Date of Approval: July 10, 2025

FREEDOM OF INFORMATION (FOI) SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION (NADA)

NADA 141-599

BRAVECTO® QUANTUM

(fluralaner for extended-release injectable suspension)

Dogs

BRAVECTO® QUANTUM kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*) and for 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 months in dogs and puppies 6 months of age and older.

BRAVECTO® QUANTUM is also indicated for the treatment and control of *Amblyomma americanum* (lone star tick) infestations for 8 months in dogs and puppies 6 months of age and older.

Sponsored by:

Intervet, Inc.

Executive Summary

BRAVECTO® QUANTUM (fluralaner for extended-release injectable suspension) is approved to kill adult fleas and for the treatment and prevention of flea infestations (*Ctenocephalides felis*) and for 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 months in dogs and puppies 6 months of age and older.

BRAVECTO® QUANTUM is also approved for the treatment and control of *Amblyomma americanum* (lone star tick) infestations for 8 months in dogs and puppies 6 months of age and older.

BRAVECTO® QUANTUM is an antiparasitic drug that is administered as a single subcutaneous injection every 12 months. It should be administered every 8 months in the case of potential exposure to *A. americanum* ticks.

The Food and Drug Administration (FDA) previously approved fluralaner, the active ingredient in BRAVECTO® QUANTUM, in other dosage forms for dogs under other NADAs: BRAVECTO® chewable tablets for dogs under NADA 141-426 and BRAVECTO® topical solution for dogs under NADA 141-459.

Safety and Effectiveness

Killing Adult Fleas and Treating and Preventing Flea Infestations
The sponsor conducted one field study in client-owned adult dogs of both sexes and a range of ages and body weights. Dogs in the treatment groups received BRAVECTO® QUANTUM at 15 mg fluralaner/kg of body weight by subcutaneous injection either once every 6 months (on Days 0, 180, and 365) or once every 12 months (on Days 0 and 365). Dogs in the active control group received fluralaner chewable tablets, at labeled doses, every 12 weeks for a total of 6 doses. BRAVECTO® QUANTUM was over 99% effective at treating and preventing flea infestations for 365 days (12 months).

Adverse reactions seen in dogs in the field study included lethargy, decreased appetite, vomiting, diarrhea, elevated liver enzymes, pruritus, lumps or swelling at the injection site, a hypersensitivity reaction, and seizures.

The sponsor conducted 2 laboratory studies in healthy dogs that (1) demonstrated that BRAVECTO® QUANTUM is effective at treating existing flea infestations and preventing flea infestations by killing fleas before they can lay eggs for 365 days (12 months); and (2) confirmed that BRAVECTO® QUANTUM begins killing adult fleas 48 hours post-treatment. Mild, transient swelling at the injection site was observed in some dogs in the second study.

Treating and Controlling Tick Infestations
The sponsor conducted three laboratory studies in healthy dogs to show that BRAVECTO® QUANTUM is effective at treating and controlling tick infestations. In all three studies, the drug was effective at reducing the number of live ticks (treatment) and increasing the number of dead ticks (control). No adverse reactions were reported in any of the three studies.

Out of *I. scapularis*, *D. variabilis*, and *R. sanguineus*, the latter tick species is the least susceptible to fluralaner at 48 hours after treatment or infestation. This was determined in the studies conducted to support the previous approvals of BRAVECTO® chewable tablets and BRAVECTO® topical solution. Therefore, the two laboratory studies (described below) conducted against *R. sanguineus* established the effectiveness of BRAVECTO® QUANTUM against all 3 tick species at 48 hours after infestation.

Because of differences in the duration of effectiveness of BRAVECTO® chewable tablets and BRAVECTO® topical solution against *A. americanum* compared to the other tick species listed in the indication, the sponsor conducted three laboratory studies (described below) to assess the effectiveness of BRAVECTO® QUANTUM against *A. americanum* at 72 hours after infestation.

The three laboratory studies are as follows:

- One study demonstrated that BRAVECTO® QUANTUM is effective at treating and controlling *R. sanguineus* for 365 days (12 months) when assessed at 48 hours after infestation. The study also demonstrated that BRAVECTO® QUANTUM is effective at treating and controlling *A. americanum* for 331 days (11 months) when assessed at 72 hours after infestation, but the study did not demonstrate adequate effectiveness at 12 months.

- One study demonstrated that BRAVECTO® QUANTUM is effective at treating and controlling *R. sanguineus* for 365 days (12 months) when assessed at 48 hours after infestation. The study also demonstrated that BRAVECTO® QUANTUM is effective at treating and controlling *A. americanum* for 61 days (2 months) when assessed at 72 hours after infestation, but the study did not demonstrate adequate effectiveness consistently beyond 2 months.

- One study demonstrated that BRAVECTO® QUANTUM is effective at treating and controlling *A. americanum* for 241 days (8 months) when assessed at 72 hours after infestation starting on Day 8, but the study did not demonstrate adequate effectiveness consistently beyond 8 months.

Overall Conclusion for A. americanum
In the three studies described above, the average effectiveness of BRAVECTO® QUANTUM against *A. americanum* from Day 8 through Day 241 is ≥90%. Therefore, the combined data demonstrate that BRAVECTO® QUANTUM is effective at treating and controlling *A. americanum* infestations from Day 8 through 8 months post-treatment when assessed at 72 hours after infestation.

Overall Conclusion for Onset of Effectiveness Against Ticks
In the three studies described above, BRAVECTO® QUANTUM was not effective against *R. sanguineus* and *A. americanum* at 2 and 3 days, respectively, after treatment. Therefore, the sponsor conducted a fourth laboratory study that confirmed that BRAVECTO® QUANTUM begins killing ticks within 3 days post-treatment for *D. variabilis* and *I. scapularis*, 4 days for *R. sanguineus*, and 5 days for *A. americanum*.

Target Animal Safety
The sponsor conducted a margin of safety laboratory study in young, healthy, intact male and female beagles. The dogs were administered BRAVECTO® QUANTUM at 0X, 1X, 3X, and 5X the label dose (0, 15, 45, and 75 mg/kg, respectively) by subcutaneous injection once every 4 months for 6 doses. Adverse reactions associated with BRAVECTO® QUANTUM included swelling at the injection site with corresponding gross pathology and histopathology findings. One male dog in the 3X treatment group had seizures and polyarteritis that were considered possibly drug related. Pharmacokinetics findings showed that exposure to fluralaner increased in a dose-proportional manner with significant accumulation.

In other foreign laboratory effectiveness studies, adverse reactions associated with BRAVECTO® QUANTUM in dogs included slight mucosal hyperemia, a swollen eyelid, and transient erythema and pain after injection.

User Safety
The labeling for BRAVECTO® QUANTUM includes safety information for people who handle, administer, or are exposed to the drug and provides specific instructions in case of accidental self-injection, skin contact, and eye exposure.

Conclusions
Based on the data submitted by the sponsor for the approval of BRAVECTO® QUANTUM, FDA determined that the drug is safe and effective when used according to the labeling.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-599

B. Sponsor

Intervet, Inc.
126 E Lincoln Ave.
Rahway, NJ 07065

Drug Labeler Code: 000061

C. Proprietary Name

BRAVECTO® QUANTUM

D. Drug Product Established Name

fluralaner for extended-release injectable suspension

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Powder for extended-release injectable suspension

G. Amount of Active Ingredient

Each mL of constituted suspension contains 150 mg fluralaner

H. How Supplied

BRAVECTO® QUANTUM (fluralaner for extended-release injectable suspension) 20 mL vial product is available in a 1-pack presentation that includes one vial containing 2.51 grams of sterile fluralaner and one vial containing the required 15 mL of sterile vehicle for constitution.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

BRAVECTO® QUANTUM should be administered as a single subcutaneous dose every 12 months. BRAVECTO® QUANTUM should be administered every 8 months in the case of potential exposure to *Amblyomma americanum* ticks.

The subcutaneous dose volume is 0.1 mL of the constituted suspension/kg body weight (0.045 mL/lb). This volume provides a dose of 15 mg fluralaner/kg body

weight (6.8 mg/lb). The dog should be weighed at the time of dosing to calculate an accurate dose.

K. Route of Administration

Subcutaneous

L. Species

Dogs

M. Indication

BRAVECTO® QUANTUM kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*) and for 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 months in dogs and puppies 6 months of age and older.

BRAVECTO® QUANTUM is also indicated for the treatment and control of *Amblyomma americanum* (lone star tick) infestations for 8 months in dogs and puppies 6 months of age and older.

II. EFFECTIVENESS

A. Dosage Characterization

Studies conducted to demonstrate the effectiveness of BRAVECTO® chewable tablets for dogs (NADA 141-426) and BRAVECTO® topical solution for dogs (NADA 141-459) demonstrated that, for both products, *Rhipicephalus sanguineus* and *Amblyomma americanum* were the least susceptible tick species at 48 and 72 hours post-treatment or infestation, respectively (effectiveness against *A. americanum* was not demonstrated at 48 hours). Additionally, fleas were more susceptible to fluralaner than ticks. Therefore, to determine the BRAVECTO® QUANTUM dose required for a minimum 6-month treatment interval for fleas and ticks, two studies were conducted to assess effectiveness against the least-susceptible tick species, adult *R. sanguineus* (48 hours), and one study was conducted against adult *A. americanum* (72 hours) using doses ranging from 10 to 20 mg/kg. Both *R. sanguineus* and *A. americanum* ticks were evaluated due to the expectation that the duration of effectiveness against *R. sanguineus* would exceed that of *A. americanum*. The results of these studies demonstrated consistent effectiveness at the 15 mg/kg dose for up to a year against *R. sanguineus*. The 15 mg/kg dose also demonstrated a quicker onset of effectiveness over the 10 mg/kg dose against *R. sanguineus*. The results of these studies also demonstrated consistent effectiveness at the 15 and 20 mg/kg doses, but not at the 10 mg/kg dose, for 6 months against *A. americanum*. There was no appreciable benefit of increasing the dose to 20 mg/kg as compared to the 15 mg/kg dose against adult *R. sanguineus* or *A. americanum*. Therefore, a single subcutaneous dose of 15 mg/kg was selected for BRAVECTO® QUANTUM.

B. Substantial Evidence

The effectiveness of BRAVECTO® QUANTUM was demonstrated in one field and six laboratory studies described below. These studies demonstrated that BRAVECTO® QUANTUM is effective against *Ixodes scapularis*, *Rhipicephalus sanguineus*, and *Dermacentor variabilis* tick infestations, and *Ctenocephalides felis* flea infestations, for 12 months in dogs 6 months of age and older. These studies also demonstrated that BRAVECTO® QUANTUM is effective against *Amblyomma americanum* for 8 months in dogs and puppies 6 months of age and older.

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

Because of differences in the onset and duration of effectiveness of BRAVECTO® chewable tablet for dogs and BRAVECTO® topical solution for dogs against *A. americanum* compared to the other tick species included in the approved indications, three laboratory studies were conducted to demonstrate the effectiveness of BRAVECTO® QUANTUM against *A. americanum* at 72 hours after treatment or infestation.

1. Treatment and Prevention of Flea Infestations

   a. **Title:** Clinical Safety and Effectiveness of Fluralaner 150 mg/mL Injectable Suspension Against Fleas: A Multi-Center Pivotal Field Trial. (Study No. S19038-00)

      Study Dates: August 2019 to July 2023

      Study Locations:

      Athens, AL
      Ocala, FL
      Plant City, FL
      Starke, FL
      West Palm Beach, FL
      Acworth, GA
      Savannah, GA
      Decatur, IL
      Brownstown, IN
      Franklin, IN
      Jeffersonville, IN
      Zachary, LA
      Springfield, MO
      Mantua Township, NJ
      Liverpool, NY
      Perry, NY
      Harrisburg, PA
      Quakertown, PA
      Dallas, TX
      Yorktown, VA

Study Design:

Objective: To assess the safety and effectiveness of BRAVECTO® QUANTUM against fleas and the improvement of signs of flea allergy dermatitis (FAD), for at least 6 months and up to 12 months, at the recommended dose (15 mg/kg subcutaneously) in dogs.

Study Animals: A total of 435 dogs (274 households) were enrolled and randomized to 4 treatment groups as described in Table II.1 below. The study included purebred and mixed breed dogs. Fluralaner Group 1 received BRAVECTO® QUANTUM (15 mg/kg; 0.10 mL/kg) subcutaneously every 12 months, and Fluralaner Group 2 and the Open Label Group received BRAVECTO® QUANTUM (15 mg/kg; 0.10 mL/kg) every 6 months. All 3 groups received 15 mg/kg (0.10 mL/kg) of BRAVECTO® QUANTUM. The active control group received fluralaner chewable tablets dosed orally every 12 weeks.

Table II.1. Field Study S19038-00 Treatment Groups

Treatment Group	Number of Households	Number of Dogs (Number per Sex)	Age Range (years)	Weight Range (lbs)
Fluralaner Group 1	152	225 (118 Female, 107 Male)	0.5 – 15.5	4.9 -114.6
Fluralaner Group 2	30	51 (21 Female, 30 Male)	0.7 – 16.0	4.0 – 118.5
Open Label	36	63 (29 Female, 34 Male)	0.6 – 13. 8	3.4 – 110.9
Active Control	56	96 (51 Female, 45 Male)	0.5 – 15.0	4.9 – 123.0

Enrollment activities occurred on Visit 1. Enrollment eligibility included:

- Households with no more than 5 dogs, all of which were at least 6 months of age, and generally in good health.
- At least 1 dog in the household had to have a minimum of 10 live fleas for the household to be included in the effectiveness analysis.
- Households with dogs <4.4 lbs or households with each dog having less than 10 fleas were eligible to enroll in the Open Label Group.
- There were no breed or sex restrictions, but households with pregnant or lactating dogs were not eligible.
- There were restrictions on use of medications or products with flea treatment or control activity in any household dog or premise prior to or during the study.

Experimental Design: Eligible households were randomly assigned to treatment with either BRAVECTO® QUANTUM or the active control. Households were randomized at each study site by order of enrollment in a ratio of 6:3:2 (Fluralaner Group 1: Fluralaner Group 2: Active Control). A primary dog from each household was randomly selected from dogs with 10 or more live fleas. Only the primary dog was assessed for effectiveness. The

first full dose of fluralaner administered to any dog in the household established Day 0 for the entire household. All dogs from each household returned to the site on Visit 2 (Day 30±3), Visit 3 (Day 84±3), Visit 4 (Day 168±3), Visit 5 (Day 180±3), Visit 6 (Day 252±3), Visit 7 (Day 270±3), Visit 8 (Day 336±3), Visit 9 (Day 365±3), Visit 10 (Day 420±3), and Visit 11 (Day 455±3).The protocol was amended during the study to change the enrollment to a ratio of 6:2 (Fluralaner Group 1: Active Control). At the time of the amendment, dogs assigned to Fluralaner Group 2 who had not yet received treatment on Visit 5 (Day 180) were reassigned to Fluralaner Group 1 and had effectiveness assessed at 12 months. After the amendment, all dogs dosed at 6-month intervals (Fluralaner Group 2 and the Open Label Group) were combined into 1 group for safety analysis. Of the dogs treated every 6 months (Fluralaner Group 2 and the Open Label Group), only dogs in Fluralaner Group 2 were included in the effectiveness analysis.

Investigators who performed FAD and safety assessments (physical exams, adverse events, and clinical pathology), and personnel that performed flea counts were masked to treatment. Treatment administrators at each study location and owners were not masked. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Drug Administration: Dogs assigned to the BRAVECTO® QUANTUM groups received 15 mg fluralaner/kg body weight (0.10 mL/kg) subcutaneously on Days 0 and 365 (Fluralaner Group 1) or Days 0, 180, and 365 (Fluralaner Group 2 and Open Label Group) based on body weights determined on the day of administration. Dogs assigned to the active control group were administered fluralaner chewable tablets, at labeled doses, every 12 weeks for a total of 6 doses, based on body weights determined at the corresponding study visit.

Measurements and Observations: Live flea counts, physical examinations, and FAD assessments were performed on all dogs at Visit 1. At Visits 2, 3, 5, 7, and 9, live flea counts were performed on primary dogs only, and FAD assessments and physical examinations were performed on all dogs in the household.

The following clinical signs of FAD were evaluated: alopecia, crusts, erythema, excoriations, papules, and scales. Adverse events were recorded throughout the study. Additional variables included recovery of ticks and clinical pathology.

Statistical Methods:
Live flea counts were transformed using the natural logarithm of (count + 1) transformation prior to analysis. The transformed data from each treatment group at each visit were analyzed separately using a linear mixed model. The model included visit (pre-treatment vs. post-treatment) as a fixed effect and site and the visit-by-site interaction as random effects. The difference between visits was evaluated at a significance level of 0.05.

Percent Effectiveness = 100 x [(C - T) / C] where C = Geometric mean of baseline (Visit 1) flea counts and T = Geometric mean of flea counts at a post-treatment visit. Geometric mean flea counts were obtained by back transforming the least squares means from the model. This calculation was performed for each treatment group at each post-treatment visit separately.

BRAVECTO® QUANTUM was considered effective against fleas based on the following criteria: 1) the percent effectiveness at Visits 2, 3, 5, 7, and 9 compared to Visit 1 (the pre-treatment flea counts) was ≥90%; and 2) the difference of the geometric mean flea counts at Visits 2, 3, 5, 7, and 9 compared to Visit 1 was significant at a significance level of 0.05.

Results: For each Visit 2, 3, 5, 7, and 9, the effectiveness of BRAVECTO® QUANTUM, based on geometric means, was greater than 99%. Within each treatment group, geometric mean flea counts were significantly different ($p<0.0001$) from Visit 1 at all post-treatment visits (Visits 2, 3, 5, 7, and 9).

Table II.2. Field Study S19038-00 Live Flea Count and Percent Effectiveness

Visit	Fluralaner Group 1	Fluralaner Group 2	Active Control Group
Visit 1 (Day 0) Number of Primary Dogs	150	30	55
Visit 1 (Day 0) Geometric Mean Flea Count	37.6	32.4	36.0
Visit 2 (Day 30) Number of Primary Dogs	138	25	50
Visit 2 (Day 30) Geometric Mean Flea Count	0.3	0.3	0.2
Visit 2 (Day 30) Percent Effectiveness	99.2%	99.1%	99.6%
Visit 3 (Day 84) Number of Primary Dogs	129	27	49
Visit 3 (Day 84) Geometric Mean Flea Count	0.1	0.1	0.0
Visit 3 (Day 84) Percent Effectiveness	99.9%	99.8%	100%
Visit 5 (Day 180) Number of Primary Dogs	121	24	47
Visit 5 (Day 180) Geometric Mean Flea Count	0.0	0.0	0.0
Visit 5 (Day 180) Percent Effectiveness	99.9%	100%	99.9%

Visit	Fluralaner Group 1	Fluralaner Group 2	Active Control Group
Visit 7 (Day 270) Number of Primary Dogs	111	24	36
Visit 7 (Day 270) Geometric Mean Flea Count	0.0	0.0	0.0
Visit 7 (Day 270) Percent Effectiveness	99.9%	100%	100%
Visit 9 (Day 365) Number of Primary Dogs	112	22	35
Visit 9 (Day 365) Geometric Mean Flea Count	0.1	0.0	0.0
Visit 9 (Day 365) Percent Effectiveness	99.8%	100%	100%

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

At least 91% of the dogs treated with BRAVECTO® QUANTUM (at either 6- or 12-month dosing intervals) with signs attributed to FAD at Visit 1, and not on medications that could affect the assessment of FAD, had improvement of the signs by Visit 9, except for 3 dogs with unresolved scales.

Table II.3. Field Study S19038-00 Number and Percentage of Dogs with Improvement in Clinical Signs of FAD at Visits 3 and 9 from Baseline (Visit 1)

FAD Sign	Visit	Fluralaner Group 1	Fluralaner Group 2	Active Control Group
Alopecia	Visit 3 (Day 84)	87.2% (68/78)	100% (15/15)	89.3% (25/28)
Alopecia	Visit 9 (Day 365)	100% (56/56)	91.7% (11/12)	100% (15/15)
Crusts	Visit 3 (Day 84)	96.9% (31/32)	66.7% (4/6)	100% (16/16)
Crusts	Visit 9 (Day 365)	100% (24/24)	100% (5/5)	100% (12/12)
Erythema	Visit 3 (Day 84)	89% (73/82)	93.8% (15/16)	94.3% (33/35)
Erythema	Visit 9 (Day 365)	100% (65/65)	100% (14/14)	100% (22/22)
Excoriation	Visit 3 (Day 84)	96.3% (26/27)	100% (6/6)	100% (10/10)
Excoriation	Visit 9 (Day 365)	100% (21/21)	100% (8/8)	100% (5/5)
Papules	Visit 3 (Day 84)	96% (24/25)	NA*	83.3% (5/6)
Papules	Visit 9 (Day 365)	100% (21/21)	NA*	100% (5/5)

FAD Sign	Visit	Fluralaner Group 1	Fluralaner Group 2	Active Control Group
Scales	Visit 3 (Day 84)	66.7% (38/57)	50% (3/6)	66.7% (14/21)
Scales	Visit 9 (Day 365)	97.2% (35/36)	50% (2/4)	100% (11/11)

*Not applicable: no dogs met the definition to be included in the summary

Adverse Reactions: Potential adverse reactions are provided in Table II.4.

Table II.4. Field Study S19038-00 Percentage of Dogs with Adverse Reactions

Adverse Reaction (AR)	BRAVECTO® QUANTUM 12-Month Dosing Interval (n=225 dogs)	BRAVECTO® QUANTUM 6-Month Dosing Interval (n=114 dogs)	Active Control (n=96 dogs)
Lethargy	4.9%	1.8%	3.1%
Decreased appetite	4.4%	1.8%	4.2%
Vomiting	4.0%	0.9%	0%
Diarrhea	2.7%	1.8%	3.1%
Liver enzymes (serum ALT or ALP*) greater than twice the upper reference range	2.7%	1.8%	2.1%
Pruritus	1.8%	1.8%	2.1%
Injection site lumps or swelling†	1.3%	0%	0%
Seizures‡	0.9%	0.9%	0%

*Alanine aminotransferase (ALT); Alkaline phosphatase (ALP)
†Mild injection site reactions described as a lump, bump, or knot occurred in 3 fluralaner injectable suspension treated dogs and all were observed within 3 days of injection. All injection site reactions were self-limiting and resolved following 1, 4, and 27 days after the initial observation.
‡Three dogs reported having seizures following treatment with fluralaner injectable suspension. One dog (Fluralaner Group 2) experienced 3 seizures in 2 months starting 4 days after being administered the third fluralaner dose at 12 months (i.e., 3 doses 6 months apart). No additional seizures were observed in the study following the initiation of anticonvulsant medications. A second dog (Fluralaner Group 1), with a history of at least 1 seizure within 3 months prior to the start of the study, experienced 6 seizures in 9 months, starting 23 days after the initial fluralaner dose. Anticonvulsant medications were not started, and no additional seizures were observed in the study following the second fluralaner dose at 12 months. The third dog (Fluralaner

Group 1) experienced 8 seizures in 4 weeks starting 57 days after the initial fluralaner dose. The dog was removed on Day 84 and managed with anticonvulsant medications.

One dog treated with BRAVECTO® QUANTUM (Fluralaner Group 1) had a hypersensitivity reaction which included hives, facial edema, vomiting, and heavy breathing within the first 12 hours following initial treatment. The dog was treated with oral antihistamines and recovered within 24 hours. No additional hypersensitivity reactions were observed in subsequent dosing 12 months later when premedicated with diphenhydramine.

Conclusion: This study demonstrated that BRAVECTO® QUANTUM was safe and effective for the treatment and prevention of flea infestations when administered to adult client-owned dogs every 6 and 12 months at 15 mg fluralaner/kg body weight (0.10 mL/kg). Dogs with signs of FAD showed improvement in erythema, alopecia, papules, scales, crusts, and excoriation as a direct result of eliminating the flea infestation.

b. **Title:** Effectiveness of Fluralaner 150 mg/mL Injectable Suspension Against Experimental Infestations of *Ctenocephalides felis* in Dogs. (Study No. S19041-00)

Study Dates: August 2019 to January 2021

Study Location: Turlock, CA

Study Design:

Objective: To confirm the effectiveness of BRAVECTO® QUANTUM at the recommended dose (15 mg/kg) to kill adult fleas (*C. felis*) and prevent and treat flea infestations in dogs.

Study Animals: Twenty healthy dogs (pure and mixed breed, 6 males and 14 females), 1.7 to 1.8 years of age, and 20.8 to 28.6 kg body weight.

Experimental Design: Prior to allocation to treatment groups on Day -6, an initial flea infestation and count was conducted to evaluate susceptibility of each dog to experimental infestation (host suitability). Dogs were randomly assigned to the untreated control group (10 dogs) or the BRAVECTO® QUANTUM group (10 dogs). The study was conducted in accordance with GCP guidelines.

Drug administration was on Day 0. Flea infestations were conducted on Days -1, 6, 13, 29, 59, 89, 119, 149, 179, 209, 239, 269, 299, 329, and 364. At each infestation, each dog was infested with approximately 100 unfed, adult fleas. Flea counts were conducted on Day 1, 24 hours after drug administration, and on Days 7, 14, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 365. Fleas were not returned to the dog after counting.

Drug Administration: On Day 0, the 10 dogs in the BRAVECTO® QUANTUM group were administered a subcutaneous injection in the dorsoscapular region, at a dose of 15 mg/kg (0.10 mL/kg). The injection volumes administered ranged from 2.1 to 2.8 mL. Dogs in the control group were sham-dosed.

Measurements and Observations: The primary variable for effectiveness was the counts of live fleas collected from the dogs. The secondary variable for effectiveness was the flea egg counts. At flea counts on Days 1, 7, 14, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 365, fleas were removed, and the numbers of live fleas recorded. Additionally, flea eggs were collected for approximately 24 hours post-treatment or infestation (Days 1, 7, 14, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 365). Following collection, eggs were counted, placed in a petri dish containing flea media, and incubated for 35 days. The number of adult fleas which emerged was determined. General health observations were conducted daily and at approximately 1, 3, and 6 hours following drug administration. Each dog was observed for injection site reactions on Days 1, 2, 3, 4, 7, 10, and 14. Dogs were weighed on Day -2 for dose calculations. Flea counts, egg counts, and health observations were conducted masked to treatment.

Statistical Methods: A linear mixed model analysis with treatment as a fixed effect was used to analyze live flea, flea egg, and adult flea emergence counts at each time point. The test of treatment effect was performed at a two-sided 5% significance level. Percent effectiveness against the control group was calculated based on the least squares means.

Results: At each flea count day, all 10 dogs in the control group had an adequate infestation, defined as at least 50 live fleas (50% of the infestations of 100 fleas per dog).

The BRAVECTO® QUANTUM group had ≥90% reduction in live flea counts at 24 hours following infestation from Day 7 through Day 365 (infestation on Day 364) but failed to demonstrate ≥90% effectiveness on Day 1 (24 hours post-treatment), compared to the corresponding control group. On all count days following drug administration, live flea counts for the BRAVECTO® QUANTUM group were significantly different ($p<0.05$) from the corresponding control group.

Table II.5. S19041-00 Live Flea Count and Percent Effectiveness, 24-hour Counts

Day for 24-hour Counts	Control Group Flea Counts*	BRAVECTO® QUANTUM Group Flea Counts*	Percent Effectiveness
1	78.9	58.8	25.5%
7	79.6	0.0	100%
14	83.3	0.0	100%
30	74.6	0.0	100%
60	71.5	0.0	100%
90	75.0	0.0	100%

Day for 24-hour Counts	Control Group Flea Counts*	BRAVECTO® QUANTUM Group Flea Counts*	Percent Effectiveness
120	62.3	0.1	99.8%
150	66.3	0.0	100%
180	65.7	0.0	100%
210	68.9	0.2	99.7%
240	74.1	0.1	99.9%
270	79.1	0.2	99.7%
300	65.7	0.1	99.8%
330	76.5	0.0	100%
365	77.6	0.0	100%

*Flea counts are least squares means. Percent effectiveness is based on least squares means.

On Days 7, 14, 30, 60, 180, 240, 270, 300, 330, and 365, at least 6 of the 10 dogs in the control group each had an adequate flea egg count, defined as ≥5 eggs. On Days 7, 14, 30, 60, 180, 240, 270, 300, 330, and 365 following drug administration, flea egg counts for the BRAVECTO® QUANTUM group were significantly different ($p \leq 0.0423$) from the corresponding control group.

Effectiveness for the prevention indication was concluded if flea egg counts from the BRAVECTO® QUANTUM group dogs were essentially zero on Day 7 and later (eggs present on Day 1 were expected, given BRAVECTO® QUANTUM was not an effective adulticide on Day 1 and egg production from the fleas infested on Day -1 may have begun prior to treatment administration).

Table II.6. S19041-00 Flea Egg Counts, 24-hour Counts

Day of Flea Egg Collection	Control Group Flea Egg Counts (Range)*	BRAVECTO® QUANTUM Group Flea Egg Counts (Range)*
1	248.0 (35 - 540)	204.2 (93 - 402)
7	149.5 (48 - 308)	0.0
14	161.7 (54 - 353)	0.0
30	111.3 (13 - 291)	0.0
60	20.6 (5 - 82)	0.0
180	9.3 (2 - 47)	0.0
240	7.2 (2 - 18)	0.0
270	8.4 (3 - 20)	0.0
300	8.7 (3 - 18)	0.0
330	5.5 (2 - 11)	0.0
365	9.0 (2 - 35)	0.0

*Flea egg counts are arithmetic means.

Adverse Reactions: Two BRAVECTO® QUANTUM treated dogs had dermatitis (1 with moist dermatitis on caudal dorsum, 1 with moist dermatitis in periauricular area) from Days 7 to 18 and Days 340 to 347, respectively. One untreated control dog had moist dermatitis on the caudal dorsum on

Days 280 to 289, 302 to 311, and 334 to 341, and 1 untreated control dog had moist dermatitis on the caudal dorsum on Days 305 to 311. The signs in all four dogs were consistent with FAD.

Conclusion: This study demonstrated the effectiveness of BRAVECTO® QUANTUM for the treatment of existing flea infestations and prevention of flea infestations by killing fleas before they can lay eggs for 365 days (12 months).

The study failed to demonstrate effectiveness for the treatment of existing flea infestations and prevention of flea infestations by killing fleas before they can lay eggs on Day 1.

c. **Title:** Onset of Efficacy of Fluralaner 150 mg/mL Injectable Suspension for Dogs at a Dose of 15 mg/kg Body Weight Against *Ctenocephalides felis* Infestations in Dogs After 24, 48, and 72 Hours. (Study No. S19107-00)

Study Date: November 2019 to November 2020

Study Location: Bloemfontein, South Africa

Study Design:

Objective: To confirm the onset of activity of BRAVECTO® QUANTUM at the recommended dose (15 mg/kg) to kill adult fleas (*C. felis*) in dogs.

Study Animals: Forty-eight healthy dogs (pure and mixed breed, 19 males and 29 females), 1.5 to 6.7 years of age, and 10.8 to 23.7 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 dog to experimental infestation (host suitability). Dogs were blocked by the pre-treatment flea counts and then randomly assigned to six groups within each block. Eight dogs were randomly assigned to 6 groups, including a BRAVECTO® QUANTUM group and untreated control group for each of the 3 flea count time points (24, 48, and 72 hours post-treatment). The study was conducted in accordance with GCP guidelines.

Drug administration was on Day 0. Flea infestations were conducted on Day -2. Each dog was infested with approximately 100 unfed, adult fleas (United States (U.S.) source). Flea counts were conducted at 24, 48, or 72 hours following drug administration. Fleas were not returned to the dog after counting.

Drug Administration: On Day 0, the 24 dogs in the BRAVECTO® QUANTUM groups were administered a subcutaneous injection in the dorsoscapular region, at a dose of 15 mg/kg (0.10 mL/kg). The injection volumes administered ranged from 1.2 to 2.4 mL. Dogs in the control groups were sham-dosed.

Measurements and Observations: The primary variable for effectiveness was the counts of live fleas collected from the dogs. At the flea counts on Days 1, 2, or 3, fleas were removed, and the numbers of live fleas recorded. General health observations were conducted daily. Each dog was observed for injection site reactions hourly for the first 4 hours post-treatment and then daily for 3 days. Dogs were weighed on Day -2 for dose calculations. Flea counts and health observations were conducted by individuals masked to treatment.

Statistical Methods: A linear mixed model analysis with treatment as a fixed effect and block as a random effect was used to analyze live flea counts at each time point. The test of treatment effect was performed at a two-sided 5% significance level. Percent effectiveness against the control group was calculated based on the least squares means.

Results: At each time point, at least 6 dogs in each control group had an adequate infestation, defined as at least 50 live fleas (50% of the infestations of 100 fleas per dog).

The BRAVECTO® QUANTUM group had ≥90% reduction in live flea counts at 48 and 72 hours post-treatment but failed to demonstrate ≥90% reduction at 24 hours post-treatment, compared to the corresponding control group. At each time point after drug administration, live flea counts for the BRAVECTO® QUANTUM group was significantly different ($p<0.0001$) from the corresponding control group.

Table II.7. S19107-00 Live Flea Count and Percent Effectiveness

Time of Flea Count after Dosing	Control Group Flea Counts*	BRAVECTO® QUANTUM Group Flea Counts*	Percent Effectiveness
24 hours	58.3	6.4	89.1%
48 hours	75.6	0.0	100%
72 hours	66.4	0.0	100%

*Flea counts are least squares means. Percent effectiveness is based on least squares means.

Adverse Reactions: At approximately 1 hour and 4 hours following administration, respectively, 2 dogs in the BRAVECTO® QUANTUM group were observed to have swelling at the injection site. No treatment to address the swellings were administered and the dogs returned to normal without treatment within 1 hour and 24 hours, respectively.

Conclusion: This study demonstrated the onset of effectiveness (i.e., ≥90% effectiveness) of BRAVECTO® QUANTUM to kill adult fleas is 48 hours after drug administration. Mild, transient injection-site swelling was observed.

2. Treatment and Control of Tick Infestations:

   a. **Title**: Effectiveness of Fluralaner 150 mg/mL Injectable Suspension Against Experimental Infestations of *Rhipicephalus sanguineus* and *Amblyomma americanum* Ticks on Dogs. (Study No. S19039-00)

      Study Dates: August 2019 to January 2021

      Study Location: Bloemfontein, South Africa

      Study Design:

      Objective: To confirm the effectiveness of BRAVECTO® QUANTUM at the recommended dose (15 mg/kg) for the treatment and control of infestations of *R. sanguineus* and *A. americanum* in dogs.

      Study Animals: Forty healthy dogs (mixed breed; 15 males and 25 females), 1.5 to 6.8 years of age, and 12.7 to 24.1 kg body weight.

      Experimental Design: Prior to allocation to treatment groups on Day -4, an initial *R. sanguineus* 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 1 dog from each block was randomly assigned to 1 of 2 untreated control groups (10 dogs/group) or 1 of 2 BRAVECTO® QUANTUM groups (10 dogs/group). The study was conducted in accordance with GCP guidelines.

      Drug administration was on Day 0. Tick infestations were conducted on Days -2, 5, 12, 28, 58, 88, 118, 148, 178, 208, 238, 268, 298, 328, and 363. At each infestation, each dog in Groups 1 and 2 was infested with approximately 50 adult, unfed *R. sanguineus* (U.S. source) ticks and each dog in Groups 3 and 4 was infested with approximately 50 adult, unfed *A. americanum* (U.S. source) ticks.

      Tick counts for Groups 1 and 2 were conducted on Day 2, 48 hours after drug administration, and on Days 7, 14, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 365, 48 hours after *R. sanguineus* infestations. Tick counts for Groups 3 and 4 were conducted on Day 3, 72 hours after drug administration, and on Days 8, 15, 31, 61, 91, 121, 151, 181, 211, 241, 271, 301, 331, and 366, 72 hours after *A. americanum* infestations. Ticks were not returned to the dog after counting.

      Drug Administration: On Day 0, the 10 dogs in each of the BRAVECTO® QUANTUM groups were administered a subcutaneous injection in the dorsoscapular region, at a dose of 15 mg/kg (0.10 mL/kg). The injection volumes administered ranged from 1.4 to 2.2 mL. Dogs in the control groups were sham-dosed.

      Measurements and Observations: The primary variable for effectiveness was the counts of live ticks collected from the dogs.

At tick counts on Days 2, 7, 14, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 365 (*R. sanguineus*); and on Days 3, 8, 15, 31, 61, 91, 121, 151, 181, 211, 241, 271, 301, 331, and 366 (*A. americanum*), ticks were removed, and the numbers of live and dead ticks were recorded. General health observations were conducted daily, and at approximately 1, 3, and 6 hours following drug administration. Each dog was observed for injection site reactions on Days 1, 2, 3, 4, 7, 10, and 14. Dogs were weighed on Day -2 for dose calculations. Tick counts and health observations were conducted masked to treatment.

Statistical Methods: A linear mixed model analysis with treatment group as a fixed effect was used to analyze live tick counts for each tick species at each time point. The test of treatment effect was performed at a two-sided 5% significance level. Percent effectiveness against the respective control group was calculated based on the least squares means.

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

The BRAVECTO® QUANTUM group (Group 2) had a ≥90% reduction in live *R. sanguineus* tick counts at 48 hours following infestation from Day 7 through Day 365 (infestation on Day 363) but failed to demonstrate ≥90% effectiveness on Day 2 (48 hours post-treatment), compared to the corresponding control group. On all count days following drug administration, except for Day 2, live *R. sanguineus* tick counts for the BRAVECTO® QUANTUM group were significantly different ($p \leq 0.0001$) from the corresponding control group.

Table II.8. S19039-00 *R. sanguineus* Live Tick Count and Percent Effectiveness

Day for Tick Counts	Control Group Live Tick Counts*	BRAVECTO® QUANTUM Group Live Tick Counts*	Percent Effectiveness
2	15.8	11.6	26.6%
7	20.6	0.0	100%
14	23.7	0.0	100%
30	26.8	0.0	100%
60	23.9	0.0	100%
90	26.5	0.0	100%
120	19.9	0.0	100%
150	24.4	0.3	98.8%
180	27.2	0.1	99.6%
210	19.1	0.2	99%
240	23.2	0.0	100%
270	16.7	0.0	100%
300	25.2	0.1	99.6%
330	19.2	0.0	100%
365	26.9	0.2	99.3%

*Tick counts are least squares means. Percent effectiveness is based on least squares means.

On Days 14, 30, 60, 120, 150, 180, 240, 300, 330, and 365 following drug administration, dead *R. sanguineus* tick counts for the BRAVECTO® QUANTUM group (Group 2) were significantly different ($p \leq 0.05$) from the corresponding control group.

Table II.9. S19039-00 *R. sanguineus* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts*	BRAVECTO® QUANTUM Group Dead Tick Counts*
2	0.5	1.2
7	0.4	1.5
14	0.8	4.1
30	0.6	3.7
60	0.4	1.8
90	0.7	3.2
120	1.0	4.9
150	0.7	6.0
180	1.2	4.2
210	1.1	3.4
240	1.1	6.0
270	0.9	2.2
300	1.0	3.4
330	0.5	3.1
365	0.2	2.5

*Tick counts are arithmetic means

The BRAVECTO® QUANTUM group (Group 4) had a ≥90% reduction in live *A. americanum* tick counts at 72 hours following infestation from Day 8 through Day 331 (infestation on Day 328) but failed to demonstrate ≥90% effectiveness on Days 3 and 366 (72 hours post-treatment), compared to the corresponding control group. On all count days following drug administration, live *A. americanum* tick counts for the BRAVECTO® QUANTUM group were significantly different (p≤0.0003) from the corresponding control group.

Table II.10. S19039-00 *A. americanum* Live Tick Count and Percent Effectiveness

Day for Tick Counts	Control Group Live Tick Counts*	BRAVECTO® QUANTUM Group Live Tick Counts*	Percent Effectiveness
3	15.5	4.8	69%
8	19.5	0.8	95.9%
15	21.7	1.9	91.2%
31	23.5	0.9	96.2%
61	17.1	0.1	99.4%
91	28.0	0.0	100%
121	24.9	0.3	98.8%
151	21.0	0.0	100%
181	22.2	0.2	99.1%
211	24.9	0.1	99.6%
241	21.1	0.5	97.6%
271	17.7	0.0	100%
301	23.4	1.4	94%
331	19.6	1.8	90.8%
366	19.7	2.3	88.3%

*Tick counts are least squares means. Percent effectiveness is based on least squares means.

On all count days following drug administration, dead *A. americanum* tick counts for the BRAVECTO® QUANTUM group (Group 4) were significantly different (p≤0.05) from the corresponding control group.

Table II.11. S19039-00 *A. americanum* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts*	BRAVECTO® QUANTUM Group Dead Tick Counts*
3	0.5	8.8
8	1.1	8.8
15	2.4	9.6
31	0.5	8.0
61	2.6	9.8
91	1.2	14.0
121	1.0	9.5
151	0.7	10.8
181	1.0	11.4
211	0.2	9.0
241	0.5	8.5
271	1.0	6.2
301	1.4	9.9
331	0.0	7.0
366	0.6	7.1

*Tick counts are arithmetic means

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

Conclusion: The study failed to demonstrate initial effectiveness against *R. sanguineus* and *A. americanum* at 2 and 3 days, respectively, following treatment. Thereafter, the study demonstrated the effectiveness of BRAVECTO® QUANTUM for the control (reduced live ticks) and treatment (increased dead ticks) of *R. sanguineus* for 365 days (12 months) when assessed at 48 hours after infestation. The study also demonstrated the effectiveness of BRAVECTO® QUANTUM for the control (reduced live ticks) and treatment (increased dead ticks) of *A. americanum* for 331 days (11 months) when assessed at 72 hours after infestation.

b. **Title:** Effectiveness of Fluralaner 150 mg/mL Injectable Suspension Against Experimental Infestations of *Rhipicephalus sanguineus* and *Amblyomma americanum* Ticks on Dogs. (Study No. S19040-00)

Study Dates: August 2019 to January 2021

Study Location: Greenbrier, AR

Study Design:

Objective: To confirm the effectiveness of BRAVECTO® QUANTUM at the recommended dose (15 mg/kg) for the treatment and control of infestations of *R. sanguineus* and *A. americanum* in dogs.

Study Animals: Forty healthy dogs (beagle and mixed breed; 23 males and 17 females), 4.3 to 8.1 years of age, and 8.2 to 15.0 kg body weight.

Experimental Design: Prior to allocation to treatment groups on Day -3, an initial *R. sanguineus* 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 1 dog from each block was randomly assigned to 1 of 2 untreated control groups (10 dogs/group) or 1 of 2 BRAVECTO® QUANTUM treatment groups (10 dogs/group). The study was conducted in accordance with GCP guidelines.

Drug administration was on Day 0. Tick infestations with *R. sanguineus* were conducted on Days -2, 5, 12, 28, 58, 88, 118, 148, 179, 208, 238, 268, 298, 328, and 363 in Groups 1 and 2. Tick infestations with *A. americanum* were conducted on Days -2, 5, 12, 28, 58, 88, 118, 148, and 178 in Groups 3 and 4. At each infestation, each dog in Groups 1 and 2 was infested with approximately 50 adult, unfed *R. sanguineus* ticks and each dog in Groups 3 and 4 was infested with approximately 50 adult, unfed *A. americanum* ticks.

Tick counts for Groups 1 and 2 were performed on Day 2, 48 hours after drug administration, and on Days 7, 14, 30, 60, 90, 120, 150, 181, 210, 240, 270, 300, 330, and 365, 48 hours after *R. sanguineus* infestations. Tick counts for Groups 3 and 4 were performed on Day 3, 72 hours after drug administration, and on Days 8, 15, 31, 61, 91, 121, 151, and 182, 72 hours after *A. americanum* infestations. Groups 3 and 4 were removed from the study at Day 182 because the tick counts failed to demonstrate ≥90% effectiveness. Ticks were not returned to the dog after counting.

Drug Administration: On Day 0, the 10 dogs in each of the BRAVECTO® QUANTUM groups were administered a subcutaneous injection in the dorsoscapular region, at a dose of 15 mg/kg (0.10 mL/kg). The injection volumes administered ranged from 0.8 to 1.5 mL. Dogs in the control groups were sham-dosed.

Measurements and Observations: The primary variable for effectiveness was the counts of live ticks collected from the dogs.

At all tick counts, ticks were removed, and the numbers of live and dead ticks were recorded. General health observations were conducted daily, and at approximately 1, 3, and 6 hours following drug administration. Each dog was observed for injection site reactions on Days 1, 2, 3, 4, 7, 10, and 14. Dogs were weighed on Day -2 for dose calculations. Tick counts and health observations were conducted masked to treatment.

Statistical Methods: A linear mixed model analysis with treatment group as a fixed effect was used to analyze live tick counts for each tick species at each time point. The test of treatment effect was performed at a two-sided 5% significance level. Percent effectiveness against the respective control group was calculated based on the least squares means.

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

The BRAVECTO® QUANTUM group (Group 2) had a ≥90% reduction in live *R. sanguineus* tick counts at 48 hours following infestation from Day 7 through Day 365 (infestation on Day 363) but failed to demonstrate ≥90% effectiveness on Day 2 (48 hours post-treatment), compared to the corresponding control group. On all count days following drug administration, live *R. sanguineus* tick counts for the BRAVECTO® QUANTUM group were significantly different ($p<0.0001$) from the corresponding control group.

Table II.12. S19040-00 *R. sanguineus* Live Tick Count and Percent Effectiveness

Day for Tick Counts	Control Group Live Tick Counts*	BRAVECTO® QUANTUM Group Live Tick Counts*	Percent Effectiveness
2	40.9	12.4	69.7%
7	32.2	0.0	100%
14	29.9	1.1	96.3%
30	27.6	0.0	100%
60	31.6	0.1	99.7%
90	30.2	0.1	99.7%
120	28.4	0.3	98.9%
150	32.6	0.0	100%
181	31.3	0.0	100%
210	26.6	0.0	100%
240	34.3	0.0	100%
270	30.9	0.1	99.7%
300	31.9	0.0	100%
330	30.3	0.1	99.7%
365	29.3	1.7	94.2%

*Tick counts are least squares means. Percent effectiveness is based on least squares means.

On all count days following drug administration, dead *R. sanguineus* tick counts for the BRAVECTO® QUANTUM group (Group 2) were significantly different ($p\leq0.05$) from the corresponding control group.

Table II.13. S19040-00 *R. sanguineus* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts*	BRAVECTO® QUANTUM Group Dead Tick Counts*
2	0.0	3.8
7	0.0	3.9
14	0.0	5.2
30	0.0	7.3
60	0.0	3.1
90	0.5	5.4
120	0.0	5.7
150	0.0	6.5
181	0.0	7.1
210	0.0	10.6
240	0.0	7.3
270	0.0	5.5
300	0.0	8.8
330	0.0	4.1
365	0.0	5.9

*Tick counts are arithmetic means.

The BRAVECTO® QUANTUM group (Group 4) had a ≥90% reduction in live *A. americanum* tick counts at 72 hours following infestation from Day 8 through Day 61 (infestation on Day 58) but failed to demonstrate ≥90% effectiveness on Days 3, 91, 151, and 182 (72 hours post-treatment), compared to the corresponding control group. On all count days following drug administration, live *A. americanum* tick counts for the BRAVECTO® QUANTUM group were significantly different ($p<0.0001$) from the corresponding control group. Groups 3 and 4 were removed from the study after Day 182 due to the percent reduction being below the 90% effectiveness threshold for 2 consecutive counts.

Table II.14. S19040-00 *A. americanum* Live Tick Count and Percent Effectiveness

Day for Tick Counts	Control Group Live Tick Counts*	BRAVECTO® QUANTUM Group Live Tick Counts*	Percent Effectiveness
3	32.9	9.3	71.7%
8	38.0	1.8	95.3%
15	35.4	2.3	93.5%
31	28.8	0.4	98.6%
61	25.1	0.9	96.4%
91	21.8	3.0	86.2%
121	19.8	1.3	93.4%
151	28.9	4.0	86.2%
182	27.3	3.2	88.3%

*Tick counts are least squares means. Percent effectiveness is based on least squares means.

On all count days following drug administration, dead *A. americanum* tick counts for the BRAVECTO® QUANTUM group (Group 4) were significantly different ($p<0.003$) from the corresponding control group.

Table II.15. S19040-00 *A. americanum* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts*	BRAVECTO® QUANTUM Group Dead Tick Counts*
3	0.0	13.0
8	0.0	9.6
15	0.0	11.1
31	0.0	3.4
61	0.0	8.9
91	0.0	11.2
121	0.0	5.2
151	0.0	5.3
182	0.0	10.2

*Tick counts are arithmetic means.

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

Conclusion: This study failed to demonstrate initial effectiveness against *R. sanguineus* and *A. americanum* at 2 and 3 days, respectively, following treatment. Thereafter, the study demonstrated the effectiveness of BRAVECTO® QUANTUM for the control (reduced live tick) and treatment (increased dead ticks) of *R. sanguineus* for 365 days (12 months) when assessed at 48 hours after infestation. The study also demonstrated the effectiveness of BRAVECTO® QUANTUM for the control (reduced live ticks) and treatment (increased dead ticks) of *A. americanum* for 61 days (2 months) when assessed 72 hours after infestation but failed to demonstrate adequate (≥90%) effectiveness consistently beyond 2 months.

c. **Title:** Effectiveness of Fluralaner 150 mg/mL Injectable Suspension Against Experimental Infestations of *Amblyomma americanum* Ticks on Dogs. (Study S21023-00)

Study Dates: March 2021 to August 2022

Study Location: Greenbrier, AR

Study Design:

Objective: To confirm the effectiveness of BRAVECTO® QUANTUM at the recommended dose (15 mg/kg) for the treatment and control of infestations of *A. americanum* in dogs.

Study Animals: Twenty healthy dogs (beagle and mixed breed; 16 males and 4 females), 1.5 to 7.7 years of age, and 4.6 to 14.6 kg body weight.

Experimental Design: Prior to allocation to treatment groups on Day -3, an initial *A. americanum* infestation and count was conducted to evaluate susceptibility of each dog to experimental infestation (host suitability). Dogs were randomly assigned to either an untreated control group (10 dogs) or a BRAVECTO® QUANTUM group (10 dogs). The study was conducted in accordance with GCP guidelines.

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 5, 12, 28, 58, 88, 118, 148, 178, 208, 238, 268, 298, 328, and 363. At each infestation, each dog was infested with approximately 50 adult, unfed *A. americanum* ticks.

Tick counts were conducted on Day 3, 72 hours after drug administration, and on Days 8, 15, 31, 61, 91, 121, 151, 181, 211, 241, 271, 301, 331, and 366, 72 hours after *A. americanum* infestations. Ticks were not returned to the dog after counting.

Drug Administration: On Day 0, the 10 dogs in the BRAVECTO® QUANTUM group were administered a subcutaneous injection in the dorsoscapular region, at a dose of 15 mg/kg (0.10 mL/kg). The injection volumes administered ranged from 0.8 to 1.5 mL. Dogs in the control group were sham-dosed.

Measurements and Observations: The primary variable for effectiveness was the counts of live ticks collected from the dogs.

At tick counts on Days 3, 8, 15, 31, 61, 91, 121, 151, 181, 211, 241, 271, 301, 331, and 366, ticks were removed, and the numbers of live and dead ticks were recorded. General health observations were conducted daily, and at approximately 1, 3, and 6 hours following drug administration. Each dog was observed for injection site reactions on Days 1, 2, 3, 4, 7, 10, and 14. Dogs were weighed on Day -2 for dose calculations. Tick counts and health observations were conducted masked to treatment.

Statistical Methods: A linear mixed model analysis with treatment group as a fixed effect was used to analyze live tick counts at each time point. The test of treatment effect was performed at a two-sided 5% significance level. Percent effectiveness against the control group was calculated based on the least squares means.

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

The BRAVECTO® QUANTUM group had a ≥90% reduction in live *A. americanum* tick counts at 72 hours following infestation from Day 8 through Day 241 (infestation on Day 238) but failed to demonstrate ≥90% effectiveness on Days 3 (72 hours post-treatment), 271, 331, and 366 (72 hours post-infestation), compared to the control group. On all count days, following drug administration, live *A. americanum* tick counts for the

BRAVECTO® QUANTUM group were significantly different (p≤0.015) from the corresponding control group.

Table II.16. S21023-00 *A. americanum* Live Tick Count and Percent Effectiveness

Day for Tick Counts	Control Group Live Tick Counts*	BRAVECTO® QUANTUM Group Live Tick Counts*	Percent Effectiveness
3	30.4	7.6	75.0%
8	22.2	1.0	95.5%
15	28.4	0.0	100%
31	23.0	0.0	100%
61	34.9	0.0	100%
91	23.1	0.0	100%
121	21.5	0.0	100%
151	24.9	0.1	99.6%
181	21.6	1.5	93.1%
211	27.0	0.4	98.5%
241	26.2	0.6	97.7%
271	26.8	3.4	87.3%
301	20.3	1.0	95.1%
331	33.5	4.1	87.8%
366	29.3	21.2	27.6%

*Tick counts are least squares means. Percent effectiveness is based on least squares means.

On Days 3 through 331 following drug administration, dead *A. americanum* tick counts for the BRAVECTO® QUANTUM group were significantly different (p≤0.05) from the corresponding control group.

Table II.17. S21023-00 *A. americanum* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts*	BRAVECTO® QUANTUM Group Dead Tick Counts*
3	0.0	10.4
8	0.0	7.3
15	0.0	9.5
31	1.4	9.3
61	0.0	7.0
91	0.0	4.8
121	0.0	5.4
151	0.0	6.3
181	0.0	5.9
211	0.0	6.7
241	0.0	9.1
271	0.0	7.5
301	0.0	9.6
331	0.0	10.6
366	0.0	3.2

*Tick counts are arithmetic means.

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

Conclusion: The study failed to demonstrate initial effectiveness against *A. americanum* at 3 days following treatment. Thereafter, the study demonstrated the effectiveness of BRAVECTO® QUANTUM for the control (reduced live ticks) and treatment (increased dead ticks) of *A. americanum* for 241 days (8 months) when assessed at 72 hours after infestation starting on Day 8 but failed to demonstrate adequate (≥90%) effectiveness consistently beyond 8 months.

Overall Conclusion for A. americanum

Although Study S19040-00 failed to demonstrate ≥90% effectiveness against *A. americanum* consistently after 2 months post-treatment, when combined with Studies S19039-00 and S21023-00, the average effectiveness at Days 8 through 241 is >90%. Therefore, the combined data demonstrates that BRAVECTO® QUANTUM is effective for the treatment and control of *A. americanum* infestations starting Day 8 through 8 months after treatment when assessed 72 hours after treatment or infestation.

3. Onset of Tick Effectiveness

Studies S19039-00 and S19040-00 demonstrated that the onset of effectiveness (≥90%) of BRAVECTO® QUANTUM against *R. sanguineus* was between 2 and 7 days post-treatment. Studies S19039-00, S19040-00, and S21023-00 demonstrated that the onset of effectiveness (≥90%) of fluralaner injectable suspension against *A. americanum* was between 3 and 8 days post-treatment. Therefore, to further characterize the onset of effectiveness of BRAVECTO® QUANTUM against ticks, the following study was conducted.

a. **Title**: Onset of Effectiveness of Fluralaner 150 mg/mL Injectable Suspension Against Experimental Infestations of *Amblyomma americanum, Rhipicephalus sanguineus, Dermacentor variabilis, and Ixodes scapularis* Ticks on Dogs. (Study No. S21057-00)

Study Dates: September 2021 to July 2022

Study Location: Bloemfontein, South Africa

Study Design:

Objective: To confirm the onset of effectiveness of BRAVECTO® QUANTUM at the recommended dose (15 mg/kg) for the treatment and control of infestations of *D. variabilis, I. scapularis, R. sanguineus,* and *A. americanum* in dogs.

Study Animals: One hundred and sixty healthy dogs (beagle and mixed breed; 72 males and 88 females), 1.1 to 8.8 years of age, and 10.5 to 33.5 kg body weight.

Experimental Design: Prior to allocation to treatment groups, dogs were divided into cohorts. A cohort was defined as the entire group of dogs infested with a specific species of ticks. Within each cohort there were sets of 20 dogs (10 untreated controls and 10 treated dogs) for each specific post-treatment count day. If ≥90% effectiveness was not achieved on the earliest count day for a cohort (i.e., first set), then the next set of dogs was infested and evaluated for effectiveness on the subsequent day. This process was repeated until ≥90% effectiveness was demonstrated on a count day within a cohort. The study was conducted in accordance with GCP guidelines.

Drug administration was on Day 0. Tick infestations for each cohort and post-treatment count day were conducted on Day -2. At each infestation, each dog in Cohort A (*D. variabilis*), Cohort C (*R. sanguineus*), and Cohort D (*A. americanum*) were infested with approximately 50 unfed adult ticks of the indicated species (all from U.S. sources). Dogs in Cohort B were infested with approximately 80 unfed adult *I. scapularis* ticks (U.S. source).

For Cohorts A (*D. variabilis*) and B (*I.* scapularis) there were a total of four possible post-treatment count days (Days 2, 3, 4, and 5). Cohort C (*R. sanguineus*) had a total of three possible post-treatment count days (Days 3, 4, and 5) and Cohort D (*A. americanum*) had two possible post-treatment count days (Days 4 and 5). In all cases, ticks were not returned to the dog after counting.

Drug Administration: On Day 0, the 10 dogs in each of the BRAVECTO® QUANTUM groups were administered a subcutaneous injection in the dorsoscapular region, at a dose of 15 mg/kg (0.10 mL/kg). The injection volumes administered ranged from 1.1 to 2.7 mL. Dogs in the control groups were sham-dosed.

Measurements and Observations: The primary variable for effectiveness was the counts of live ticks collected from the dogs.

At all tick counts, ticks were removed, and the numbers of live and dead ticks were recorded. General health observations were conducted daily and at approximately 1 and 6 hours following drug administration. Each dog was observed for injection site reactions on Days 2 and 7. Dogs were weighed on Day -2 for dose calculations. Tick counts and health observations were conducted masked to treatment.

Statistical Methods: Within each cohort, a linear mixed model analysis with treatment group as a fixed effect was used to analyze live tick counts for each tick species at each time point. The test of treatment effect was performed at a two-sided 5% significance level. Percent effectiveness against the respective control group was calculated based on the least squares means.

Results: At each tick count day, at least 8 of the 10 dogs in the *D. variabilis*, *I. scapularis*, *R. sanguineus*, and *A. americanum* control groups had an adequate infestation, defined as 25% of the initial infestation (at least 13 live ticks per dog for *D. variabilis*, *R. sanguineus*, and *A. americanum* and at least 20 live ticks per dog for *I. scapularis*).

D. variabilis cohort: The BRAVECTO® QUANTUM group had a ≥90% reduction in live *D. variabilis* counts by Day 3 following treatment administration (Cohort A). On Day 3 following drug administration, live *D. variabilis* tick counts for the fluralaner injectable suspension group were significantly different ($p<0.0001$) from the corresponding control group.

Table II.18. S21057-00 *D. variabilis* Live Tick Count and Percent Effectiveness

Day for Tick Counts	Control Group Live Tick Counts*	BRAVECTO® QUANTUM Group Live Tick Counts*	Percent Effectiveness
2	26.7	18.3	31.5%
3	32.0	0.8	97.5%

*Tick counts are least squares means. Percent effectiveness is based on least squares means.

On Days 2 and 3 following drug administration, dead *D. variabilis* tick counts for the BRAVECTO® QUANTUM group were significantly different ($p\leq0.05$) from the corresponding control group.

Table II.19. S21057-00 *D. variabilis* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts*	BRAVECTO® QUANTUM Group Dead Tick Counts*
2	0.5	3.4
3	0.0	16.9

*Tick counts are arithmetic means.

I. scapularis cohort: The BRAVECTO® QUANTUM group had a ≥90% reduction in live *I. scapularis* counts by Day 3 following treatment administration (Cohort B). On Days 2 and 3 following drug administration, live *I. scapularis* tick counts for the BRAVECTO® QUANTUM group were significantly different ($p<0.0001$) from the corresponding control group.

Table II.20. S21057-00 *I. scapularis* Live Tick Count and Percent Effectiveness

Day for Tick Counts	Control Group Live Tick Counts*	BRAVECTO® QUANTUM Group Live Tick Counts*	Percent Effectiveness
2	35.2	8.5	75.9%
3	27.4	1.9	93.1%

*Tick counts are least squares means. Percent effectiveness is based on least squares means.

On Days 2 and 3 following drug administration, dead *I. scapularis* tick counts for the BRAVECTO® QUANTUM group were significantly different (p≤0.0007) from the corresponding control group.

Table II.21. S21057-00 *I. scapularis* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts*	BRAVECTO® QUANTUM Group Dead Tick Counts*
2	1.2	19.5
3	1.6	12.8

*Tick counts are arithmetic means.

R. sanguineus cohort: The BRAVECTO® QUANTUM group had a ≥90% reduction in live *R. sanguineus* counts by Day 4 following treatment administration (Cohort C). On Days 3 and 4 following drug administration, live *R. sanguineus* tick counts for the BRAVECTO® QUANTUM group were significantly different (p<0.0001) from the corresponding control group.

Table II.22. S21057-00 *R. sanguineus* Live Tick Count and Percent Effectiveness

Day for Tick Counts	Control Group Live Tick Counts*	BRAVECTO® QUANTUM Group Live Tick Counts*	Percent Effectiveness
3	31.4	4.7	85%
4	26.9	1.9	92.9%

*Tick counts are least squares means. Percent effectiveness is based on least squares means.

On Day 4 following drug administration, dead *R. sanguineus* tick counts for the BRAVECTO® QUANTUM group were significantly different (p≤0.0002) from the corresponding control group.

Table II.23. S21057-00 *R. sanguineus* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts*	BRAVECTO® QUANTUM Group Dead Tick Counts*
3	0.6	1.4
4	0.4	5.4

*Tick counts are arithmetic means.

A. americanum cohort: The BRAVECTO® QUANTUM group had a ≥90% reduction in live *A. americanum* counts by Day 5 following treatment administration (Cohort D). On Days 4 and 5 following drug administration, live *A. americanum* tick counts for the BRAVECTO® QUANTUM group were significantly different (p<0.0001) from the corresponding control group.

Table II.24. S21057-00 *A. americanum* Live Tick Count and Percent Effectiveness

Day for Tick Counts	Control Group Live Tick Counts*	BRAVECTO® QUANTUM Group Live Tick Counts*	Percent Effectiveness
4	23.1	4.4	81%
5	33.3	3.1	90.7%

*Tick counts are least squares means. Percent effectiveness is based on least squares means.

On Days 4 and 5 following drug administration, dead *A. americanum* tick counts for the BRAVECTO® QUANTUM group were significantly different ($p \leq 0.05$) from the corresponding control group.

Table II.25. S21057-00 *A. americanum* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts*	BRAVECTO® QUANTUM Group Dead Tick Counts*
4	2.0	8.0
5	0.5	10.0

*Tick counts are arithmetic means.

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

Conclusion: This study demonstrated that the onset of effectiveness of BRAVECTO® QUANTUM (defined as a ≥90% reduction in live tick counts) occurred within 3 days following treatment administration for *D. variabilis* and *I. scapularis*, 4 days for *R. sanguineus*, and 5 days for *A. americanum*.

III. TARGET ANIMAL SAFETY

A. Margin of Safety Study

Title: Target Animal Safety Study of 'Fluralaner 15% Injectable Suspension for Dogs' Administered Subcutaneously on Six Occasions 4 Months Apart to Beagle Dogs. (Study No. S18237-00)

Study Dates: July 12, 2019 to March 11, 2022

Study Location: Spencerville, OH

Study Design:

Objective: To demonstrate the margin of safety of BRAVECTO® QUANTUM, administered by subcutaneous injection, once every 4 months for 6 doses, in 6-month-old puppies at 1, 3, and 5 times the label dose of 15 mg/kg body weight.

Study Animals: Thirty-two intact, healthy puppies (beagles, 16 males and 16 females), 6 months of age, and 5.3 to 9.5 kg. One dog was removed from the study due to a prolapsed rectum on Day 8 and was replaced on Day 15.

Experimental Design: Within each sex, a complete randomization of dogs to dose group was performed. Within each sex and dose group, dogs were then randomly

assigned to pairs, and the pairs were randomized to cage location. Dogs were individually housed in stainless steel cages located in the same room and allowed social interaction with a dog of the same sex and treatment group in an adjacent cage for 3 to 4 hours each day. All study personnel conducting clinical observations were masked to treatment assignment. The study was conducted in accordance with Good Laboratory Practice (GLP) regulations.

Table III.1. Study No. S18237-00 Treatment Groups

Group	Number and Sex of Dogs	Test Article	Dose (mg/kg)	Dose Volume (mL/kg)
0X (control)	4 males/4 females	0.9% saline	0	0.5
1X	4 males/4 females	BRAVECTO® QUANTUM	15	0.1
3X	4 males/4 females	BRAVECTO® QUANTUM	45	0.3
5X	4 males/4 females	BRAVECTO® QUANTUM	75	0.5

Drug Administration: Dogs were administered BRAVECTO® QUANTUM at 1, 3, and 5 times the label dose of 15 mg/kg or the control article (0.9% saline) subcutaneously in the interscapular region on Days 1, 120, 239, 358, 477, and 596 (4-month intervals). The replacement dog was first dosed on Day 15 and then followed the regular dosing schedule. The dose volume for each dog was based on the most recent body weight measurement. The volume for each dose was administered as a single injection within the demarcated area that had been shaved to facilitate injection site observations.

Measurements and Observations: General health checks were conducted twice daily; cage-side observations were conducted at least once daily, beginning on Day -14 through Day 638, and throughout the dosing period on days of dosing, pre-dose, and approximately 10, 20, 30, 40, 50, and 60 minutes post-dose. Clinical assessments were conducted by a veterinarian pre-dose and at approximately 2, 8, 24, 168, 336, and 504 hours post-dose. Body weight was recorded weekly. Individual food consumption was recorded daily. Veterinary physical examinations were conducted on Days -14, -7, -1, 57, 119, 176, 238, 295, 357, 413, 476, 533, 595, and 638.

Hair was clipped at the injection site 1 week prior to administration of each dose and as needed to clearly visualize the injection site. Scheduled injection site assessments were conducted on dosing days and up to 17 days after an administered dose, with unscheduled injection site assessments conducted daily for any unresolved swellings. The following scoring system was used:

- Erythema:
  “0” = no reaction
  “1” = slight reaction
  “2” = moderate reaction
  “3” = severe reaction

- Swelling (yes/no)
  When yes, either visible swelling or swelling evident only on palpation was indicated

- Swelling size and consistency:
  Measurement of length x width x height
  Soft/hard/NA

- Heat:
  "0" = no reaction
  "1" = slight reaction
  "2" = moderate reaction
  "3" = severe reaction

- Pain:
  "0" = no reaction
  "1" = slight reaction
  "2" = moderate reaction
  "3" = severe reaction

Samples were collected for clinical pathology (hematology, coagulation profile, clinical chemistry, phospholipids, C-reactive protein, and urinalysis) pre-dose and on Days 56, 175, 294, 413, 532, and 634; and for plasma fluralaner concentrations pre-dose and 3, 7, 14, 21, 28, 35, 42, 49, 56, 70, 84, 98, and 118 days following the first day of each dose interval. The plasma concentrations of fluralaner were measured using a validated liquid chromatography–mass spectrometry (LCMS/MS) method and the pharmacokinetic parameters were estimated using a non-compartmental analysis.

Forty-two days following the sixth dose (Day 638), all dogs underwent full gross necropsy, organ weight determination, and histopathological evaluation.

Statistical Methods: The experimental unit was the individual dog. The clinical assessments, body weight, weekly food consumption, clinical pathology parameters (hematology, clinical chemistry, coagulation, phospholipids, C-reactive protein, and urinalysis [numeric parameters only]) were analyzed using Repeated Measures Analysis of Covariance (RMANCOVA) model, which included treatment, day, sex, treatment-by-sex, treatment-by-day, day-by-sex, and treatment-by-sex-by-day interaction as fixed effects. The last available pre-treatment value was included as a covariate except for the analysis for body weight. Body weight and weekly food consumption were analyzed by dosing cycle. The absolute organ weight and the relative organ weight were analyzed using Analysis of Variance (ANOVA) model, which included treatment, sex, and sex-by-treatment interaction (when applicable) as fixed effects. All fixed effects were tested at a two-sided significance level $\alpha=0.10$ except that the three-way treatment-by-sex-by-day interaction, which was tested at a two-sided significance level $\alpha=0.05$.

Frequency distributions of the number of dogs with abnormalities per group were summarized for categorical parameters (e.g., clinical assessments, scheduled veterinary physical examinations, injection site reactions).

Results:

Mortality: There were two unscheduled deaths in 3X group males during this study.

One dog was euthanized due to a prolapsed rectum, which was not considered treatment related, and replaced on Day 15.

The other dog was found unresponsive on Day 475. This dog then developed convulsions with bilateral forelimb stiffness and was noted to have injected mucous membranes, mild salivation, and retching. The dog experienced two additional seizures and was euthanized the same day. Clinical pathology findings included neutrophilia (neutrophil count 12.47 x 10^3/µL; reference range: 3.27 – 9.48 x 10^3/µL) and elevated C-reactive protein (32,556.29 ng/mL; reference range: 540.78 – 32,104.76 ng/mL). On necropsy, gross findings included dark discoloration of all lung lobes and dark discoloration of the mucosa of the ileum. Microscopically, there was mild mixed cell vascular/perivascular inflammation of the right extramural coronary artery of the heart, minimal congestion, and mixed cell perivascular infiltration of the lung, erythrophagocytosis of the bronchial lymph node, and minimal to mild vascular and/or perivascular inflammation affecting arteries in the submucosa of the stomach and tunica muscularis of the urinary bladder. There was also minimal to moderate vascular fibrinoid necrosis in the affected arteries of the stomach, urinary bladder, and in the mucosa of the duodenum. The cause of death was determined to be polyarteritis.

Injection Site Assessments: The administration of BRAVECTO® QUANTUM resulted in injection site swellings that resolved over time. After administration of the first dose, injection site swellings were observed for up to 32 days in the 1X dogs. After subsequent doses in 1X dogs, injection site swellings were observed for up to 62 days after the second injection and persisted in some dogs throughout the dosing interval after the third through sixth injections. After administration of all doses for dogs in the 3X and 5X groups, injection site swellings were observed after each injection and persisted in some dogs throughout the dosing interval. No pain observations were recorded during any injection site assessment. Erythema was occasionally observed at the injection site in all groups, including dogs in the control group. Abnormal macroscopic changes at the injection sites included accumulation of tan material only in dogs administered BRAVECTO® QUANTUM. On histopathology, abnormal microscopic observation of the injection sites in dogs administered BRAVECTO® QUANTUM included fibrosis (minimal to moderate), granulomatous inflammation (minimal to moderate), and/or histiocytic infiltration (minimal).

Pharmacokinetics: Maximum fluralaner concentrations (C_{max}) of 444±169 ng/mL were observed over a range from 28 to 70 days following the first dose, in 8 dogs receiving the clinically recommended dosage. Exposure to fluralaner increased in a dose-proportional manner. The observed C_{max} and area under the curve (AUC) values after repeated administrations 4 months apart showed significant accumulation with ratios between the first and fifth doses of 3.9, 4.6, and 3.5 for the 1X, 3X, and 5X groups, respectively. Steady state was reached by the fourth dose (357 days) in the 1X and 3X groups and by the third dose (238 days) in the 5X group.

Conclusions: The study supports the safe use of BRAVECTO® QUANTUM when used according to the label directions. Dose-proportional exposure and accumulation of fluralaner were observed. Treatment-related findings included swelling at the injection site with associated gross pathology and histopathology findings. The seizures and polyarteritis in the one 3X male dog were considered possibly drug related.

B. Foreign Experience

In well-controlled foreign laboratory effectiveness studies (Study Numbers S15205-00, S15206-00, S15207-00), after administration of BRAVECTO® QUANTUM, 2 dogs exhibited slight mucosal hyperemia the day following administration that resolved the following day, 1 dog exhibited transient injection site erythema 10 minutes post-injection that resolved within 1 hour, and 1 dog had a non-painful swollen upper eyelid observed 24 hours following administration.

In a large European field study, pain on injection of BRAVECTO® QUANTUM was reported in five dogs.

C. Reproductive Safety

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

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. Because this new animal drug is not intended for use in food-producing animals, the Center for Veterinary Medicine (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® QUANTUM:

User Safety Warnings:
Not for use in humans. Keep this and all drugs out of reach of children.

In case of accidental self-injection:
- Seek medical advice immediately and show the package insert or label to the physician.

In case of accidental skin contact:
- Wash the exposed skin with water for at least 15 minutes.
- If redness and swelling occur, seek medical advice immediately and show the package insert or label to the physician.

In case of accidental eye exposure:
- Wash the eyes with water for at least 15 minutes.
- If wearing contact lenses, rinse the eyes first, then remove contacts and continue to rinse with water.

- If redness and swelling occur, seek medical advice immediately and show the package insert or label to the physician.

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® QUANTUM, when used according to the label, is safe and effective for the conditions of use in the General Information Section above.

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 properly administer the injection, to monitor for and respond to adverse reactions, and to define the appropriate treatment interval (8 versus 12 months) based on the species of ticks the dog is likely to encounter.

B. Exclusivity

BRAVECTO® QUANTUM, 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® QUANTUM.

C. Patent Information

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