner Group Tick Counts[a]	Percent Effectiveness
1	34.4	18.6	46.0
8	29.1	0.0	100
29	32.1	0.0	100
57	26.3	0.2	99.3
85	21.1	9.5	54.9

[a] Tick counts are geometric means and percent effectiveness is based on geometric means.

Adverse Reactions:
One dog in the fluralaner group had moderate redness, slight flaking, moderate crusts/scabs, and moderate alopecia at the application site on Day 1. These signs were mild by Day 3 and resolved after Day 14.

Conclusions:
This study demonstrated that fluralaner topical solution killed *C. felis* fleas and reduced the numbers of live fleas on dogs by greater than 99% within 24 hours after treatment or infestation for 12 weeks. Fluralaner topical solution did not demonstrate adequate (> 90%) effectiveness against *R. sanguineus* ticks within 24 hours after treatment or infestation for 12 weeks. One dog had a dermal reaction to fluralaner topical solution at the application site.

e. Laboratory Dose Confirmation Study S12016-00: Bathing Study in Dogs with *Ctenocephalides felis* Fleas and *Ixodes ricinus* Ticks

Title:
Study to investigate a potential effect of water immersion or shampooing on the efficacy after topical administration of 28% w/v fluralaner spot-on solution for dogs against ticks infestations (*Ixodes ricinus*) and fleas infestations (*Ctenocephalides felis*)

Study Location and Dates:
Mayo, Ireland
October 8, 2012, to February 7, 2013

Study Design:
The study was conducted in compliance with Good Clinical Practices (GCP) guidelines.

Study Animals:
32 healthy, intact dogs (Beagles, 16 males and 16 females), 0.5 to 5.8 years of age, and 8.1 to 18.9 kg body weight

Experimental Design:
Prior to allocation to treatment groups on Day 0, an initial flea infestation and count was conducted to evaluate susceptibility of each dog to experimental infestation (host suitability). Dogs were ranked and blocked by live flea count, and one dog from each block was randomly assigned to each of the following groups: (Group 1) fluralaner and water immersion; (Group 2) untreated control and water immersion; (Group 3) fluralaner and shampooing; and (Group 4) untreated control and shampooing. Groups 1 and 2 were immersed in water on Days 3, 21, 49, 77 and 105 following treatment. Groups 3 and 4 were bathed with a non-insecticidal shampoo on Days 3, 21, 49, 77 and 105.

Drug administration was on Day 0. Flea and tick co-infestations were conducted on Days 4, 28, 56, 84, and 112. At each infestation, each dog was infested with approximately 100 unfed, adult fleas and approximately 60 unfed adult *I. ricinus* ticks (approximate 50:10 ratio of female to male ticks).

Drug Administration:
On Day 0, fluralaner topical solution was administered topically to the 16 dogs in the fluralaner groups, at doses as close as possible to 25 mg/kg. Doses ranged from 25 to 46 mg/kg. Hair at the administration site(s) was parted and fluralaner topical solution was applied to the skin in one or more spots along the dog's top-line, starting at the shoulder blades and moving toward the tail.

Measurements and Observations:
The primary variables for effectiveness were the counts of live fleas and ticks collected from the dogs. At flea and tick counts on Days 6, 30, 58, 86, and 114, fleas and ticks were removed and the numbers of live fleas and ticks were recorded. General health observations were conducted daily. Dogs were weighed on Day -1. Tick counts and health observations were conducted masked to treatment.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed flea and tick counts, with 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:
At each flea and tick count, with the exception of the fleas on Group 4 dogs at the Day 6 count, at least 6 of the 8 dogs in the control group each had an adequate infestation, defined as at least 50 live fleas (50% of the infestations of 100 fleas per dog) and 15 live *I. ricinus* ticks (25% of the infestations of 60 ticks per dog). On Day 6, 4 of the 8 dogs in Group 4 had > 50 fleas.

Both fluralaner groups had greater than 90% reduction in live flea and tick counts at 48 hours following infestation for 16 weeks (infestation on Day 114). On all count days following drug administration, live flea and tick counts for the fluralaner groups were significantly different from their respective control group ($p < 0.0001$).

Table II.13: Study S12016-00 Live Flea Count Effectiveness Following Water Immersion on Days 3, 21, 49, 77, and 105

Day for Flea Counts	Control Group Flea Counts[a]	Fluralaner Group Flea Counts[a]	Percent Effectiveness
6	92.2	0.0	100.0
30	88.6	0.0	100.0
58	88.3	0.0	100.0
86	81.7	0.0	100.0
114	90.4	0.0	100.0

[a] Flea counts are geometric means and percent effectiveness is based on geometric means

Table II.14: Study S12016-00 Live Flea Count Effectiveness Following Shampooing on Days 3, 21, 49, 77, and 105

Day for Flea Counts	Control Group Flea Counts[a]	Fluralaner Group Flea Counts[a]	Percent Effectiveness
6	34.5	0.0	100.0
30	80.2	0.0	100.0
58	87.7	0.0	100.0
86	89.1	0.0	100.0
114	87.7	0.3	99.7

[a] Flea counts are geometric means and percent effectiveness is based on geometric means

Table II.15: *I. ricinus* Study S12016-00 Live Tick Count Effectiveness Following Water Immersion on Days 3, 21, 49, 77, and 105

Day for Tick Counts	Control Group Live Tick Counts[a]	Fluralaner Group Live Tick Counts[a]	Percent Effectiveness
6	27.5	0.0	100.0
30	29.7	0.1	99.7
58	19.3	0.0	100.0
86	28.7	0.1	99.7
114	29.9	0.5	98.5

[a] Tick counts are geometric means and percent effectiveness is based on geometric means

Table II.16: *I. ricinus* Study S12016-00 Live Tick Count Effectiveness Following Shampooing on Days 3, 21, 49, 77, and 105

Day for Tick Counts	Control Group Live Tick Counts[a]	Fluralaner Group Live Tick Counts[a]	Percent Effectiveness
6	28.9	0.0	100.0
30	28.5	0.0	100.0
58	14.3	0.0	100.0
86	29.6	0.2	99.2
114	28.4	0.5	98.3

[a] Tick counts are geometric means and percent effectiveness is based on geometric means

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

Conclusion:
This study demonstrated that the effectiveness of fluralaner topical solution against *C. felis* fleas and *I. ricinus* ticks is maintained after multiple immersion or shampooing occasions, the first occurring 3 days after administration, for up to 16 weeks.

f. Laboratory Dose Confirmation Study S11172-02: *Rhipicephalus sanguineus* Ticks

Title:
Efficacy of 28% w/v fluralaner spot-on solution for dogs at the proposed recommended dose against *Rhipicephalus sanguineus* infestations in dogs

Study Location and Dates:
Greenbrier, AR
October 16, 2011, to February 17, 2012

Study Design:
The study was conducted in compliance with Good Clinical Practices (GCP) guidelines.

Study Animals:
20 healthy dogs (mostly mixed breed, 11 males and 9 females), 2.4 to 7.8 years of age, and 6.8 to 14.9 kg body weight

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

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 28, 56, 84, and 112. At each infestation, each dog was infested with approximately 50 adult, unfed *R. sanguineus* ticks.

Drug Administration:
On Day 0, fluralaner topical solution was administered topically to the ten dogs in the fluralaner group, at doses as close as possible to 25 mg/kg. Doses ranged from 23.7 to 25.8 mg/kg. Hair at the administration site(s) was parted and fluralaner topical solution was applied to the skin in one or more spots along the dog's top-line, starting at the shoulder blades and moving toward the tail.

Measurements and Observations:
The primary variables for effectiveness were the counts of live ticks collected from the dogs. At tick counts on Days 2, 30, 58, 86 and 114, ticks were removed and the numbers of live and dead ticks were recorded. General health observations were conducted daily and at 1, 3, and 6 hours after drug administration. Dogs were weighed on Day -2. Tick counts and health observations were conducted masked to treatment.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed tick counts, with 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:
At each tick count day, at least 8 of the 10 dogs in the control group each had an adequate infestation, defined as at least 13 live *R. sanguineus* ticks (25% of the infestations of 50 ticks per dog).

The fluralaner group had greater than 90% reduction in live tick counts at 48 hours following treatment or infestation for 12 weeks (infestation on Day 84).

On all count days following drug administration, except Day 114, live tick counts for the fluralaner group were significantly different from the control group ($p < 0.001$).

Table II.17: *R. sanguineus* S11172-02 Live Tick Count Effectiveness

Day for Tick Counts	Control Group Live Tick Counts[a]	Fluralaner Group Live Tick Counts[a]	Percent Effectiveness
2	37.4	0.9	97.6
30	26.1	0.0	100
58	18.1	0.2	98.9
86	19.4	0.6	96.7
114	18.8	12.9	31.5

[a] Tick counts are geometric means and percent effectiveness is based on geometric means.

On all count days following drug administration except Day 58, dead tick counts for the fluralaner group were significantly different from the control group ($p < 0.05$).

Table II.18: *R. sanguineus* S11172-02 Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts[a]	Fluralaner Group Dead Tick Counts[a]
2	0.1	5.5
30	0.6	3.6
58	1.3	1.4
86	0.4	3.5
114	0.0	0.9

[a] Tick counts are geometric means.

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

Conclusion:
This study demonstrated the effectiveness of fluralaner topical solution for the control (reduced live ticks) and treatment (increased dead ticks) of *R. sanguineus* ticks for 12 weeks when assessed at 48 hours after drug administration or infestation.

g. Laboratory Dose Confirmation Study S11172-03: *Rhipicephalus sanguineus* Ticks

Title:
Efficacy of 28% w/v fluralaner spot-on solution for dogs at the proposed recommended dose against *Rhipicephalus sanguineus* infestations in dogs

Study Location and Dates:
Turlock, CA
November 18, 2011, to February 27, 2012

Study Design:
The study was conducted in compliance with Good Clinical Practices (GCP) guidelines.

Study Animals:
20 healthy dogs (Beagles, 14 males and 6 females), 5.5 to 6.6 years of age, and 8.4 to 16.3 kg body weight

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

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 28, 56, and 84. At each infestation, each dog was infested with approximately 50 adult, unfed *R. sanguineus* ticks.

Drug Administration:
On Day 0, fluralaner topical solution was administered topically to the ten dogs in the fluralaner group, at doses as close as possible to 25 mg/kg. Doses ranged from 23.7 to 26.5 mg/kg. Hair at the administration site(s) was parted and fluralaner topical solution was applied to the skin in one or more spots along the dog's top-line, starting at the shoulder blades and moving toward the tail.

Measurements and Observations:
The primary variables for effectiveness were the counts of live ticks collected from the dogs. At tick counts on Days 2, 30, 58, and 86, ticks were removed and the numbers of live and dead ticks were recorded. General health observations were conducted daily and at 1, 3, and 6 hours after drug administration. Dogs were weighed on Day -2. Tick counts and health observations were conducted masked to treatment.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed tick counts, with 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:
At each tick count day, at least 9 of the 10 dogs in the control group each had an adequate infestation, defined as at least 13 live *R. sanguineus* ticks (25% of the infestations of 50 ticks per dog).

The fluralaner group had greater than 90% reduction in live tick counts at 48 hours following treatment or infestation for 12 weeks (infestation on Day 84).

On all count days following drug administration, live tick counts for the fluralaner group were significantly different from the control group ($p < 0.001$).

Table II.19: *R. sanguineus* S11172-03 Live Tick Count Effectiveness

Day for Tick Counts	Control Group Live Tick Counts[a]	Fluralaner Group Live Tick Counts[a]	Percent Effectiveness
2	21.1	0.7	96.6
30	26.4	0.0	100
58	28.8	0.0	100
86	22.3	0.1	99.7

[a] 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 group were significantly different from the control group ($p < 0.001$).

Table II.20: *R. sanguineus* S11172-03 Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts[a]	Fluralaner Group Dead Tick Counts[a]
2	0.0	2.0
30	0.0	1.2
58	0.0	3.5
86	0.0	2.8

[a] Tick counts are geometric means.

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

Conclusion:
This study demonstrated the effectiveness of fluralaner topical solution for the control (reduced live ticks) and treatment (increased dead ticks) of *R. sanguineus* ticks for 12 weeks when assessed at 48 hours after drug administration or infestation.

h. Laboratory Dose Confirmation Study S11115-02: *Ixodes scapularis* Ticks

Title:
Effectiveness of 28% w/v fluralaner spot-on solution for dogs at the proposed recommended dose against *Ixodes scapularis* infestations in dogs

Study Location and Dates:
Turlock, CA
August 19, 2011, to December 21, 2011

Study Design:
The study was conducted in compliance with Good Clinical Practices (GCP) guidelines.

Study Animals:
20 healthy dogs (mostly mixed breed, 7 males and 13 females), 3.5 to 13.6 years of age, and 13.5 to 30.7 kg body weight

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

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 28, 56, 84, and 112. At each infestation, each dog was infested with approximately 75 adult, newly emerged, unfed *I. scapularis* ticks (approximate 50:50 ratio of male to female ticks).

Drug Administration:
On Day 0, fluralaner topical solution was administered topically to the ten dogs in the fluralaner group, at doses as close as possible to 25 mg/kg. Doses ranged from 24.4 to 25.9 mg/kg. Hair at the administration site(s) was parted and fluralaner topical solution was applied to the skin in one or more spots along the dog's top-line, starting at the shoulder blades and moving toward the tail.

Measurements and Observations:
The primary variables for effectiveness were the counts of live ticks collected from the dogs. At tick counts on Days 2, 30, 58, 86, and 114, ticks were removed and the numbers of live and dead ticks were recorded. General health observations were conducted daily and at 1, 3, and 6 hours after drug administration. Dogs were weighed on Day -1. Tick counts and health observations were conducted masked to treatment.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed tick counts, with 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:
At each tick count day, at least 8 of the 10 dogs in the control group each had an adequate infestation, defined as at least 19 live *I. scapularis* ticks (25% of the infestations of 75 ticks per dog).

The fluralaner group had greater than 90% reduction in live tick counts at 48 hours following treatment or infestation for 16 weeks (infestation on Day 112).

On all count days following drug administration, live tick counts for the fluralaner group were significantly different from the control group ($p < 0.001$).

Table II.21: *I. scapularis* S11115-02 Live Tick Count Effectiveness

Day for Tick Counts	Control Group Live Tick Counts[a]	Fluralaner Group Live Tick Counts[a]	Percent Effectiveness
2	42.6	2.9	93.3
30	43.2	0.4	99.1
58	39.0	0.2	99.5
86	34.0	0.6	98.2
114	32.7	0.5	98.5

[a] 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 group were significantly different from the control group ($p < 0.001$).

Table II.22: *I. scapularis* S11115-02 Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts[a]	Fluralaner Group Dead Tick Counts[a]
2	0.6	10.9
30	0.3	5.0
58	0.0	7.8
86	0.1	8.5
114	0.0	12.4

[a] Tick counts are geometric means.

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

Conclusion:
This study demonstrated the effectiveness of fluralaner topical solution for the control (reduced live ticks) and treatment (increased dead ticks) of *I. scapularis* ticks for 16 weeks when assessed at 48 hours after drug administration or infestation.

i. Laboratory Dose Confirmation Study S11115-03: *Ixodes scapularis* Ticks

Title:
Effectiveness of 28% w/v fluralaner spot-on solution for dogs at the proposed recommended dose against *Ixodes scapularis* infestations in dogs

Study Location and Dates:
Greenbrier, AR
February 3, 2013, to May 10, 2013

Study Design:
The study was conducted in compliance with Good Clinical Practices (GCP) guidelines.

Study Animals:
20 healthy dogs (pure- and mixed-bred, 7 males and 13 females), 0.5 to 10.0 years of age, and 5.8 to 22.2 kg body weight

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

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 28, 56, and 84. At each infestation, each dog was infested with approximately 75 adult, newly emerged, unfed *I. scapularis* ticks (approximate 50:50 ratio of male to female ticks).

Drug Administration:
On Day 0, fluralaner topical solution was administered topically to the ten dogs in the fluralaner group, at doses as close as possible to 25 mg/kg. Doses ranged from 24 to 26 mg/kg. Hair at the administration site(s) was parted and fluralaner topical solution was applied to the skin in one or more spots along the dog's top-line, starting at the shoulder blades and moving toward the tail.

Measurements and Observations:
The primary variables for effectiveness were the counts of live ticks collected from the dogs. At tick counts on Days 2, 30, 58, and 86, ticks were removed and the numbers of live and dead ticks were recorded. General health observations were conducted daily and at 1, 3, 6 hours after drug administration. Treatment site observations were made at 24 and 48 hours after drug administration, on Day 7 and then weekly until completion of the study. Dogs were weighed on Day -1. Tick counts and health observations were conducted masked to treatment.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed tick counts, with 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:
At each tick count day, at least 9 of the 10 dogs in the control group each had an adequate infestation, defined as at least 19 live *I. scapularis* ticks (25% of the infestations of 75 ticks per dog).

The fluralaner group had greater than 90% reduction in live tick counts at 48 hours following treatment or infestation for 12 weeks (infestation on Day 84).

On all count days following drug administration, live tick counts for the fluralaner group were significantly different from the control group ($p < 0.001$).

Table II.23: *I. scapularis* S11139-03 Live Tick Count Effectiveness

Day for Tick Counts	Control Group Live Tick Counts[a]	Fluralaner Group Live Tick Counts[a]	Percent Effectiveness
2	35.3	1.2	96.6
30	38.3	0.0	100
58	43.8	0.0	100
86	36.6	0.0	100

[a] 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 group were significantly different from the control group ($p < 0.001$).

Table II.24: *I. scapularis* S11139-03 Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts[a]	Fluralaner Group Dead Tick Counts[a]
2	0.5	12.1
30	0.0	14.1
58	0.0	14.3
86	0.0	9.4

[a] Tick counts are geometric means

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

Conclusion:
This study demonstrated the effectiveness of fluralaner topical solution for the control (reduced live ticks) and treatment (increased dead ticks) of *I. scapularis* ticks for 12 weeks when assessed at 48 hours after drug administration or infestation.

j. Laboratory Dose Confirmation Study S13090-01: *Dermacentor variabilis* Ticks

Title:
Effectiveness of 28% w/v fluralaner spot-on solution for dogs at the proposed recommended dose against *Dermacentor variabilis* infestations on dogs using two different tick infestation schedules

Study Location and Dates:
Greenbrier, AR
June 8, 2013, to September 12, 2013

Study Design:
The study was conducted in compliance with good clinical practice (GCP) guidelines.

Study Animals:
40 healthy, intact dogs (pure- and mixed-bred, 20 males and 20 females), 0.8 to 6.8 years of age, and 5.7 to 15.8 kg body weight

Experimental Design:
Prior to allocation to treatment groups on Day -4, an initial tick infestation and count was conducted to evaluate susceptibility of each dog to experimental infestation (host suitability). There were two infestations schedules used in this study (Days -2, 28 and 56; and Day 84 only), with an untreated control and a fluralaner treatment group within each schedule. Dogs were ranked and blocked by live tick count in groups of four, and one dog from each block was randomly assigned to one of four groups (10 dogs per group).

Drug administration was on Day 0. Tick infestations were conducted on one fluralaner and one control group of dogs on Days -2, 28 and 56 and only on Day 84 for the remaining fluralaner and control groups. At each infestation, each dog was infested with approximately 50 adult, unfed *D. variabilis* ticks (approximate 50:50 ratio of male to female ticks).

Drug Administration:
On Day 0, fluralaner topical solution was administered topically to the 20 dogs in the fluralaner group, at doses as close as possible to 25 mg/kg. Doses ranged from 24 to 26 mg/kg. Hair at the administration site(s) was parted and fluralaner topical solution was applied to the skin in one or more spots along the dog's top-line, starting at the shoulder blades and moving toward the tail.

Measurements and Observations:
The primary variables for effectiveness were the counts of live ticks collected from the dogs. At tick counts on Days 2, 30, 58, and 86, ticks were removed and the numbers of live and dead ticks were recorded. General health observations were conducted daily, and at 1, 3 and 6 hours after drug administration. Treatment site observations were made at 24 and 48 hours after drug administration, on Day 7 and then weekly until completion of the study. Dogs were weighed on Day -2. Tick counts and health observations were conducted masked to treatment.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed tick counts, with 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:
At each tick count day, at least 9 of the 10 dogs in the control group each had an adequate infestation, defined as at least 13 live *D. variabilis* ticks (25% of the infestations of 50 ticks per dog).

The fluralaner group had a 100% reduction in live tick counts at 48 hours following treatment or infestation for 12 weeks (infestation on Day 84). On all count days following drug administration, live tick counts for the fluralaner group were significantly different from the control group ($p < 0.001$).

Table II.25: *D. variabilis* S13090-01 Live Tick Count Effectiveness

Day for Tick Counts	Control Group Live Tick Counts[a]	Fluralaner Group Live Tick Counts[a]	Percent Effectiveness
2	31.9	0.0	100
30	24.4	0.0	100
58	32.0	0.0	100
86	29.2	0.0	100

[a] 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 group were significantly different from the control group ($p \leq 0.018$).

Table II.26: *D. variabilis* S13090-01 Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts[a]	Fluralaner Group Dead Tick Counts[a]
2	0.0	7.2
30	0.0	3.6
58	0.0	2.2
86	0.0	1.6

[a] Tick counts are geometric means

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

Conclusion:
This study demonstrated the effectiveness of fluralaner topical solution for the control (reduced live ticks) and treatment (increased dead ticks) of *D. variabilis* ticks for 12 weeks when assessed at 48 hours after drug administration or infestation.

k. Laboratory Dose Confirmation Study S13090-02: *Dermacentor variabilis* Ticks

Title:
Effectiveness of 28% w/v fluralaner spot-on solution for dogs at the proposed recommended dose against *Dermacentor variabilis* infestations in dogs using two different tick infestation schedules

Study Location and Dates:
Stanwood, MI
June 16, 2013, to September 20, 2013

Study Design:
The study was conducted in compliance with good clinical practice (GCP) guidelines.

Study Animals:
40 healthy, intact dogs (Beagle and pit bull-Beagle mixes, 23 males and 17 females), 0.8 to 2.0 years of age, and 6.6 to 16.3 kg body weight

Experimental Design:
Prior to allocation to treatment groups on Day -6, an initial tick infestation and count was conducted to evaluate susceptibility of each dog to experimental infestation (host suitability). There were two infestation schedules used in this study (Days -2, 28 and 56; and Day 84 only), with an untreated control and a fluralaner treatment group within each schedule. Dogs were ranked and blocked by live tick count in groups of four, and one dog from each block was randomly assigned to one of four groups (10 dogs per group).

Drug administration was on Day 0. Tick infestations were conducted on one fluralaner and one control groups of dogs on Days -2, 28 and 56 and only on Day 84 for the remaining fluralaner and control groups. At each infestation, each dog was infested with approximately 50 adult, unfed *D. variabilis* ticks (approximate 50:50 ratio of male to female ticks).

Drug Administration:
On Day 0, fluralaner topical solution was administered topically to the 20 dogs in the fluralaner groups, at doses as close as possible to 25 mg/kg. Doses ranged from 24 to 26 mg/kg. Hair at the administration site(s) was parted and fluralaner topical solution was applied to the skin in one or more spots along the dog's top-line, starting at the shoulder blades and moving toward the tail.

Measurements and Observations:
The primary variables for effectiveness were the counts of live ticks collected from the dogs. At tick counts on Days 2, 30, 58, and 86, ticks were removed and the numbers of live and dead ticks were recorded. General health observations were conducted daily, and at 1, 3 and 6 hours after drug administration. Treatment site observations were made at 24 and 48 hours after drug administration, on Day 7 and then weekly until completion of the study. Dogs were weighed on Day -2. Tick counts and health observations were conducted masked to treatment.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed tick counts, with 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:
At each tick count day, at least 8 of the 10 dogs in the control group each had an adequate infestation, defined as at least 13 live *D. variabilis* ticks (25% of the infestations of 50 ticks per dog).

The fluralaner group had greater than 90% reduction in live tick counts at 48 hours following treatment or infestation for 12 weeks (infestation on Day 84). On all count days following drug administration, live tick counts for the fluralaner group were significantly different from the control group ($p < 0.001$).

Table II.27: *D. variabilis* S13090-02 Live Tick Count Effectiveness

Day for Tick Counts	Control Group Live Tick Counts[a]	Fluralaner Group Live Tick Counts[a]	Percent Effectiveness
2	40.2	1.0	97.5
30	19.1	0.0	100
58	20.6	0.0	100
86	16.9	0.3	98.0

[a] 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 group were significantly different from the control group ($p \leq 0.002$).

Table II.28: *D. variabilis* S13090-02 Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts[a]	Fluralaner Group Dead Tick Counts[a]
2	0.0	8.7
30	0.1	3.2
58	0.1	3.0
86	0.1	1.2

[a] Tick counts are geometric means.

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

Conclusion:
This study demonstrated the effectiveness of fluralaner topical solution for the control (reduced live ticks) and treatment (increased dead ticks) of *D. variabilis* ticks for 12 weeks when assessed at 48 hours after drug administration or infestation.

l. Laboratory Dose Confirmation Study S14023-01: *Amblyomma americanum* Ticks

Title:
Effectiveness of 28% w/v fluralaner spot-on solution for dogs at the proposed recommended dose against *Amblyomma americanum* ticks on dogs determined 72 hours after infestation

Study Location and Dates:
Turlock, CA
March 12, 2014, to June 17, 2014

Study Design:
This study was conducted in compliance with good clinical practice (GCP) guidelines.

Study Animals:
20 healthy dogs (pure- and mixed-bred; 6 males and 14 females), 2.9 to 14.8 years of age, and 9.0 to 28.4 kg body weight

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

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 28, 56, and 84. At each infestation, each dog was infested with approximately 50 adult, unfed *A. americanum* ticks.

Drug Administration:
On Day 0, fluralaner topical solution was administered topically to the ten dogs in the fluralaner group, at doses as close as possible to 25 mg/kg. Doses ranged from 23 to 25 mg/kg. Hair at the administration site(s) was parted and fluralaner topical solution was applied to the skin in one or more spots along the dog's top-line, starting at the shoulder blades and moving toward the tail.

Measurements and Observations:
The primary variables for effectiveness were the counts of live ticks collected from the dogs. At tick counts on Days 3, 31, 59, and 87, ticks were removed and the numbers of live and dead ticks were recorded. General health observations were conducted daily and at 1, 3, and 6 hours after drug administration. Treatment site observations were made at 24 and 48 hours after drug administration, on Day 7, and then weekly until completion of the study. Dogs were weighed on Day -2. Tick counts and health observations were conducted masked to treatment.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed tick counts, with 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:
At each tick count day, at least 9 of the 10 dogs in the control group each had an adequate infestation, defined as at least 13 live *A. americanum* ticks (25% of the infestations of 50 ticks per dog).

The fluralaner group failed to demonstrate greater than 90% effectiveness at Day 3 and Day 87, but had greater than 90% reduction in live tick counts at 72 hours following infestation at 4 and 8 weeks after drug administration (infestation on Days 28 and 56).

On all count days following drug administration, live tick counts for the fluralaner group were significantly different from the control group ($p \leq 0.001$).

Table II.29: *A. americanum* S14023-01 Live Tick Count Effectiveness

Day for Tick Counts	Control Group Live Tick Counts[a]	Fluralaner Group Live Tick Counts[a]	Percent Effectiveness
3	23.5	3.6	84.8
31	22.4	0.0	100
59	26.3	0.5	98.0
87	27.7	3.9	85.9

[a] 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 group were significantly different from the control group ($p < 0.001$).

Table II.30: *A. americanum* S14023-01 Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts[a]	Fluralaner Group Dead Tick Counts[a]
3	0.0	6.5
31	0.0	5.1
59	0.1	5.2
87	0.0	5.4

[a] Tick counts are geometric means.

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

Conclusion:
This study demonstrated the effectiveness of fluralaner topical solution for the control (reduced live ticks) and treatment (increased dead ticks) of *A. americanum* ticks at 4 and 8 weeks following treatment when assessed at 72 hours after infestation. This study failed to demonstrate the effectiveness of fluralaner topical solution at Day 3 (72 hours after drug administration) and Day 87 (72 hours after infestation).

m. Laboratory Dose Confirmation Study S14023-02: *Amblyomma americanum* Ticks

Title:
Effectiveness of 28% w/v fluralaner spot-on solution for dogs at the proposed recommended dose against *Amblyomma americanum* ticks on dogs determined 72 hours after infestation

Study Locations and Dates:
Greenbrier, AR
August 11, 2014, to November 20, 2014

Study Design:
This study was conducted in compliance with good clinical practice (GCP) guidelines.

Study Animals:
20 healthy dogs (Beagle, Beagle-cross and hound-cross; 14 males and 6 females), 1.0 to 4.5 years of age, and 6.6 to 12.1 kg body weight

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

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 28, 56, and 84. At each infestation, each dog was infested with approximately 50 adult, unfed *A. americanum* ticks.

Drug Administration:
On Day 0, fluralaner solution was administered topically to the ten dogs in the fluralaner group, at doses as close as possible to 25 mg/kg. Doses ranged from 24 to 27 mg/kg. Hair at the administration site(s) was parted and fluralaner topical solution was applied to the skin in one or more spots along the dog's top-line, starting at the shoulder blades and moving toward the tail.

Measurements and Observations:
The primary variables for effectiveness were the counts of live ticks collected from the dogs. At tick counts on Days 3, 31, 59, and 87, ticks were removed and the numbers of live and dead ticks were recorded. General health observations were conducted daily and at 1, 3, and 6 hours after drug administration. Treatment site observations were made at 24 and 48 hours after drug administration, on Day 7, and then weekly until completion of the study. Dogs were weighed on Day -2. Tick counts and health observations were conducted masked to treatment.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed tick counts, with 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:
At each tick count day, at least 8 of the 10 dogs in the control group each had an adequate infestation, defined as at least 13 live *A. americanum* ticks (25% of the infestations of 50 ticks per dog).

The fluralaner group had greater than 90% reduction in live tick counts at 72 hours following treatment or infestation on Day 3 and at 4 weeks after drug administration (infestation on Day 28), but failed to demonstrate greater than 90% effectiveness beyond 4 weeks.

On all count days following drug administration, live tick counts for the fluralaner group were significantly different from the control group ($p \leq 0.028$).

Table II.31: *A. americanum* S14023-02 Live Tick Count Effectiveness

Day for Tick Counts	Control Group Live Tick Counts[a]	Fluralaner Group Live Tick Counts[a]	Percent Effectiveness
3	38.6	2.1	94.6
31	22.2	0.1	99.5
59	25.1	2.7	89.1
87	14.5	4.4	69.5

[a] 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 group were significantly different from the control group ($p \leq 0.002$).

Table II.32: *A. americanum* S14023-02 Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts[a]	Fluralaner Group Dead Tick Counts[a]
3	0.0	11.8
31	0.2	5.0
59	0.6	6.5
87	1.0	3.3

[a] Tick counts are geometric means.

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

Conclusions:
This study demonstrated the effectiveness of fluralaner topical solution for the control (reduced live ticks) and treatment (increased dead ticks) of *A. americanum* ticks for 4 weeks when assessed at 72 hours after drug administration or infestation. This study failed to demonstrate the effectiveness of fluralaner topical solution for the control of *A. americanum* for 8 or 12 weeks when assessed at 72 hours after infestation.

n. Laboratory Dose Confirmation Study S14023-03: *Amblyomma americanum* Ticks

Title:
Effectiveness of 28% w/v fluralaner spot-on solution for dogs at the proposed recommended dose against *Amblyomma americanum* ticks on dogs determined 72 hours after infestation

Study Location and Dates:
Greenbrier, AR
May 12, 2015, to August 21, 2015

Study Design:
This study was conducted in compliance with good clinical practice (GCP) guidelines.

Study Animals:
20 healthy dogs (Beagle, Beagle-cross and hound-cross; 7 males and 13 females), 1.8 to 6.8 years of age, and 7.5 to 13.7 kg body weight

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

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 28, 56, and 84. At each infestation, each dog was infested with approximately 50 adult, unfed *A. americanum* ticks.

Drug Administration:
On Day 0, fluralaner topical solution was administered topically to the ten dogs in the fluralaner group, at doses as close as possible to 25 mg/kg. Doses ranged from 24 to 26 mg/kg. Hair at the administration site(s) was parted and fluralaner topical solution was applied to the skin in one or more spots along the dog's top-line, starting at the shoulder blades and moving toward the tail.

Measurements and Observations:
The primary variables for effectiveness were the counts of live ticks collected from the dogs. At tick counts on Days 3, 31, 59, and 87, ticks were removed and the numbers of live and dead ticks were recorded. General health observations were conducted daily and at 1, 3, and 6 hours after drug administration. Treatment site observations were made at 24 and 48 hours after drug administration, on Day 7, and then weekly until completion of the study. Dogs were weighed on Day -2. Tick counts and health observations were conducted masked to treatment.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed tick counts, with 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:
At each tick count day, at least 9 of the 10 dogs in the control group each had an adequate infestation, defined as at least 13 live *A. americanum* ticks (25% of the infestations of 50 ticks per dog).

The fluralaner group had greater than 90% reduction in live tick counts at 72 hours following treatment or infestation on Day 3 and at 4, 8 and 12 weeks after drug administration (infestation on Days -2, 28, 56 and 84).

On all count days following drug administration, live tick counts for the fluralaner group were significantly different from the control group ($p < 0.001$).

Table II.33: *A. americanum* S14023-03 Live Tick Count Effectiveness

Day for Tick Counts	Control Group Live Tick Counts[a]	Fluralaner Group Live Tick Counts[a]	Percent Effectiveness
3	24.1	1.5	93.7
31	18.8	0.0	100.0
59	20.1	0.1	99.6
87	22.7	1.8	92.0

[a] 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 group were significantly different from the control group ($p \leq 0.018$).

Table II.34: *A. americanum* S14023-03 Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts[a]	Fluralaner Group Dead Tick Counts[a]
3	0.0	8.9
31	0.0	1.4
59	0.0	7.2
87	0.1	6.4

[a] Tick counts are geometric means

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

Conclusion:
This study demonstrated the effectiveness of fluralaner topical solution for the control (reduced live ticks) and treatment (increased dead ticks) of *A. americanum* ticks for 12 weeks when assessed at 72 hours after drug administration or infestation.

o. Overall Conclusion for *A. americanum:*

Although Studies S14023-01 and S14023-02 failed to demonstrate $\geq$ 90% effectiveness at Days 3, and Days 59 and 87, respectively, when combined with Study S140230-03, the average effectiveness through 8 weeks is $\geq$ 90%. In addition, at least two of the three studies demonstrated $\geq$ 90% effectiveness on Days 3, 31, and 59. The average effectiveness at 12 weeks remains < 90%. Therefore, the combined data demonstrate that fluralaner topical solution is effective for the treatment and control of *A.*

americanum infestations for 8 weeks when assessed at 72 hours after drug administration or infestation.

2. Cats

   a. Laboratory Dose Confirmation Study S11140-01: Effectiveness for Fleas

Title:
Effectiveness of 28% w/v fluralaner spot-on solution for cats at the proposed recommended dose against *Ctenocephalides felis* infestations in cats

Study Location and Dates:
Turlock, CA
October 4, 2011, to January 12, 2012

Study Design:
The study was conducted in compliance with Good Clinical Practices (GCP) guidelines.

Study Animals:
20 healthy cats (Domestic short- and long-haired, 10 males and 10 females), 1.0 to 12.7 years of age, and 2.6 to 6.9 kg body weight

Experimental Design:
Prior to allocation to treatment groups on Day -2, an initial flea infestation and count was conducted to evaluate 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 the untreated control (10 cats) or the fluralaner (10 cats) treatment group.

Drug administration was on Day 0. Flea infestations were conducted on Days -1, 28, 56, and 84. At each infestation, each cat was infested with approximately 100 unfed adult fleas.

Drug Administration:
On Day 0, fluralaner topical solution was administered topically to ten cats in the fluralaner group, at doses as close as possible to 40 mg/kg. Doses ranged from 37.3 to 43.1 mg/kg. Hair at the administration site was parted and fluralaner topical solution was applied to the skin in one spot along the cat's top-line.

Measurements and Observations:
The primary variable for effectiveness was the counts of live fleas collected from the cats. At flea counts on Days 2, 30, 58, and 86, fleas were removed and the numbers of live fleas recorded. General health observations were conducted daily and at 1, 3, and 6 hours after drug administration. Treatment site observations were made at 24 and 48 hours post-treatment, on Day 7 and then weekly until completion of the study. Cats were weighed on Day -1. Flea counts and health observations were conducted masked to treatment.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed flea counts, with 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:
At each flea count, there were a minimum of six cats in the control group that had an adequate infestation, defined as at least 50 live fleas (50% of the infestations of 100 fleas per cat). On all count days following drug administration, live flea counts between the two groups were significantly different ($p < 0.001$).

Table II.35: S11140-01 Effectiveness Against Fleas

Day of Flea Count	Control Group Flea Counts[a]	Fluralaner Group Flea Counts[a]	Percent Effectiveness
2	56.9	0.0	100
30	58.6	0.0	100
58	56.8	0.0	100
86	57.5	0.2	99.7

[a] Flea counts are geometric means and percent effectiveness is based on geometric means.

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

Conclusion:
This study demonstrated the effectiveness of fluralaner topical solution for the treatment of existing flea infestations for 12 weeks when assessed 48 hours after drug administration or infestation.

b. Field Study S11158-00: Effectiveness for Fleas

Title:
Clinical effectiveness of 28% w/v fluralaner spot-on solution for cats against fleas: a multi-center pivotal field study in client-owned cats

Study Locations and Dates:
Cropwell, AL
Largo, FL
Starke, FL
Chicago, IL
Decatur, IL
Lake Charles, LA
Zachary, LA
Augusta, ME
Springfield, MO
Columbia, NJ
Harleysville, PA
Philadelphia, PA
Quakertown, PA
Providence, RI

Germantown, TN
Austin, TX
New Braunfels, TX
Seguin, TX

May 9, 2013, to April 9, 2014

Study Design:
The study was conducted in compliance with good clinical practice (GCP) guidelines.

Objectives:
The field study assessed safety, effectiveness against fleas, and signs of flea allergy dermatitis.

Study Animals:
The study included 311 client-owned cats from 161 households; 224 cats (116 households) treated with fluralaner topical solution and 87 cats (45 households) treated with a topical solution containing fipronil and (s)-methoprene (control). The study enrolled 162 females and 149 males, 12 weeks to 19 years of age, and 2.6 to 25.3 lb body weight. The study included purebred and mixed breed cats.

Enrollment eligibility included: households with no more than 5 cats, at least one cat with a minimum of 5 live fleas, and no other pets that could harbor fleas. There were no breed or sex restrictions, but households with 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.

Experimental Design:
Households were randomly assigned to treatment with fluralaner or control in a ratio of three fluralaner households to one control household. Owners treated all cats in the fluralaner group with fluralaner topical solution after Visit 1 on Day 0 and again after Visit 4 on Day 84 for a total of two treatments. The fluralaner group finished the study at Visit 5 on Day 105. Owners treated all cats in the control group with a fipronil and (s)-methoprene topical solution after Visit 1 on Day 0 and again after Visits 2 and 3 on Days 28 and 56 for a total of three treatments. The control group finished the study at Visit 4 on Day 84. All cats within a household were in the same treatment group. A primary cat from each household was randomly selected from cats with 5 or more live fleas at Visit 1. Only the primary cat was assessed for effectiveness against fleas. Owners administered the treatments and they treated all cats in the household at the same times.

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

Drug Administration:
In the fluralaner group, Owners administered fluralaner topical solution, at labeled doses, on Days 0 and 84. In the control group, Owners applied the fipronil + (s)-methoprene topical solution at labeled doses on Days 0, 28, and 56.

Measurements and Observations:
The primary variable was the difference in live flea counts on the primary cats on Days 28 (Visit 2), 56 (Visit 3), and 84 (Visit 4) versus pre-treatment (Visit 1). Additional variables included progression of signs of flea allergy dermatitis, physical examinations, and clinical pathology. Statistical analyses were not performed for these additional variables.

Statistical Methods:
Log-transformed flea counts were analyzed using a mixed model at two-sided 5% significance level. Percent effectiveness against the pretreatment flea counts was calculated based on geometric means.

For each of Visits 2, 3, and 4, the effectiveness of fluralaner, based on geometric means, was greater than 90%.

Table II.36: Field Study S11158-00 Effectiveness against Fleas

Visit	Fluralaner Group	Control Group
Visit 1 Number of Cats	116	45
Visit 1 Geometric Mean Flea Count	28.0	28.0
Visit 2 Number of Cats	114	40
Visit 2 Geometric Mean Flea Count	0.2	15.0
Visit 2 Percent Effectiveness	99.1%	46.5%
Visit 3 Number of Cats	106	38
Visit 3 Geometric Mean Flea Count	0.1	9.4
Visit 3 Percent Effectiveness	99.5%	66.6%
Visit 4 Number of Cats	105	34
Visit 4 Geometric Mean Flea Count	0.3	6.8
Visit 4 Percent Effectiveness	99.0%	75.8%

Within each treatment group, geometric mean flea counts were significantly different ($p \leq 0.0001$) from Visit 1 at Visits 2, 3, and 4.

At least 80% of the cats treated with fluralaner topical solution with signs attributed to Flea Allergy Dermatitis (FAD) at Visit 1, and not administered other medications that could affect the assessment of FAD, had resolution of the signs by Visit 4 at Week 12.

Table II.37: Field Study S11158-00 Resolution of Signs of Flea Allergy Dermatitis

FAD Sign	Percent of Fluralaner Group Cats with the FAD Sign at Visit 1 that was Resolved at Week 12	Percent of Control Group Cats with the FAD Sign at Visit 1 that was Resolved at Week 12
Erythema	81% (21/26 cats)	33% (2/6 cats)
Alopecia	84% (38/45 cats)	50% (6/12 cats)
Papules	100% (6/6 cats)	100% (1/1 cats)
Scales	100% (15/15 cats)	100% (2/2 cats)
Crusts	96% (23/24 cats)	57% (4/7 cats)
Excoriation	100% (25/25 cats)	75% (3/4 cats)

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

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

Table II.38: Field Study S11158-00 Adverse Reactions

Adverse Reaction (AR)	Fluralaner Group: Percent of Cats with the AR During the 105-Day Study (n=224 cats)	Control Group: Percent of Cats with the AR During the 84-Day Study (n=87 cats)
Vomiting	7.6%	6.9%
Pruritus	5.4%	11.5
Diarrhea	4.9%	1.1%
Alopecia	4.9%	4.6%
Decreased appetite	3.6%	0.0%
Lethargy	3.1%	2.3%
Scabs/Ulcerated lesions	2.2%	3.4%

In the field study, two cats treated with fluralaner topical solution experienced ataxia. One cat became ataxic with a right head tilt 34 days after the first dose. The cat improved within one week of starting antibiotics. The ataxia and right head tilt, along with lateral recumbency, reoccurred 82 days after administration of the first dose. The cat recovered with antibiotics and was redosed with fluralaner topical solution 92 days after administration of the first dose, with no further abnormalities during the study. A second cat became ataxic 15 days after receiving its first dose and recovered the next day. The cat was redosed with fluralaner topical solution 82 days after administration of the first dose, with no further abnormalities during the study.

Conclusion:
This study demonstrated that fluralaner topical solution was safe and effective for the treatment and prevention of flea infestations when administered to client-owned cats.

c. Laboratory Dose Confirmation Study S11429-00: Simulated Home Environment for Fleas

Title:
Effectiveness of 28% w/v fluralaner spot-on solution for cats at the proposed recommended dose for the control of *Ctenocephalides felis* in a simulated home environment for cats

Study Location:
Turlock, CA
April 16, 2012, to August 20, 2012

Study Design:
The study was conducted in compliance with good clinical practice (GCP) guidelines.

Study Animals:
20 healthy cats (Domestic short- and long-hair, 6 males and 13 females), 0.4 to 13.7 years of age, and 2.2 to 5.6 kg body weight

Experimental Design:
Prior to allocation to treatment groups on Day -32, an initial flea infestation and count was conducted to evaluate 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 the untreated control (10 cats) or the fluralaner (10 cats) treatment group. One control cat was removed from the study on Day -3 due to abnormal health.

Beginning on Day -28, cats were housed in individual cages that contained a carpet area. To establish a self-perpetuating flea life cycle in each pen, all cats were infested with approximately 100 newly emerged, unfed adult *C. felis* fleas on Day -28 and again on Day -21. To simulate introductions of new fleas into a home environment, each cat was infested with 50 newly emerged, unfed adult fleas on Days 22, 50, and 78.

All live fleas counted on cats on Day -1 were recovered and recorded but not replaced on the cats. After the flea counts were completed, the cats were held overnight in clean pens to prevent re-infestation prior to drug administration on Day 0. Flea counts were performed on all cats on Day 1 (24 ± 4 hours post-treatment) and on Days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, and 77. Live fleas recovered during these flea counts were used to re-infest cats. The final flea count was on Day 84.

Drug Administration:
On Day 0, fluralaner topical solution was administered topically to the ten cats in the fluralaner group, at doses as close as possible to 40 mg/kg.

Doses ranged from 36.5 to 43.0 mg/kg. Hair at the administration site was parted and fluralaner topical solution was applied to the skin in one spot along the cat's top-line.

Measurements and Observations:
The primary variable for effectiveness was the counts of live fleas collected from the cats. Flea counts were conducted on all cats on Days -1, 1, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, and 84. General health observations were conducted daily and at 1, 3, and 6 hours after drug administration. Treatment site observations were made at 24 and 48 hours post-treatment, on Day 7 and then weekly until completion of the study. Cats were weighed on Day -1, 28, and 56. Flea counts and health observations were conducted masked to treatment.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed flea counts, with 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:
On Day -1, the geometric mean flea counts on control and fluralaner group cats were 15.9 and 10.6, respectively. The Day -1 live flea counts were not significantly different ($p = 0.386$) between the two groups. Live flea counts between the two groups were significantly different ($p \leq 0.007$) on all count days following drug administration, with the exception of Days 7 and 14 ($p = 0.076$ and $p = 0.104$, respectively).

Table II.39: Simulated Home Environment S11429-00 Effectiveness

Day	Control Group Flea Counts[a]	Fluralaner Group Flea Counts[a]	Percent Effectiveness
-1	15.9	10.6	Not applicable
1	1.9	0.1	96.1
7	0.4	0.0	100
14	0.4	0.0	100
21	12.1	0.0	100
28	33.3	0.0	100
35	17.1	0.0	100
42	9.9	0.0	100
49	10.0	0.0	100
56	21.5	0.0	100
63	15.4	0.0	100
70	12.9	0.0	100
77	14.9	0.0	100
84	32.7	0.0	100

[a] Flea counts are geometric means and percent effectiveness is based on geometric means.

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

Conclusion:
This study demonstrated that fluralaner topical solution was effective for the prevention of flea infestations on cats in a simulated home environment for 12 weeks.

d. Laboratory Dose Confirmation Study S11287-00: Speed of Kill for *Ctenocephalides felis* Fleas and *Ixodes ricinus* Ticks

Title:
Determination of the speed of kill of fluralaner administered once topically at a dose of 40 mg/kg body weight against tick infestations (*Ixodes ricinus*) and flea infestations (*Ctenocephalides felis*) on cats

Study Location:
Schwabenheim, Germany
January 11, 2013, to April 18, 2013

Study Design:
The study was conducted in compliance with the Good Laboratory Practice (GLP) principles of the Organisation for Economic Co-Operation and Development (OECD).

Study Animals:
28 healthy cats (European short-hair, 15 males and 13 females), 2 to 6 years of age, and 3.4 to 5.8 kg body weight

Experimental Design:
Prior to allocation to treatment groups on Day -4, an initial flea infestation and count was conducted to evaluate 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 (7 cats/group) or one of two fluralaner (7 cats/group) treatment groups.

Drug administration was on Day 0. For Groups A and B (one fluralaner and one control group), flea and tick co-infestations were conducted on Days -2 and 28. On Days 56 and 84, Groups A and B were only infested with fleas. For Groups C and D (one fluralaner and one control), flea and tick co-infestations were conducted on Days -2, 28, 56, and 84. At each infestation, each cat was infested with approximately 80 unfed adult fleas and approximately 50 female and 10 male unfed adult *I. ricinus* ticks.

For Groups A and B, flea and tick counts were performed on Day 0, 8 hours after drug administration, and on Days 28, 56 and 84, 8 hours after flea and tick (only Days 56 and 84) infestations. For Groups C and D, flea and tick counts were performed on Day 1, 12 hours after drug administration, and on Days 29, 57, and 85, 12 hours after flea and tick infestations for Groups C and D. Fleas and ticks were not returned to the cat after counting.

Drug Administration:
On Day 0, the 14 cats in the fluralaner groups were dosed with a volume of fluralaner topical solution, at doses as close as possible to 40 mg/kg. Doses ranged from 37.8 mg/kg to 43.0 mg/kg per cat. Hair at the administration site was parted and fluralaner topical solution was applied to the skin in one spot along the cat's top-line.

Measurements and Observations:
The primary variables for effectiveness were the counts of live fleas and ticks collected from the cats. At flea and tick counts on Days 0/1, 28/29, 56/57 and 84/85, fleas and ticks were removed and the number of live and dead fleas and ticks were recorded. General health observations were conducted daily. Cats were weighed on Day -1. Flea and tick counts and health observations were conducted masked to treatment.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed tick counts, with 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:
At each flea count, the seven cats in each control group each had an adequate infestation, defined as at least 40 live fleas (50% of the infestations of 80 fleas per cat). At each tick count, at least six cats in each control group each had an adequate infestation, defined as at least 15 live *I. ricinus* ticks (25% of the infestations of 60 ticks per cat).

The 8-hour fluralaner group had greater than 90% reduction in live flea counts at 8 hours following treatment or infestation for 4 weeks (infestation on Day 28).

The 12-hour fluralaner group had greater than 90% reduction in live flea counts at 12 hours following treatment or infestation for 12 weeks (infestation on Day 84).

On all count days following drug administration, live flea counts for the fluralaner group were significantly different from the control group ($p < 0.05$) with the exception of the 8-hour assessment at Day 84 ($p = 0.2588$).

Table II.40: Speed of Kill S11287-00 Live Flea Count Effectiveness, 8-hour Counts

Day for 8-hour Counts	Control Group Flea Counts[a]	Fluralaner Group Flea Counts[a]	Percent Effectiveness
0	78.2	0.0	100
28	75.5	0.7	99.0
56	71.8	9.8	86.3
84	75.1	54.1	27.9

[a] Flea counts are geometric means and percent effectiveness is based on geometric means.

Table II.41: Speed of Kill S11287-00 Live Flea Count Effectiveness, 12-hour Counts

Day for 12-hour Counts	Control Group Flea Counts[a]	Fluralaner Group Flea Counts[a]	Percent Effectiveness
1	77.0	0.0	100
29	75.0	0.1	99.9
57	75.1	0.0	100
85	74.4	0.9	98.8

[a] Flea counts are geometric means and percent effectiveness is based on geometric means.

The 8-hour fluralaner group had greater than 90% reduction in live tick counts at 8 hours following treatment at Day 0.

The 12-hour fluralaner group had greater than 90% reduction in live tick counts at 12 hours following treatment or infestation for 4 weeks (infestation on Day 28).

Live tick counts between the fluralaner and control groups were significantly different ($p < 0.05$) at the 8-hours assessment at Day 0 and Day 28. No significant difference in live tick counts between the fluralaner and controls groups was observed at the 12-hour assessment at Day 57 and Day 85 ($p = 0.1365$ and $p = 0.1055$, respectively).

Table II.42: *I. ricinus* Speed of Kill S11287-00 Live Tick Count Effectiveness, 8-hour Counts

Day for 8-hour Counts[a]	Control Group Tick Counts[b]	Fluralaner Group Tick Counts[b]	Percent Effectiveness
0	18.1	0.6	96.5
28	34.0	20.7	39.3

[a] Because of insufficient effectiveness on Day 28, tick infestations on Day 56 and Day 84 were not done for Groups A and B.
[b] Tick counts are geometric means and percent effectiveness is based on geometric means.

Table II.43: *I. ricinus* Speed of Kill S11287-00 Live Tick Count Effectiveness, 12-hour Counts

Day for 12-hour Counts	Control Group Tick Counts[a]	Fluralaner Group Tick Counts[a]	Percent Effectiveness
1	23.2	0.0	100
29	23.1	0.0	100
57	23.5	10.5	55.4
85	26.0	18.2	29.9

[a] Tick counts are geometric means and percent effectiveness is based on geometric means.

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

Conclusions:

This study demonstrated that fluralaner topical solution killed *C. felis* fleas and reduced the number of live *C. felis* fleas on cats by greater than 98% within 12 hours after treatment or infestation for 12 weeks. Fluralaner topical solution killed *C. felis* fleas 8 hours after treatment but failed to demonstrate adequate (≥90%) effectiveness against *C. felis* fleas within 8 hours after infestation for 12 weeks. Fluralaner topical solution failed (<90% effectiveness) to kill *I. ricinus* ticks and reduce the number of live *I. ricinus* ticks on cats within 8 or 12 hours after infestation for 12 weeks.

e. Laboratory Dose Confirmation Study S11123-04: *Ixodes scapularis* Ticks

Title:
Effectiveness of 28% w/v fluralaner spot-on solution for cats at the proposed recommended dose against Ixodes scapularis infestations in cats

Study Location and Dates:
Turlock, CA
June 11, 2013, to September 19, 2013

Study Design:
The study was conducted in compliance with Good Clinical Practices (GCP) guidelines.

Study Animals:
20 healthy cats (Domestic short- and long-hair, 9 males and 11 females), 1.8 to 15.3 years of age, and 2.2 to 6.0 kg body weight

Experimental Design:
Prior to allocation to treatment groups on Day -6, an initial tick infestation and count was conducted to evaluate susceptibility of each 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 (10 cats) or the fluralaner (10 cats) treatment group.

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 28, 56, and 84. 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).

Drug Administration:
On Day 0, fluralaner topical solution was administered topically to the ten cats in the fluralaner group, at doses as close as possible to 40 mg/kg. Doses ranged from 34.2 to 42.7 mg/kg per cat. Hair at the administration site was parted and fluralaner topical solution was applied to the skin in one spot along the cat's top-line.

Measurements and Observations:
The primary variables for effectiveness were the counts of live ticks collected from the cats. At tick counts on Days 2, 30, 58, and 86, ticks were removed and the numbers of live and dead ticks were recorded.

General health observations were conducted daily, and at 1, 3, and 6 hours after drug administration. Treatment site observations were made at 24 and 48 hours post-treatment, on Day 7, and then weekly until completion of the study. Cats were weighed on Day -2. Tick counts and health observations were conducted masked to treatment.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed tick counts, with 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:
At each tick count day, all 10 cats in the control group each had an adequate infestation, defined as at least 19 live *I. scapularis* ticks (25% of the infestations of 75 ticks per cat).

The fluralaner group had greater than 90% reduction in live tick counts at 48 hours following treatment or infestation for 12 weeks (infestation on Day 84).

On all count days following drug administration, live tick counts for the fluralaner group were significantly different from the control group ($p < 0.001$).

Table II.44: *I. scapularis* S11123-04 Live Tick Count Effectiveness

Day for Tick Counts	Control Group Live Tick Counts[a]	Fluralaner Group Live Tick Counts[a]	Percent Effectiveness
2	44.0	0.3	99.4
30	52.1	0.0	100
58	45.9	0.0	100
86	43.5	0.6	98.6

[a] 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 group were significantly different from the control group ($p < 0.001$).

Table II.45: *I. scapularis* S11123-04 Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts[a]	Fluralaner Group Dead Tick Counts[a]
2	0.0	22.4
30	0.0	12.9
58	0.0	15.6
86	0.0	17.1

[a] Tick counts are geometric means

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

Conclusion:
This study demonstrated the effectiveness of fluralaner topical solution for the control (reduced live ticks) and treatment (increased dead ticks) of *I. scapularis* ticks for 12 weeks when assessed at 48 hours after drug administration or infestation.

f. Laboratory Dose Confirmation Study S11123-05: *Ixodes scapularis* Ticks

Title:
Effectiveness of 28% w/v fluralaner spot-on solution for cats at the proposed recommended dose against *Ixodes scapularis* infestations in cats

Study Location and Dates:
Greenbrier, AR
January 1, 2014, to April 18, 2014

Study Design:
The study was conducted in compliance with Good Clinical Practices (GCP) guidelines.

Study Animals:
20 healthy cats (Domestic short-hair, 10 males and 10 females), approximately 0.7 to 2.9 years of age, and 2.5 to 5.0 kg body weight

Experimental Design:
Prior to allocation to treatment groups on Day -5, an initial tick infestation and count was conducted to evaluate 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 (10 cats) or the fluralaner (10 cats) treatment group.

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 28, 56, 84, and 91. 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).

Drug Administration:
On Day 0, fluralaner topical solution was administered topically to the ten cats in the fluralaner group, at doses as close as possible to 40 mg/kg. Doses ranged from 37.8 to 43.8 mg/kg per cat. Hair at the administration site was parted and fluralaner topical solution was applied to the skin in one spot along the cat's top-line.

Measurements and Observations:
The primary variables for effectiveness were the counts of live ticks collected from the cats. At tick counts on Days 2, 30, 58, and 86, ticks were removed and the numbers of live and dead ticks were recorded. General health observations were conducted daily and at 1, 3, and 6 hours after drug administration. Treatment site observations were made at 24 and 48 hours post-treatment, on Day 7 and then weekly until completion of the study. Cats were weighed on Day -2. Tick counts and health observations were conducted masked to treatment.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed tick counts, with 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:
At each tick count day, at least 9 of the 10 cats in the control group each had an adequate infestation, defined as at least 19 live *I. scapularis* ticks (25% of the infestations of 75 ticks per cat).

The fluralaner group had greater than 90% reduction in live tick counts at 48 hours following treatment or infestation for 12 weeks (infestation on Day 84).

On all count days following drug administration, live tick counts for the fluralaner group were significantly different from the control group ($p < 0.001$).

Table II.46: *I. scapularis* S11123-05 Live Tick Count Effectiveness

Day for Tick Counts	Control Group Live Tick Counts[a]	Fluralaner Group Live Tick Counts[a]	Percent Effectiveness
2	37.6	0.0	100
30	52.2	0.0	100
58	49.7	0.0	100
86	53.4	2.9	94.6

[a] 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 group were significantly different from the control group ($p < 0.001$).

Table II.47: *I. scapularis* S11123-05 Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts[a]	Fluralaner Group Dead Tick Counts[a]
2	0.2	7.6
30	0.0	14.6
58	0.0	13.9
86	0.0	11.9

[a] Tick counts are geometric means.

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

Conclusion:
This study demonstrated the effectiveness of fluralaner topical solution for the control (reduced live ticks) and treatment (increased dead ticks) of *I. scapularis* ticks for 12 weeks when assessed at 48 hours after drug administration or infestation.

g. Laboratory Dose Confirmation Study S11175-02: *Dermacentor variabilis* Ticks

Title:
Effectiveness of 28% w/v fluralaner spot-on solution for cats at the proposed recommended dose against *Dermacentor variabilis* infestations in cats

Study Location and Dates:
Turlock, CA
March 14, 2012, to June 22, 2012

Study Design:
The study was conducted in compliance with Good Clinical Practices (GCP) guidelines.

Study Animals:
20 healthy cats (Domestic short- and long-hair cats, 12 males and 8 females), 0.6 to 5.3 years of age, and 2.1 to 5.7 kg body weight

Experimental Design:
Prior to allocation to treatment groups on Day -7, an initial tick infestation and count was conducted to evaluate 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 (10 cats) or the fluralaner (10 cats) treatment group.

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 28, 56 and 84. 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).

Drug Administration:
On Day 0, fluralaner topical solution was administered topically to the ten cats in the fluralaner group, at doses as close as possible to 40 mg/kg. Doses ranged from 35.0 to 42.0 mg/kg per cat. Hair at the administration site was parted and fluralaner topical solution was applied to the skin in one spot along the cat's top-line.

Measurements and Observations:
The primary variables for effectiveness were the counts of live ticks collected from the cats. At tick counts on Days 2, 30, 58, and 86, ticks were removed and the numbers of live and dead ticks were recorded. General health observations were conducted daily and at 1, 3, and 6 hours after drug administration. Treatment site observations were made at 24 and 48 hours post-treatment, on Day 7 and then weekly until completion of the study. Cats were weighed on Day -2. Tick counts and health observations were conducted masked to treatment.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed tick counts, with 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:
At each tick count day, at least 7 of the 10 cats in the control group each had an adequate infestation, defined as at least 13 live *D. variabilis* ticks (25% of the infestations of 50 ticks per cat).

The fluralaner group had greater than 90% reduction in live tick counts at 48 hours following treatment or infestation for 8 weeks (infestation on Day 56).

On all count days following drug administration, live tick counts for the fluralaner group were significantly different from the control group ($p \leq 0.003$).

Table II.48: *D. variabilis* S11175-02 Live Tick Count Effectiveness

Day for Tick Counts	Control Group Live Tick Counts[a]	Fluralaner Group Live Tick Counts[a]	Percent Effectiveness
2	27.3	0.1	99.7
30	16.3	0.0	100
58	17.2	0.2	98.7
86	35.8	8.3	76.8

[a] 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 group were significantly different from the control group ($p \leq 0.001$).

Table II.49: *D. variabilis* S11175-02 Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts[a]	Fluralaner Group Dead Tick Counts[a]
2	0.0	7.2
30	0.0	6.7
58	0.0	4.8
86	0.0	3.3

[a] Tick counts are geometric means.

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

Conclusions:
This study demonstrated the effectiveness of fluralaner topical solution for the control (reduced live ticks) and treatment (increased dead ticks) of *D. variabilis* ticks for 8 weeks when assessed at 48 hours after drug administration or infestation, but failed to demonstrate greater than 90% effectiveness beyond 8 weeks.

h. Laboratory Dose Confirmation Study S13261-00: *Dermacentor variabilis* Ticks

Title:
Effectiveness of 28% w/v fluralaner spot-on solution for cats at the proposed recommended dose against *Dermacentor variabilis* infestations in cats

Study Location:
Greenbrier, AR
November 5, 2013, to February 13, 2014

Study Design:
The study was conducted in compliance with Good Clinical Practices (GCP) guidelines.

Study Animals:
20 healthy cats (Domestic short-hair 6 males and 14 females), 1.3 to 7.5 years of age, and 1.8 to 5.1 kg body weight

Experimental Design:
Prior to allocation to treatment groups on Day -4, an initial tick infestation and count was conducted to evaluate 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 (10 cats) or the fluralaner (10 cats /group) treatment group.

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 28, 56 and 84. At each infestation, each cat was infested with approximately 50 adult, unfed *D. variabilis* ticks.

Drug Administration:
On Day 0, fluralaner topical solution was administered topically to the ten cats in the fluralaner group, at doses as close as possible to 40 mg/kg. Doses ranged from 39.6 to 40.4 mg/kg per cat. Hair at the administration site was parted and fluralaner topical solution was applied to the skin in one spot along the cat's top-line.

Measurements and Observations:
The primary variables for effectiveness were the counts of live ticks collected from the cats. At tick counts on Days 2, 30, 58, and 86, ticks were removed and the numbers of live and dead ticks were recorded. General health observations were conducted daily and at 1, 3, and 6 hours after drug administration. Treatment site observations were made at 24 and 48 hours post-treatment, on Day 7 and then weekly until completion of the study. Cats were weighed on Day -2. Tick counts and health observations were conducted masked to treatment.

Statistical Methods:
A mixed model analysis was used to analyze log-transformed tick counts, with 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:
At each tick count day, at least 9 of the 10 cats in the control group each had an adequate infestation, defined as at least 13 live *D. variabilis* ticks (25% of the infestations of 50 ticks per cat).

The fluralaner group had greater than 90% reduction in live tick counts at 48 hours following treatment or infestation for 12 weeks (infestation on Day 84).

On all count days following drug administration, live tick counts for the fluralaner group were significantly different from the control group ($p < 0.001$).

Table II.50: *D. variabilis* S13261-00 Live Tick Count Effectiveness

Day for Tick Counts	Control Group Live Tick Counts[a]	Fluralaner Group Live Tick Counts[a]	Percent Effectiveness
2	23.0	0.0	100
30	29.0	0.0	100
58	37.4	0.0	100
86	24.5	1.5	93.7

[a] 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 group were significantly different from the control group ($p \leq 0.001$).

Table II.51: *D. variabilis* S13261-00 Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts[a]	Fluralaner Group Dead Tick Counts[a]
2	0.0	2.8
30	0.0	11.9
58	0.0	12.2
86	0.0	3.6

[a] Tick counts are geometric means.

Adverse Reactions:
One cat in the fluralaner group vomited on Day 1. No treatment was administered and the cat was considered normal the following day.

Conclusion:
This study demonstrated the effectiveness of fluralaner topical solution for the control (reduced live ticks) and treatment (increased dead ticks) of *D. variabilis* ticks for 12 weeks when assessed at 48 hours after drug administration or infestation.

III. TARGET ANIMAL SAFETY

A. Dogs

1. Margin of Safety Study D009\11-002

Title:
Target animal safety study in pups when administered 29% w/v fluralaner spot-on solution for dogs/cats topically on three occasions 56 days apart

Study Location and Dates:
Mayo, Ireland
August 12, 2011, to May 29, 2012

Study Design:
The study was conducted in compliance with the Good Laboratory Practice (GLP) principles of the Organisation for Economic Co-Operation and Development (OECD).

Objective:
To assess the safety of fluralaner, administered topically, at doses of 1X, 3X, and 5X the maximum label dose (56, 168, and 280 mg/kg) to dogs three times at eight weeks intervals.

Study Animals:
32 healthy, weaned puppies (Beagles, 16 male and 16 female), 56 to 63 days of age, and 2.0 to 3.7 kg body weight.

Experimental Design:
Dogs were randomized to one of four treatment groups of eight dogs per group (four per sex) within sex by body weight. Dogs were either administered fluralaner topical solution at 56, 168, or 280 mg/kg (1X, 3X, and 5X the maximum label dose) 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(s) was parted and fluralaner topical solution or mineral oil was applied to the skin in one or more spots along the dog's top-line, starting at the shoulder blades and moving toward the tail.

Measurements and Observations:
Clinical observations were made twice daily and at 1, 2, 3, 4, and 8 hours after treatment on Days 0, 56, and 112. Body weight was recorded weekly. Individual food consumption was recorded daily. Blood samples were collected for clinical pathology [hematology, coagulation profile, clinical chemistry, adrenocorticotrophic hormone (ACTH), and acute phase (C-reactive) protein] on Days -14, 21, 50, 106, and 162; and for plasma fluralaner concentrations on Days -6, 3, 7, 14, 28, 55, 59, 63, 70, 84, 111, 115, 119, 126, 140, and 167. Urine samples were collected overnight for urinalysis on Days -6/-5, 20/21, 49/50, 105/106, and 161/162. All dogs were euthanized on Day 168 and underwent full gross necropsy, organ weight, and histopathological evaluation.

Statistical Methods:
Hematology, clinical chemistry, ACTH, coagulation, C-reactive protein, numerical urinalysis variables, and weekly food consumption were analyzed using a repeated measured mixed model analysis of covariance. Pre-treatment measurement was included as a covariate. Body weight was analyzed using a repeated measured 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, coagulation profiles and urinalysis), gross pathology, histopathology, or organ weights. Cosmetic changes at the application site included matting/clumping/spiking of hair, wetness, or a greasy appearance.

Plasma concentrations of fluralaner confirmed systemic exposure in all puppies administered fluralaner. The dogs achieved steady-state plasma concentrations between the second and third doses. Systemic exposure was proportional to dose during each dosing period.

Conclusion:
The study supports the safe use of fluralaner topical solution in dogs when used at the labeled dose and duration.

2. Oral Safety Study D009\006

Title:
Target animal safety study in dogs when administered 28% w/v fluralaner spot-on solution for dogs/cats orally on one occasion

Study Location and Dates:
Mayo, Ireland
October 11, 2011, to February 16, 2012

Study Design:
The study was conducted in compliance with the Good Laboratory Practice (GLP) principles of the Organisation for Economic Co-Operation and Development (OECD).

Objective:
To provide safety information on the effects of fluralaner topical solution in dogs following oral administration at a dose of 1X of the maximum treatment dose (56 mg/kg).

Study Animals:
12 healthy dogs (Beagles, 6 male and 6 female), 8 to 10 months of age, and 10.0 to 14.0 kg body weight

Experimental Design:
Dogs were randomized to two treatment groups of six dogs per group (three per sex) within sex by body weight. Dogs were either administered fluralaner topical solution at 56 mg/kg (1X the maximum treatment dose) once or were administered saline (control group).

Drug Administration:
The dogs were fed prior to oral administration of fluralaner topical solution.

Measurements and Observations:
Clinical observations were made twice daily and at 15 minutes, 30 minutes, and 1, 2, 3, 4, and 8 hours after treatment on Day 0. Body weight was recorded weekly. Individual food consumption was recorded daily. Blood samples were collected for clinical pathology [hematology, coagulation profile, clinical chemistry, and acute phase (C-reactive) protein] on Days -14 and 8; and for plasma fluralaner concentrations on Days -5, 2, 7, 14, and 28. Urine samples were collected overnight for urinalysis on Days -7/-6 and 7/8. All dogs were euthanized on Day 28 and underwent full gross necropsy, organ weight, and histopathological evaluation.

Statistical Methods:
Weekly food consumption was analyzed using a repeated measures mixed model analysis of covariance. Body weight, heart rate, and rectal temperature were analyzed by repeated measures mixed model analysis of variance. Hematology, clinical chemistry, coagulation, C-reactive protein, and numerical urinalysis variables were analyzed by mixed model analysis of covariance with the pre-treatment measurement included as a covariate. 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, coagulation profiles and urinalysis), gross pathology, histopathology, or organ weights. Salivation was observed in five of the six dogs orally administered fluralaner during the five minutes immediately after dosing. No evidence of salivation was observed during the same period in control dogs. One dog administered fluralaner experienced diarrhea with blood 3 hours after treatment. Another dog administered fluralaner experienced vomiting 8 hours after dosing.

Plasma concentrations of fluralaner confirmed systemic exposure in all dogs administered fluralaner. The systemic fluralaner exposure after a single oral dose was about seven-fold greater than the exposure after the third topical dose in the margin of safety study.

Conclusion:
The oral administration of fluralaner topical solution at 56 mg/kg was well tolerated in dogs. Potential treatment-related effects include salivation immediately after dosing, diarrhea with blood, and vomiting.

3. Reproductive Safety in Dogs

Two pharmacokinetic studies (Studies S28003 and S29386) were conducted to provide information regarding the bioavailability of the topical and oral formulations. Because the bioavailability of both formulations is approximately 25%, the reproductive safety of fluralaner for both the oral and topical formulations was evaluated in a reproductive safety study in dogs using only the oral formulation (Refer to Reproductive Safety Study 671596 in the FOI summary for BRAVECTO Chewable Tablets (NADA 141-426)).

Pharmacokinetic Studies in Dogs (Studies S28003 and S29386)

Titles:
Pivotal pharmacokinetic study in Beagle dogs after topical administration of 28% w/v spot-on solution for dogs and intravenous administration of fluralaner 2.5% IV solution for dogs, including the evaluation of dose proportionality/linearity and bioavailability (Study S28003)

Pivotal pharmacokinetic study in Beagle dogs after oral administration of 13.64% w/w fluralaner flavored chewable tablet for dogs including the evaluation of dose proportionality/linearity (Study S29386)

Study Location: Barcelona, Spain

Study Design:

Objective:
To provide pharmacokinetic information on fluralaner following topical, oral, and intravenous (IV) administration.

Study Animals: 6 healthy dogs (Beagles, 3 male and 3 female) per group

Experimental Design:
Dogs were administered either fluralaner topical solution topically at 12.5 to 50 mg/kg, fluralaner tablets orally at 12.5 to 50 mg/kg, or fluralaner injection intravenously at 12.5 mg/kg.
Measurements and Observations:
Plasma samples were analyzed for fluralaner concentrations. Pharmacokinetic parameters were calculated using non-compartmental analysis.

Results:
The table below lists the geometric mean (± CV) maximum concentration (C_{max}), area-under-the-curve to infinity ($AUC_{0-\infty}$), and bioavailability (F) values as well as for the median [Range] time to Cmax (Tmax) and mean (± 1 SD) terminal half-life for fluralaner following topical, oral, or IV administration.

Table III.1: Fluralaner Systemic Exposure and Pharmacokinetics Parameters.

Dose, mg/kg	Route of Administration	C_{max}, ng/mL	T_{max}, day	$AUC_{(0-\infty)}$, day*ng/mL	Half-life, day	F[e], %
12.5	IV	7061[a] (14%)[b]	Not applicable	87141[a] (14%)[b]	15 (2)	Not applicable
12.5	Topical	347 (31%)	42[c] [21, 63][d]	19242 (23%)	17 (4)	22[a] (23%)[b]
12.5	Oral	1995 (53%)	1 [0.1, 2]	27553 (56%)	13 (1)	32 (56%)
25	Topical	707 (29%)	25 [14, 56]	46266 (31%)	21(3)	27 (31%)
25	Oral	3577 (67%)	1 [1, 2]	42611 (62%)	12 (3)	24 (62%)
50	Topical	1673 (21%)	25 [7, 42]	87818 (21%)	19 (5)	25 (21%)
50	Oral	5117 (44%)	1 [0.2, 3]	66692 (44%)	14 (1)	19 (44%)

[a] All values for C_{max}, $AUC_{(0-\infty)}$, and F are geometric means.
[b] All values in () for C_{max}, $AUC_{(0-\infty)}$, and F are geometric coefficients of variation (CV).
[c] All values for T_{max} are medians.
[d] Values in [] represent range.
[e] For oral and topical administration at each dose level, individual $AUC_{(0-\infty)}$values were compared to the mean $AUC_{(0-\infty)}$ following IV administration.

Conclusion: The bioavailability of fluralaner following oral and topical administration is approximately 25%.

B. Cats

1. Margin of Safety Study D009\11-03

Title:
Target animal safety study in kittens when administered 28% w/v fluralaner spot-on solution for dogs/cats topically on three occasions 56 days apart

Study Location and Dates:
Mayo, Ireland
September 21, 2011, to August 29, 2012

Study Design:
The study was conducted in compliance with the Good Laboratory Practice (GLP) principles of the Organisation for Economic Co-Operation and Development (OECD).
Objective:
To assess the safety of fluralaner following the topical administration at doses of 1X, 3X, and 5X the maximum label dose (93, 279, and 465 mg/kg) to kittens three times at eight week intervals.

Study Animals:
32 healthy weaned kittens (mixed-breed, 16 male and 16 female), 78 to 91 days of age, and 1.2 to 1.5 kg body weight

Experimental design:
Cats were randomized to one of four treatment groups of eight kittens per group (four per sex) within sex by body weight. Cats were either administered fluralaner at 93, 279, or 465 mg/kg (1X, 3X, and 5X the maximum label dose) 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(s) was parted and fluralaner topical solution or mineral oil was applied to the skin in one or more spots 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 and at 1, 2, 3, 4, and 8 hours after treatment 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, 70, 111, 126 and 167. Blood samples were collected for clinical pathology [hematology, coagulation profile, clinical chemistry, adrenocorticotrophic hormone (ACTH), and serum amyloid A] on Days -14, -6 (coagulation and ACTH only), 21, 50, 106, 154 (ACTH only), and 162 (no ACTH); and for plasma fluralaner concentrations on Days -6, 3, 7, 14, 28, 55, 59, 63, 70, 84, 111, 115, 119, 126, 140, 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, and histopathological evaluation.

Statistical Methods:
Hematology, clinical chemistry, ACTH, coagulation, serum amyloid A, numerical urinalysis variables, and food consumption were analyzed using a repeated measured mixed model analysis of covariance. Pre-treatment measurement was included as a covariate. Body weight was analyzed using a repeated measured 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. Cosmetic changes at the application site included matting/clumping/spiking of hair, wetness, or a greasy appearance. Histopathological examination of the kidneys showed an increased incidence of minimal tubular degeneration/regeneration in the higher dose groups (one kitten in the control group, none in the 1X group, five in the 3X group, and three in the 5X group). None of the kittens had abnormal clinical pathology results associated with the microscopic findings.

Plasma concentrations of fluralaner confirmed systemic exposure in all kittens administered fluralaner. The kittens in the 1X and 3X group did not achieve steady-state plasma concentrations during the study. Systemic exposure was proportional to dose during each dosing period.

Conclusion:
The study supports the safe use of fluralaner topical solution in cats when used at the labeled dose and duration. Renal tubular degeneration/regeneration is considered a potential drug-related effect with unknown clinical impact.

2. Oral Safety Study D009\11-004

Title:
Target animal safety study in cats when administered 28% w/v fluralaner spot-on solution for dogs/cats orally on one occasion

Study Location and Dates:
Mayo, Ireland
October 11, 2011, to February 16, 2012

Study Design:
The study was conducted in compliance with the Good Laboratory Practice (GLP) principles of the Organisation for Economic Co-Operation and Development (OECD).

Objective:
To assess the effects of fluralaner topical solution in kittens following oral administration at a dose of 1X of the maximum treatment dose (93 mg/kg).

Study Animals:
12 healthy cats (mixed-breed, 6 male and 6 female), 6 to 7 months of age, and 2.7 to 3.9 kg body weight

Experimental Design:
Cats were randomized to two treatment groups of six cats per group (three per sex) within sex by body weight. Cats were either orally administered fluralaner at 93 mg/kg (1X the maximum treatment dose) once or were administered saline (control group).

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

Measurements and Observations:
Clinical observations were made twice daily and at 15 minutes, 30 minutes, and 1, 2, 3, 4, and 8 hours after treatment on Day 0. Body weight was recorded weekly. Individual food consumption was recorded daily. Physical examinations were performed on Days -14, -7, -1, 1 and 27. 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 concentrations on Days -5, 2, 7, 14, and 28. Urine samples were collected overnight for urinalysis on Days -14/-13 and 7/8. All cats were euthanized on Day 28 and underwent full gross necropsy and organ weight evaluation. Histopathological evaluation was conducted on the livers from all cats and any other abnormal tissue collected during gross necropsy.

Statistical Methods:
Weekly food consumption was analyzed using a repeated measures mixed model analysis of covariance. Body weight, heart rate, and rectal temperature were analyzed by repeated measures mixed model analysis of variance. Hematology, clinical chemistry, coagulation, serum amyloid A, and numerical urinalysis variables were analyzed by mixed model analysis of covariance with the pretreatment measurement included as a covariate. 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, coagulation profiles and urinalysis), gross pathology, histopathology, or organ weights. Salivation was observed in all six cats orally administered fluralaner. Coughing was observed in four of six cats orally administered fluralaner. One treated cat vomited 2 hours after dosing.

Plasma concentrations of fluralaner confirmed systemic exposure in all cats administered fluralaner. The systemic fluralaner exposure after a single oral dose was approximately equivalent to the exposure after the first topical dose in the margin of safety study.

Conclusion:
The oral administration of fluralaner topical solution at 93 mg/kg was well tolerated in cats. Treatment-related effects include salivation immediately after treatment, coughing, and vomiting.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs and 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:

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 dry.

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. **Wash hands and contacted skin thoroughly with soap and water immediately after use of the product.**

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, when used according to the label, is safe and effective for killing adult fleas and for the treatment and prevention of flea infestations (*Ctenocephalides felis*) and the treatment and control of tick infestations [*Ixodes scapularis* (black-legged tick)*, Dermacentor variabilis* (American dog tick)*,* and *Rhipicephalus sanguineus* (brown dog tick)] for 12 weeks and *Amblyomma americanum* (lone star tick) infestations for 8 weeks in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater. The data demonstrate that BRAVECTO, when used according to the label, is safe and effective for killing adult fleas and for the treatment and prevention of flea infestations (*Ctenocephalides felis*) and the treatment and control of *Ixodes scapularis* (black-legged tick) infestations for 12 weeks and *Dermacentor variabilis* (American dog tick) infestations for 8 weeks in cats and kittens 6 months of age and older, and weighing 2.6 pounds or greater.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to advise dog owners regarding use in breeding dogs, to monitor for and respond to adverse reactions in dogs and cats, and to define the appropriate treatment interval (8 or 12 weeks) based on the species of ticks the dog or cat is likely to encounter.

B. Exclusivity

BRAVECTO, 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.

C. Patent Information:

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

VII. Appendix 1

In the original table, the last number or percent symbol was cut off in the second column (see below):

Original table:

Table II.36: Field Study S11158-00 Effectiveness against Fleas

Visit	Fluralaner Group	Control Group
Visit 1 Number of Cats	11	45
Visit 1 Geometric Mean Flea Count	28.	28.0
Visit 2 Number of Cats	11	40
Visit 2 Geometric Mean Flea Count	0.	15.0
Visit 2 Percent Effectiveness	99.1	46.5%
Visit 3 Number of Cats	10	38
Visit 3 Geometric Mean Flea Count	0.	9.4
Visit 3 Percent Effectiveness	99.5	66.6%
Visit 4 Number of Cats	10	34
Visit 4 Geometric Mean Flea Count	0.	6.8
Visit 4 Percent Effectiveness	99.0	75.8%

The second column has been restored (see corrected table below). The changes were made on August 16, 2016.

Corrected table:

Table II.36: Field Study S11158-00 Effectiveness against Fleas

Visit	Fluralaner Group	Control Group
Visit 1 Number of Cats	116	45
Visit 1 Geometric Mean Flea Count	28.0	28.0
Visit 2 Number of Cats	114	40
Visit 2 Geometric Mean Flea Count	0.2	15.0
Visit 2 Percent Effectiveness	99.1%	46.5%
Visit 3 Number of Cats	106	38
Visit 3 Geometric Mean Flea Count	0.1	9.4
Visit 3 Percent Effectiveness	99.5%	66.6%
Visit 4 Number of Cats	105	34
Visit 4 Geometric Mean Flea Count	0.3	6.8
Visit 4 Percent Effectiveness	99.0%	75.8%