Date of Approval: October 24, 2025

FREEDOM OF INFORMATION (FOI) SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION (NADA)

NADA 141-494

Credelio™

(lotilaner)

Chewable Tablet

Dogs

This supplement provides for the addition of the indication for the treatment and control of *Haemaphysalis longicornis* (longhorned tick) tick infestations for one month in dogs and puppies 8 weeks of age and older, weighing 4.4 pounds or greater, and for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

Sponsored by:

Elanco US Inc.

Executive Summary

Credelio™ (lotilaner) chewable tablets are approved for the treatment and control of *Haemaphysalis longicornis* (longhorned tick) tick infestations for one month in dogs and puppies 8 weeks of age and older, weighing 4.4 pounds or greater, and for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

Credelio™ is already approved to kill adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*) and the treatment and control of tick infestations [*Amblyomma americanum* (lone star tick), *Dermacentor variabilis* (American dog tick), *Ixodes scapularis* (black-legged tick), and *Rhipicephalus sanguineus* (brown dog tick)] for one month in dogs and puppies 8 weeks of age and older, and weighing 4.4 pounds or greater.

Credelio™ is a an antiparasitic drug available in five strengths of flavored chewable tablets that are given orally once a month.

Safety and Effectiveness
The sponsor conducted three laboratory studies in healthy male and female, crossbred and purebred beagle dogs to demonstrate effectiveness for the treatment and control of *H. longicornis* (longhorned tick). Dogs were infested with approximately 50 unfed adult female *H. longicornis* ticks on Days -7, -1 or -2, 5, 12, 19, and 30. Dogs were administered Credelio™ on Day 0 and live (treatment) and dead (control) tick counts were conducted on Days 2, 7, 14, 21, and 32. Control dogs had adequate *H. longicornis* infestations. Credelio™ was demonstrated to be effective for the treatment and control of *H. longicornis* ticks when administered at the approved dose. One dog had an adverse reaction of diarrhea on the day of treatment; the diarrhea resolved with supportive care.

The sponsor conducted two laboratory studies in healthy male and female beagle dogs to demonstrate the prevention of *B. burgdorferi* infections by killing the *I. scapularis* vector ticks. All dogs were seronegative for *B. burgdorferi* at the start of the studies. Treatment was administered on Day 0; control dogs were sham dosed. On Day 28, each dog was infested with approximately 50 unfed, wild-caught adult *I. scapularis* ticks. The ticks had a *B. burgdorferi* infection rate of 39 and 70%, respectively, in the two studies. The ticks were counted and removed on Day 33. Control dogs had adequate tick infestations. The Credelio™ group had 100% reduction in live tick counts at Day 33. All dogs were evaluated for *B. burgdorferi* infection based on two separate serology tests and skin biopsy. Blood samples were collected from each dog on Days -7 or -4, 27, 49, 63, 77, 91, and 105, and skin biopsies were obtained on Day 104 or 105. Credelio™ was effective in preventing *B. burgdorferi* infection. One dog had an adverse reaction of diarrhea within one hour of dosing with Credelio™; the diarrhea resolved without treatment.

The FOI Summary for the original approval of Credelio™ NADA 141-494 dated January 19, 2018, contains a summary of target animal safety studies for dogs.

Conclusions
Based on the data submitted by the sponsor for the approval of Credelio™, the U.S. Food and Drug Administration (FDA) determined that the drug is safe and effective when

used according to the labeling for the treatment and control of *Haemaphysalis longicornis* (longhorned tick) infestations and for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-494

B. Sponsor

Elanco US Inc.
450 Elanco Circle
Indianapolis, IN 46221

Drug Labeler Code: 058198

C. Proprietary Name

Credelio™

D. Drug Product Established Name

lotilaner

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Chewable Tablet

G. Amount of Active Ingredient

Each chewable tablet contains 56.25 mg, 112.5 mg, 225 mg, 450 mg, or 900 mg lotilaner.

H. How Supplied

Credelio™ is available in five chewable tablet sizes for use in dogs: 56.25, 112.5, 225, 450, and 900 mg lotilaner. Each chewable tablet size is available in color-coded packages of 1, 3 or 6 chewable tablets.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Credelio™ is given orally once a month, at the minimum dosage of 9 mg/lb (20 mg/kg).

Dosage Schedule:

Body Weight	Lotilaner Per Chewable Tablet (mg)	Chewable Tablets Administered
4.4 to 6.0 lbs	56.25	One
6.1 to 12.0 lbs	112.5	One
12.1 to 25.0 lbs	225	One
25.1 to 50.0 lbs	450	One
50.1 to 100.0 lbs	900	One
Over 100.0 lbs	Administer the appropriate combination of chewable tablets	

Credelio™ must be administered with food.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

Credelio™ kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*) and the treatment and control of tick infestations [*Amblyomma americanum* (lone star tick), *Dermacentor variabilis* (American dog tick), *Ixodes scapularis* (black-legged tick), *Rhipicephalus sanguineus* (brown dog tick), and *Haemaphysalis longicornis* (longhorned tick)] for one month in dogs and puppies 8 weeks of age and older, and weighing 4.4 pounds or greater. Credelio™ is indicated for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

N. Effect of Supplement

This supplement provides for the addition of the indication for the treatment and control of *Haemaphysalis longicornis* (longhorned tick) tick infestations for one month in dogs and puppies 8 weeks of age and older, weighing 4.4 pounds or greater, and for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

II. EFFECTIVENESS

The effectiveness of Credelio™ for the treatment and control of *Haemaphysalis longicornis* tick infestations and for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks was demonstrated in a total of five well-controlled laboratory studies.

A. Dosage Characterization

This supplemental approval does not change the previously approved minimum dosage of 9 mg/lb (20 mg/kg) lotilaner, given orally once a month. The FOI Summary for the original approval of NADA 141-494 dated January 19, 2018, contains dosage characterization information for dogs.

B. Substantial Evidence

For the treatment and control of Haemaphysalis longicornis infestations

1. Laboratory Dose Confirmation Study ELA231042

Title: Dose Confirmation Laboratory Study of Credelio™ Administered Orally for the Treatment and Control of *Haemaphysalis longicornis* in Experimentally Infested Dogs. (Study No. ELA231042)

Study Dates: February 13, 2024 to January 14, 2025

Study Location: Waverly, NY

Study Design:

Objective: Confirm the effectiveness of a single oral dose of Credelio™ for the treatment and control of adult *H. longicornis* infestations on dogs at 48 hours after treatment or experimental infestation for 32 days.

Study Animals: Twenty beagle dogs (10 male and 10 female), approximately 15 to 16 months of age, weighing 6.3 to 10.8 kg.

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 by live tick count and randomly allocated within blocks to two groups. Tick infestations were conducted on Days -7, -2, 5, 12, 19, and 30. At each infestation, each dog was infested with approximately 50 unfed, adult female *H. longicornis* ticks.

Tick counts were performed 48 hours after drug administration or tick infestation. Ticks were not returned to the dog after counting. The study was conducted in accordance with Good Clinical Practices (GCP) guidelines.

Table II.1. Study ELA231042; Treatment Groups.

Treatment Group	Treatment	Target Dose	Number and Sex of Dogs
1	Control	0 mg/kg	10 (4M, 6F)
2	Credelio™	20 mg/kg lotilaner	10 (6M, 4F)

Drug Administration: On Day 0, the ten dogs in the Credelio™ group were administered one or more chewable tablets, at lotilaner doses as close as possible to 20 mg/kg without under-dosing. Lotilaner doses ranged from 21.0 to 26.8 mg/kg per dog. The ten dogs in the control group were administered a vehicle control. All dogs were administered tablets orally in a fed state.

Measurements and Observations: The primary variable for effectiveness was the *H. longicornis* counts collected from the dogs. At each tick count, the ticks were removed, and the numbers of live and dead ticks were recorded. General health observations were conducted twice daily. Clinical observations were conducted prior to treatment and at approximately 1, 2, 4, and 8 hours after treatment. Physical examinations were conducted on Day -13. Dogs were weighed on Day -5. Tick counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog. For live tick counts at each time point, percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C-T)/C] x 100, where C = the least squares (LS) mean of live tick counts for the control group and T = the LS mean of live tick counts for the treated group.

On each tick count day, untransformed live tick counts were analyzed using linear mixed models, including treatment as a fixed effect and block within room as a random effect. The comparisons were tested using the two-sided 5% significance level. Dead tick counts were analyzed at each time point using the same statistical model applied to the live ticks.

Effectiveness for the control indication was determined on the basis of the percent reduction (≥90%) in live tick counts in the treated group compared to the control group.

Effectiveness for the treatment indication was determined on the basis of a numerically higher value of the LS mean of dead ticks in the treated group compared to the control group.

Results: On Days 2, 7, 14 and 21, a minimum of six dogs in the control group had an adequate tick infestation, defined as a retention rate of at least 25% (i.e., ≥12 live ticks).

The Credelio™ group had 100% reduction in live tick counts at 48 hours (Table II.2) following treatment or infestation through Day 21. On all count days following drug administration, mean live tick counts between the Credelio™ group and the control group were significantly different ($p<0.001$).

The Credelio™ group had increased numbers of dead ticks compared to the control group 48 hours (Table II.3) following treatment or infestation through Day 21. On all count days following drug administration, mean dead tick counts between the Credelio™ group and the control group were significantly different ($p\leq0.002$).

Table II.2. Study ELA231042; *H. longicornis* Live Tick Counts and Percent Effectiveness 48 Hours After Administration or Infestation.

Days After Treatment	Control Group LS Mean	Credelio™ Group LS Mean	Percent Effectiveness
2	22.2	0	100%
7	30.8	0	100%
14	26.5	0	100%
21	17.1	0	100%

Table II.3. Study ELA231042; *H. longicornis* Dead Tick Counts 48 Hours After Administration or Infestation.

Days After Treatment	Control Group LS Mean	Credelio™ Group LS Mean
2	0.9	29.6
7	1.5	24.7
14	1.1	18.3
21	0.5	11.4

Adverse Reactions: There were no adverse reactions during the study.

Conclusion: This study demonstrated the effectiveness of Credelio™ for the control (reduced live ticks) and treatment (increased dead ticks) of *H. longicornis* ticks for 21 days when assessed 48 hours after drug administration or infestation.

2. Laboratory Dose Confirmation Study ELA231098

Title: Dose Confirmation Laboratory Study of Credelio™ Administered Orally for the Treatment and Control of *Haemaphysalis longicornis* in Experimentally Infested Dogs. (Study No. ELA231098)

Study Dates: February 12, 2024 to January 15, 2025

Study Location: Bloemfontein, South Africa

Study Design:

Objective: Confirm the effectiveness of a single oral dose of Credelio™ for the treatment and control of adult *H. longicornis* infestation on dogs at 48 hours after treatment or experimental infestation for 32 days.

Study Animals: Twenty beagle and crossbred dogs (6 male and 14 female), approximately 14 to 81 months of age, weighing between 11.4 to 17.9 kg.

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 by live attached tick count and randomly allocated within blocks to two groups. Tick infestations were conducted on Days -7, -2, 5, 12, 19, and 30. At each infestation, each dog was infested with approximately 50 unfed, adult female *H. longicornis* ticks (United States (US) source).

Tick counts were performed 48 hours after drug administration or tick infestation. Ticks were not returned to the dog after counting. The study was conducted in accordance with GCP guidelines.

Table II.4. Study ELA231098; Treatment Groups.

Treatment Group	Treatment	Target Dose	Number and Sex of Dogs
1	Control	0 mg/kg	10 (3M, 7F)
2	Credelio™	20 mg/kg lotilaner	10 (3M, 7F)

Drug Administration: On Day 0, the ten dogs in the Credelio™ group were administered one or more chewable tablets, at lotilaner doses as close as possible to 20 mg/kg without under-dosing. Lotilaner doses ranged from 20.6 to 26.2 mg/kg per dog. The ten dogs in the control group were administered a vehicle control. All dogs were administered tablets orally in a fed state.

Measurements and Observations: The primary variable for effectiveness was the *H. longicornis* counts collected from the dogs. At each tick count, the ticks were removed, and the numbers of live and dead ticks were recorded. General health observations were conducted twice daily. Clinical observations were conducted prior to treatment and at approximately 1, 2, 4, and 8 hours after treatment. Physical examinations were conducted on Day -13. Dogs were weighed on Day -5. Tick counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog. For live tick counts at each time point, percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C-T)/C] x 100, where C = the least squares (LS) mean of live tick counts for the control group and T = the LS mean of live tick counts for the treated group.

On each tick count day, untransformed live tick counts were analyzed using linear mixed models, including treatment as a fixed effect and block within room as a random effect. The comparisons were tested using the two-sided 5% significance level. Dead tick counts were analyzed at each time point using the same statistical model applied to the live ticks.

Effectiveness for the control indication was determined on the basis of the percent reduction (≥90%) in live tick counts in the treated group compared to the control group.

Effectiveness for the treatment indication was determined on the basis of a numerically higher value of the LS mean of dead ticks in the treated group compared to the control group.

Results: On Days 7, 14, 21 and 32, a minimum of six dogs in the control group had an adequate tick infestation, defined as a retention rate of at least 25% (i.e., ≥12 live ticks).

The Credelio™ group had 100% reduction in live tick counts at 48 hours (Table II.5) following infestation on Day 7 through Day 32. On all count days following drug administration, mean live tick counts between the Credelio™ group and the control group were significantly different ($p<0.001$).

The Credelio™ group had increased numbers of dead ticks compared to the control group 48 hours (Table II.6) following infestation on Day 7 through Day 32. On all count days following drug administration, mean dead tick counts between the Credelio™ group and the control group were significantly different ($p\leq0.006$).

Table II.5. Study ELA231098; *H. longicornis* Live Tick Counts and Percent Effectiveness 48 Hours After Administration or Infestation.

Days After Treatment	Control Group LS Mean	Credelio™ Group LS Mean	Percent Effectiveness
7	23.8	0	100%
14	23.3	0	100%
21	15.8	0	100%
32	11.7	0	100%

Table II.6. Study ELA231098; *H. longicornis* Dead Tick Counts 48 Hours After Administration or Infestation.

Days After Treatment	Control Group LS Mean	Credelio™ Group LS Mean
7	1.5	23.8
14	2.5	20.1
21	6.1	25.0
32	3.9	12.6

Adverse Reactions: One dog had diarrhea at 4 and 8 hours after Credelio™ administration. The dog fully recovered with supportive care.

Conclusion: This study demonstrated the effectiveness of Credelio™ for the control (reduced live ticks) and treatment (increased dead ticks) of *H. longicornis* ticks from 7 to 32 days when assessed 48 hours after infestation. Diarrhea is considered a possible drug-related adverse reaction.

3. Laboratory Dose Confirmation Study ELA241006

Title: Dose Confirmation Laboratory Study of Credelio™ Administered Orally for the Treatment and Control of *Haemaphysalis longicornis* in Experimentally Infested Dogs. (Study No. ELA241006)

Study Dates: August 19, 2024 to February 12, 2025

Study Location: Waverly, NY

Study Design:

Objective: Confirm the effectiveness of Credelio™ for the treatment and control of adult *H. longicornis* infestation when administered orally to experimentally infested dogs for 32 days.

Study Animals: Twenty beagle dogs (12 male and 8 female) approximately 15 to 45 months of age, weighing 7.8 to 13.9 kg.

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 by live tick count and randomly allocated within blocks to two groups. Tick infestations were conducted on Days -7, -1, 5, 12, 19, and 30. At each infestation, each dog was infested with approximately 50 unfed, female adult *H. longicornis* ticks.

Tick counts were performed 48 hours after drug administration or tick infestation. Ticks were not returned to the dog after counting. The study was conducted in accordance with GCP guidelines.

Table II.7. Study ELA 241006; Treatment Groups.

Treatment Group	Treatment	Target Dose	Number and Sex of Dogs
1	Control	0 mg/kg	10 (6M, 4F)
2	Credelio™	20 mg/kg lotilaner	9 (5M, 4F)*

*One Credelio™ group dog (male) was removed from the study due a dosing error, which resulted in nine Credelio™ group dogs for the effectiveness evaluations.

Drug Administration: On Day 0, the nine dogs in the Credelio™ group were administered one or more chewable tablets, at lotilaner doses as close as possible to 20 mg/kg without under-dosing. Lotilaner doses ranged from 21.1 to 25.3 mg/kg per dog. The ten dogs in the control group were administered a vehicle control. All dogs were administered tablets orally in a fed state.

Measurements and Observations: Tick counts were conducted on Days 2, 7, 14, 21, and 32. At each tick count, the ticks were removed, and the numbers of live and dead ticks were recorded. General health observations were conducted twice daily. Clinical observations were conducted prior to treatment and at approximately 1, 2, 4, and 8 hours after treatment. Physical examinations were

conducted on Day -14. Dogs were weighed on Day -5. Tick counts and health observations were conducted by personnel that were masked to treatment.

Statistical Methods: The experimental unit was the individual dog. For live tick counts at each time point, percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C-T)/C] x 100, where C = the least squares (LS) mean of live tick counts for the control group and T = the LS mean of live tick counts for the treated group.

On each tick count day, untransformed live tick counts were analyzed using linear mixed models, including treatment as a fixed effect and block as a random effect. The comparisons were tested using the two-sided 5% significance level. Dead tick counts were analyzed at each time point using the same statistical model applied to the live ticks.

Effectiveness for the control indication was determined on the basis of the percent reduction (≥90%) in live tick counts in the treated group compared to the control group.

Effectiveness for the treatment indication was determined on the basis of a numerically higher value of the LS mean of dead ticks in the treated group compared to the control group.

Results: A minimum of six dogs in the control group had an adequate tick infestation, defined as a retention rate of at least 25% (i.e., ≥12 live ticks), at all time points.

The Credelio™ group had 100% reduction in live tick counts at 48 hours (Table II.8) following treatment or infestation through Day 32. On all count days following drug administration, mean live tick counts between the Credelio™ group and the control group were significantly different ($p<0.001$).

The Credelio™ group had increased numbers of dead ticks compared to the control group 48 hours (Table II.9) following treatment or infestation through Day 32. On all count days following drug administration, mean dead tick counts between the Credelio™ group and the control group were significantly different ($p<0.001$).

Table II.8. Study ELA241006; *H. longicornis* Live Tick Counts and Percent Effectiveness 48 Hours After Administration or Infestation.

Days After Treatment	Control Group LS Mean	Credelio™ Group LS Mean	Percent Effectiveness
2	23.8	0	100%
7	22.3	0	100%
14	17.4	0	100%
21	19.2	0	100%
32	17.1	0	100%

Table II.9. Study ELA241006; *H. longicornis* Dead Tick Counts 48 Hours After Administration or Infestation.

Days After Treatment	Control Group LS Mean	Credelio™ Group LS Mean
2	0.9	21.9
7	4.3	15.8
14	1.3	14.0
21	1.8	10.7
32	2.8	12.4

Adverse Reactions: There were no adverse reactions during the study.

Conclusion: This study demonstrated the effectiveness of Credelio™ for the treatment (increased dead ticks) and control (reduced live ticks) of *H. longicornis* ticks for 32 days when assessed 48 hours after drug administration or infestation.

For the prevention of Borrelia burgdorferi infections as a direct result of killing Ixodes scapularis vector ticks

4. Laboratory Dose Confirmation Study ELA230932

Title: Evaluation of Credelio™ (lotilaner) Administered Orally, in the Prevention of *Borrelia burgdorferi* Transmission from Infected *Ixodes scapularis* to Dogs. (Study No. ELA230932)

Study Dates: October 27, 2023 to January 13, 2025

Study Location: Waverly, NY

Study Design:

Objective: Confirm the effectiveness of a single oral dose of Credelio™ to prevent *B. burgdorferi* infections from wild caught *I. scapularis* ticks by killing the ticks before transmission may occur in dogs.

Study Animals: Twenty beagle dogs (10 male and 10 female), approximately 11 to 13 months of age, weighing between 5.3 to 11.5 kg.

Experimental Design: On Day -3, dogs were randomized into treatment groups of 10 dogs each using a completely randomized design. The treatment was administered on Day 0. On Day 28, each dog was infested with approximately 50 unfed, wild-caught adult *I. scapularis* ticks. The ticks had a *B. burgdorferi* infection rate of 70%. The ticks were counted and removed on Day 33. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Table II.10. Study No. ELA230932; Treatment Groups.

Treatment Group	Treatment	Target Dose	Number and Sex of Dogs
1	Control*	0 mg/kg	10 (6M, 4F)
2	Credelio™	20 mg/kg lotilaner	10 (4M, 6F)

* Sham-dosed

Drug Administration: On Day 0, the ten dogs in the Credelio™ group were administered one or more chewable tablets, at lotilaner doses as close as possible to 20 mg/kg without under-dosing. Lotilaner doses ranged from 21.2 to 25 mg/kg per dog. The ten dogs in the control group were sham-dosed. All dogs were administered tablets orally in a fed state.

Measurements and Observations: On Day 33, the ticks were removed, and the numbers of live and dead ticks were recorded. Blood samples were collected from each dog on Days -4, 27, 49, 63, 77, 91, and 105. Samples were qualitatively tested for *B. burgdorferi* antibodies using the SNAP® 4Dx® Plus Test and quantitatively assayed for *B. burgdorferi* antibodies using the Lyme Quant C6® Test. Skin biopsy samples were collected from four sites on each dog on Day 105 from the heaviest areas of tick attachment, as marked on Day 33, and were tested by polymerase chain reaction (PCR) for the presence of *B. burgdorferi*. For dogs with fewer than four attachment sites identified, biopsies were collected from the attachment sites identified most frequently on other dogs (neck area). General health observations were conducted twice daily. Clinical observations were conducted prior to treatment and at approximately 1, 2, and 6 hours after treatment. Physical examinations were conducted on Day -7. Dogs were weighed on Day -4. Tick counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog.

Tick Counts: For live tick counts on Day 33, percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C-T)/C] x 100, where C = the least squares (LS) mean of live tick counts for the control group and T = the LS mean of live tick counts for the treated group. Untransformed live tick counts were analyzed using a linear model, including treatment as a fixed effect. The comparison was tested using the two- sided 5% significance level.

Serology and PCR of Skin Biopsies: A dog was considered to be infected with *B. burgdorferi* if a positive result was obtained on any of the SNAP® 4Dx® Plus Tests for *B. burgdorferi* after Day 28, any of the Lyme Quant C6® Tests after Day 28, and/or any of the four biopsied sites on the Day 105 PCR test.

The proportion of dogs infected with *B. burgdorferi* in the treated group was compared with the proportion of dogs infected in the control group using Fisher's

Exact test. The statistical test was performed at a significance level of 0.05 (two-sided).

Effectiveness for the prevention of *B. burgdorferi* infections as a direct result of killing *I. scapularis* ticks was determined on the basis of:

- Adequate *B. burgdorferi* infection, defined as at least 6 control dogs with a positive SNAP® 4Dx® Plus test, Lyme Quant C6® test or PCR test on skin biopsy any time after Day 28.

- ≥90% (9/10) of the dogs in the treated group were not infected with *B. burgdorferi* (dogs must have been negative on all tests conducted: SNAP® 4Dx® Plus, Lyme Quant C6® test and PCR test on skin biopsy).

- There was a statistically significant difference ($p<0.05$, two-sided) between the proportion of animals positive for *B. burgdorferi* in the treated group compared to the proportion of positive animals in the control group, with a greater proportion in the control group.

Results: All ten dogs in the control group had an adequate tick infestation, defined as a retention rate of at least 25% (i.e., ≥12 live ticks) on Day 33.

The Credelio™ group had 100% reduction in live tick counts (Table II.11) on Day 33. Mean live tick counts between the Credelio™ group and the control group were significantly different ($p<0.0001$).

Table II.11. Study ELA230932; *I. scapularis* Live Tick Counts and Percent Effectiveness.

Day of Tick Count	Control Group LS Mean	Credelio™ Group LS Mean	Percent Effectiveness
33	22.7	0	100%

All dogs completing the study were seronegative for *B. burgdorferi* before treatment and tick infestations with negative test results on both the SNAP® 4Dx® Plus Tests and Lyme Quant C6® Tests (titer <30 U/mL).

Eight of ten control dogs were determined to be infected with *B. burgdorferi* at the end of the study, with seven dogs showing positive results on the SNAP® 4Dx® Plus Test on Day 105 and eight dogs showing positive results on the Lyme Quant C6® Test (titer ≥30 U/mL) on Day 105. *B. burgdorferi* infections were detected in four control dogs from at least one of the four skin biopsies collected on Day 105.

All ten dogs (100%) in the Credelio™ group were seronegative for *B. burgdorferi*, with negative test results on both the SNAP® 4Dx® Plus Tests and the Lyme Quant C6® Tests (titer <30 U/mL), in addition to no detection of *B. burgdorferi* via PCR for all skin biopsies collected on Day 105 (Table II.12, II.13, and II.14). The proportion of dogs positive for *B. burgdorferi* in the Credelio™-treated group was

significantly different than the control group (p=0.0007).

Table II.12. Study ELA230932; Serology and PCR Results for *B. burgdorferi:* SNAP® 4Dx® Plus Results.

Day	Control Dogs Positive for *B. burgdorferi*	Credelio™ Dogs Positive for *B. burgdorferi*
-4	0/10	0/10
27	0/10	0/10
49	0/10	0/10
63	3/10	0/10
77	1/10	0/10
91	5/10	0/10
105	7/10	0/10
Overall	7/10	0/10

Table II.13. Study ELA230932; Serology and PCR Results for *B. burgdorferi*: Lyme Quant C6® Results.

Day	Control Dogs Positive for *B. burgdorferi*	Credelio™ Dogs Positive for *B. burgdorferi*
-4	0/10	0/10
27	0/10	0/10
49	1/10	0/10
63	3/10	0/10
77	6/10	0/10
91	7/10	0/10
105	8/10	0/10
Overall	8/10	0/10

Table II.14. Study ELA230932; Serology and PCR Results for *B. burgdorferi*: Skin Biopsy.

Day	Control Dogs Positive for *B. burgdorferi*	Credelio™ Dogs Positive for *B. burgdorferi*
105	4/10	0/10

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

Conclusion: A single dose of Credelio™ administered orally to dogs 28 days prior to infestation with *B. burgdorferi*-infected *I. scapularis* ticks prevented *B. burgdorferi* infections as a direct result of killing the *I. scapularis* vector ticks.

5. Laboratory Dose Confirmation Study ELA230933

Title: Evaluation of Credelio™ (lotilaner) Administered Orally, in the Prevention of *Borrelia burgdorferi* Transmission from Infected *Ixodes scapularis* to Dogs. (Study No. ELA230933)

Study Dates: October 11, 2023 to January 24, 2025

Study Location: Athens, GA

Study Design:

Objective: Confirm the effectiveness of a single oral dose of Credelio™ to prevent *B. burgdorferi* infections from wild caught *I. scapularis* ticks by killing the ticks before transmission may occur in dogs.

Study Animals: Twenty beagle dogs (10 male and 10 female), approximately 11 to 13 months of age, weighing between 6.6 to 9.7 kg.

Experimental Design: On Day -3, dogs were randomized into treatment groups of 10 dogs each using a completely randomized design. The treatment was administered on Day 0. On Day 28, each dog was infested with approximately 50 unfed, wild-caught adult *I. scapularis* ticks. The ticks had a *B. burgdorferi* infection rate of 39%. The ticks were counted and removed on Day 33. The study was conducted in accordance with GCP guidelines.

Table II.15. Study ELA230933; Treatment Groups.

Treatment Group	Treatment	Target Dose	Number and Sex of Dogs
1	Control*	0 mg/kg	10 (5M, 5F)
2	Credelio™	20 mg/kg lotilaner	10 (5M, 5F)

* Sham-dosed

Drug Administration: On Day 0, the ten dogs in the Credelio™ group were administered one or more chewable tablets, at lotilaner doses as close as possible to 20 mg/kg without under-dosing. Lotilaner doses ranged from 21.1 to 26.2 mg/kg per dog. The ten dogs in the control group were sham-dosed. All dogs were administered tablets orally in a fed state.

Measurements and Observations: On Day 33, the ticks were removed, and the numbers of live and dead ticks were recorded. Blood samples were collected from each dog on Days -7, 27, 49, 63, 77, 91, and 105. Samples were qualitatively tested for *B. burgdorferi* antibodies using the SNAP® 4Dx® Plus Test and quantitatively assayed for *B. burgdorferi* antibodies using the Lyme Quant C6® Test. Skin biopsy samples were collected from four sites on each dog on Day 104 or 105 from the heaviest areas of tick attachment, as marked on Day 33, and were tested by PCR for the quantitative presence of *B. burgdorferi*. For dogs with fewer than four attachment sites identified, biopsies were collected from the attachment sites identified most frequently on other dogs (neck area). General health observations were conducted twice daily. Clinical observations were conducted prior to treatment and at approximately 1, 2, and 6 hours after treatment. Physical examinations were conducted on Day -7. Dogs were weighed on Day -7. Tick counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog.

Tick Counts: For live tick counts on Day 33, percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C-T)/C] x 100, where C = the least squares (LS) mean of live tick counts for the control group and T = the LS mean of live tick counts for the treated group. Untransformed live tick counts were analyzed using a linear mixed model, including treatment as a fixed effect and room as a random effect. The comparisons were tested using the two-sided 5% significance level.

Serology and PCR of Skin Biopsies: A dog was considered to be infected with *B. burgdorferi* if a positive result was obtained on any of the SNAP® 4Dx® Plus Tests for *B. burgdorferi* after Day 28, any of the Lyme Quant C6® Tests after Day 28, and/or any of the four biopsied sites on the Day 104 or 105 PCR test.

The proportion of dogs infected with *B. burgdorferi* in the treated group was compared to the proportion of dogs infected in the control group using Fisher's Exact test. The statistical test was performed at a significance level of 0.05 (two-sided).

Effectiveness for the prevention of *B. burgdorferi* infections as a direct result of killing *I. scapularis* ticks was determined on the basis of:

- Adequate *B. burgdorferi* infection, defined as at least 6 control dogs with a positive SNAP® 4Dx® Plus test, Lyme Quant C6® test or PCR test on skin biopsy any time after Day 28;

- ≥90% (9/10) of the dogs in the treated group were not infected with *B. burgdorferi* (dogs must have been negative on all tests conducted: SNAP® 4Dx® Plus, Lyme Quant C6® test and PCR test on skin biopsy);

- There was a statistically significant difference ($p<0.05$, two-sided) between the proportion of animals positive for *B. burgdorferi* in the treated group compared to the proportion of positive animals in the control group, with a greater proportion in the control group.

Results: All ten dogs in the control group had an adequate tick infestation, defined as a retention rate of at least 25% (i.e., ≥12 live ticks) on Day 33. The Credelio™ group had 100% reduction in live tick counts (Table II.16) on Day 33. Mean live tick counts between the Credelio™ group and the control group were significantly different ($p<0.0001$).

Table II.16. Study ELA230933; *I. scapularis* Live Tick Counts and Percent Effectiveness.

Day of Tick Count	Control Group LS Mean	Credelio™ Group LS Mean	Percent Effectiveness
33	28.7	0	100%

All dogs were seronegative for *B. burgdorferi* before treatment with negative test results on both the SNAP® 4Dx® Plus Tests and Lyme Quant C6® Tests (titer <30 U/mL). All but one control dog was seronegative for *B. burgdorferi* before tick infestations. The one control dog was seropositive (Lyme Quant C6®) on Day 27 and was excluded from the *B. burgdorferi* effectiveness analyses.

All nine control dogs were determined to be infected with *B. burgdorferi* at the end of the study, with all nine dogs showing positive results on the SNAP® 4Dx® Plus Test and Lyme Quant C6® Test (titer ≥30 U/mL) on and after Day 91. *B. burgdorferi* infections were detected in nine control dogs from at least one of the four skin biopsies collected on Day 104 or 105.

All ten dogs (100%) in the Credelio™ group were seronegative for *B. burgdorferi*, with negative test results on both the SNAP® 4Dx® Plus Tests and the Lyme Quant C6® Tests (titer <30 U/mL) in addition to no detection of *B. burgdorferi* via PCR for all skin biopsies collected on Day 104 or 105 (Table II.17, II.18, and II.19). The proportion of dogs positive for *B. burgdorferi* in the Credelio™-treated group was significantly different than the control group ($p<0.0001$).

Table II.17. Study ELA230933; Serology and PCR Results for *B. burgdorferi:* SNAP® 4Dx® Plus Results.

Day	Control Dogs Positive for *B. burgdorferi*	Credelio™ Dogs Positive for *B. burgdorferi*
-7	0/10	0/10
27	0/10	0/10
49	0/9	0/10
63	5/9	0/10
77	7/9	0/10
91	9/9	0/10
104 or 105	9/9	0/10
Overall	9/9	0/10

Table II.18. Study ELA230933; Serology and PCR Results for *B. burgdorferi*: Lyme Quant C6® Results.

Day	Control Dogs Positive for B. burgdorferi	Credelio™ Dogs Positive for *B. burgdorferi*
-7	0/10	0/10
27	1/10	0/10
49	0/9	0/10
63	6/9	0/10
77	8/9	0/10
91	9/9	0/10
104 or 105	9/9	0/10
Overall	9/9	0/10

Table II.19. Study ELA230933; Serology and PCR Results for *B. burgdorferi*: Skin Biopsy.

Day	Control Dogs Positive for B. burgdorferi	Credelio™ Dogs Positive for B. burgdorferi
104 or 105	9/9	0/10

Adverse Reactions: One dog had diarrhea within one hour of dosing with Credelio™. The dog fully recovered without treatment.

Conclusion: A single dose of Credelio™ administered orally to dogs 28 days prior to infestation with *B. burgdorferi*-infected *I. scapularis* ticks prevented *B. burgdorferi* infections as a direct result of killing the *I. scapularis* vector ticks. Diarrhea is considered a possible drug-related adverse reaction.

III. TARGET ANIMAL SAFETY

FDA did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-494 dated January 19, 2018, contains a summary of target animal safety studies for dogs.

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, FDA 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 Credelio™:

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

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 Credelio™, when used according to the label, is safe and effective for the effect of supplement 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 diagnose and treat *Borrelia burgdorferi* infections, and to monitor for and respond to adverse reactions.

B. Exclusivity

This supplemental approval for Credelio™ qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the indications for the treatment and control of *Haemaphysalis longicornis* (longhorned tick) tick infestations for one month in dogs and puppies 8 weeks of age and older, weighing 4.4 pounds or greater, and for the prevention of *Borrelia burgdorferi* infections as a direct result of killing the *Ixodes scapularis* vector ticks.

C. Supplemental Applications

This supplement is a Category II supplement as defined in (21 CFR 514.106(b)(2)). This supplemental approval did not require a reevaluation of certain safety or effectiveness data in the application.

D. Patent Information

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