Date of Approval: October 20, 2025

FREEDOM OF INFORMATION (FOI) SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION (NADA)

NADA 141-581

Credelio Quattro™

(lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets)

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 3.3 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 Quattro™ (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets) is 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 3.3 pounds or greater, and for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

Credelio Quattro™ is already approved to prevent heartworm disease caused by *Dirofilaria immitis*, and to treat and control roundworm (immature adult and adult *Toxocara canis* and adult *Toxascaris leonina*), hookworm (fourth stage larvae, immature adult, and adult *Ancylostoma caninum* and adult *Uncinaria stenocephala*), and tapeworm (*Dipylidium caninum, Taenia pisiformis,* and *Echinococcus granulosus*) infections. Credelio Quattro™ is approved to kill adult fleas and treat and prevent flea infestations (*Ctenocephalides felis*), and treat and control 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 3.3 pounds or greater.

Credelio Quattro™ is a combination antiparasitic drug with four active ingredients and 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 Quattro™ 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 infestations with *H. longicornis* ticks. Credelio Quattro™ was demonstrated to be effective for the treatment and control of *H. longicornis* ticks when administered at the approved dose. Adverse reactions were mild diarrhea that resolved without treatment or 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 beginning 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 Quattro™ group had 100% reduction in live tick counts on 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 Quattro™ was effective in preventing *B. burgdorferi* infection. Adverse reactions of vomiting, dehydration, depression, and lethargy were observed in one Credelio Quattro™-treated dog on Day 3 after treatment. This dog recovered the next day after receiving supportive care. Two additional Credelio Quattro™-treated dogs were

observed with diarrhea within 6 hours after treatment. These two dogs fully recovered without treatment.

The FOI Summary for the original approval of NADA 141-581 dated October 7, 2024, contains a summary of target animal safety studies for dogs.

Conclusions
Based on the data submitted by the sponsor for the approval of Credelio Quattro™, 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.

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I. GENERAL INFORMATION

A. File Number

NADA 141-581

B. Sponsor

Elanco US Inc.
450 Elanco Circle
Indianapolis, IN 46221

Drug Labeler Code: 058198

C. Proprietary Name

Credelio Quattro™

D. Drug Product Established Name

lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Chewable tablet

G. Amount of Active Ingredient

Each chewable tablet contains:

56.25 mg lotilaner, 0.056 mg moxidectin, 14.25 mg praziquantel, and 14.25 mg pyrantel*
112.5 mg lotilaner, 0.113 mg moxidectin, 28.5 mg praziquantel, and 28.5 mg pyrantel*
225 mg lotilaner, 0.225 mg moxidectin, 57 mg praziquantel, and 57 mg pyrantel*
450 mg lotilaner, 0.45 mg moxidectin, 114 mg praziquantel, and 114 mg pyrantel*
900 mg lotilaner, 0.9 mg moxidectin, 228 mg praziquantel, and 228 mg pyrantel*

*As pamoate salt

H. How Supplied

Credelio Quattro™ (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets) is available in five strengths of flavored chewable tablets formulated according to the weight of the dog. Each chewable tablet size is available in packages of 1, 6, or 12 tablets.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Credelio Quattro™ is given orally once a month, at the minimum dosage of 9 mg/lb (20 mg/kg) lotilaner, 0.009 mg/lb (0.02 mg/kg) moxidectin, 2.28 mg/lb (5 mg/kg) praziquantel, and 2.28 mg/lb (5 mg/kg) pyrantel (as pamoate salt).

Dosing Schedule:

Body Weight (lbs)	Tablets to Administer	Lotilaner per Tablet (mg)	Moxidectin per Tablet (mg)	Praziquantel per Tablet (mg)	Pyrantel* per Tablet (mg)
3.3 - 6	1	56.25	0.056	14.25	14.25
6.1 - 12	1	112.5	0.113	28.5	28.5
12.1 - 25	1	225	0.225	57	57
25.1 - 50	1	450	0.45	114	114
50.1 - 100	1	900	0.9	228	228
>100	Administer the appropriate combination of tablets				

*As pamoate salt

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

Credelio Quattro™ is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and for the treatment and control of roundworm (immature adult and adult *Toxocara canis* and adult *Toxascaris leonina*), hookworm (fourth stage larvae, immature adult, and adult *Ancylostoma caninum* and adult *Uncinaria stenocephala*), and tapeworm (*Dipylidium caninum*, *Taenia pisiformis*, and *Echinococcus granulosus*) infections. Credelio Quattro™ 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 3.3 pounds or greater. Credelio Quattro™ 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 3.3 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 Quattro™ 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 dose of 9 mg/lb (20 mg/kg) of lotilaner, 0.009 mg/lb (0.02 mg/kg) of moxidectin, 2.28 mg/lb (5 mg/kg) of praziquantel, and 2.28 mg/lb (5 mg/kg) of pyrantel (as the pamoate salt), given orally once a month. The FOI Summary for the original approval of NADA 141-581 dated October 7, 2024, contains dosage characterization information for dogs.

B. Substantial Evidence

For the treatment and control of Haemaphysalis longicornis tick infestations

1. Laboratory Dose Confirmation Study ELA231042

   Title: Dose Confirmation Laboratory Study of Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel and Pyrantel Pamoate 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 Quattro™ 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 (8 male and 12 female), approximately 15 to 16 months of age, weighing 6.6 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 Quattro™	20 mg/kg lotilaner, 0.02 mg/kg moxidectin, 5 mg/kg praziquantel, 5 mg/kg pyrantel (as pamoate salt)	10 (4M, 6F)

Drug Administration: On Day 0, the ten dogs in the Credelio Quattro™ 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 21.4 to 24.8 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 Quattro™ 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 Quattro™ group and the control group were significantly different ($p<0.0001$).

The Credelio Quattro™ 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 Quattro™ group and the control group were significantly different ($p<0.001$).

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 Quattro™ 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 Quattro™ Group LS Mean
2	0.9	25.7
7	1.5	24.0
14	1.1	16.5
21	0.5	11.7

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

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ 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 Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel and Pyrantel Pamoate 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 Quattro™ 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 (5 male and 15 female), approximately 14 to 87 months of age, weighing between 11.7 to 21.6 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 Quattro™	20 mg/kg lotilaner, 0.02 mg/kg moxidectin, 5 mg/kg praziquantel, 5 mg/kg pyrantel (as pamoate salt)	10 (2M, 8F)

Drug Administration: On Day 0, the ten dogs in the Credelio Quattro™ 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 20.2 to 24.0 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 Quattro™ 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 Quattro™ group and the control group were significantly different ($p<0.001$).

The Credelio Quattro™ 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 Quattro™ group and the control group were significantly different ($p<0.001$).

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

Days After Treatment	Control Group LS Mean	Credelio Quattro™ 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 Infestation.

Days After Treatment	Control Group LS Mean	Credelio Quattro™ Group LS Mean
7	1.5	19.3
14	2.5	19.8
21	6.1	26.9
32	3.9	13.1

Adverse Reactions: Five dogs had diarrhea within 8 hours after Credelio Quattro™ administration and one of these dogs had diarrhea again on Day 9. The dogs fully recovered with supportive care.

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ 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 drug administration. Diarrhea is considered a possible drug-related adverse reaction.

3. Laboratory Dose Confirmation Study ELA241006

Title: Dose Confirmation Laboratory Study of Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel and Pyrantel Pamoate 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 Quattro™ for the treatment and control of adult *H. longicornis* ticks when administered orally to experimentally infested dogs for 32 days.

Study Animals: Twenty beagle dogs (11 male and 9 female) approximately 15 to 44 months of age, weighing 7.1 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 ELA241006; Treatment Groups.

Treatment Group	Treatment	Target Dose	Number and Sex of Dogs
1	Control	0 mg/kg	10 (6M, 4F)
2	Credelio Quattro™	20 mg/kg lotilaner, 0.02 mg/kg moxidectin, 5 mg/kg praziquantel, 5 mg/kg pyrantel (as pamoate salt)	10 (5M, 5F)

Drug Administration: On Day 0, the ten dogs in the Credelio Quattro™ 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 20.1 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: Tick counts were conducted on Days 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 Quattro™ 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 Quattro™ group and the control group were significantly different ($p<0.001$).

The Credelio Quattro™ 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 Quattro™ group and the control group were significantly different ($p\leq0.002$).

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 Quattro™ 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 Quattro™ Group LS Mean
2	0.9	17.9
7	4.3	15.5
14	1.3	14.4
21	1.8	11.7
32	2.8	17.2

Adverse Reactions: One dog had diarrhea 8 hours after Credelio Quattro™ administration. The dog fully recovered without treatment.

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ 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. Diarrhea is considered a possible drug-related adverse reaction.

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 Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel, and Pyrantel Pamoate, 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 Quattro™ 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 (11 male and 9 female), approximately 11 to 13 months of age, weighing between 6.4 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 GCP guidelines.

Table II.10. Study ELA230932; Treatment Groups.

Treatment Group	Treatment	Target Dose	Number and Sex of Dogs
1	Control*	0 mg/kg	10 (6M, 4F)
2	Credelio Quattro™	20 mg/kg lotilaner, 0.02 mg/kg moxidectin, 5 mg/kg praziquantel, 5 mg/kg pyrantel (as pamoate salt)	10 (5M, 5F)

* Sham-dosed

Drug Administration: On Day 0, the ten dogs in the Credelio Quattro™ 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 20.8 to 26.5 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 from the dogs, 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 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 -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 Quattro™ group had 100% reduction in live tick counts (Table II.11) on Day 33. Mean live tick counts between the Credelio Quattro™ 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 Quattro™ 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.

Nine of ten dogs (90%) in the Credelio Quattro™ 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 (Tables II.12, II.13, and II.14). One Credelio Quattro™-treated dog had one positive SNAP® 4Dx® Plus Test with a negative Lyme Quant C6® Test and a negative result on all skin biopsies on Day 105. The proportion of dogs positive for *B. burgdorferi* in the Credelio Quattro™-treated group was significantly different than the control group ($p=0.0055$).

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

Day	Control dogs Positive for *B. burgdorferi*	Credelio Quattro™ 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	1/10
Overall	7/10	1/10

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

Day	Control dogs Positive for *B. burgdorferi*	Credelio Quattro™ 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.

Study Day	Control dogs Positive for *B. burgdorferi*	Credelio Quattro™ dogs Positive for *B. burgdorferi*
105	4/10	0/10

Adverse Reactions: Vomiting, dehydration, depression, and lethargy were observed in one Credelio Quattro™-treated dog on Day 3 after treatment. This dog recovered the next day after receiving supportive care. Two additional Credelio Quattro™-treated dogs were observed with diarrhea within 6 hours after treatment. These two dogs fully recovered without treatment.

Conclusion: A single dose of Credelio Quattro™ 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. Vomiting, dehydration, depression, lethargy, and diarrhea are considered possible drug-related adverse reactions.

5. Laboratory Dose Confirmation Study ELA230933

Title: Evaluation of Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel, and Pyrantel Pamoate, 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 Quattro™ 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 (11 male and 9 female), approximately 11 to 13 months of age, weighing between 5.9 to 10.3 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 Quattro™	20 mg/kg lotilaner, 0.02 mg/kg moxidectin, 5 mg/kg praziquantel, 5 mg/kg pyrantel (as pamoate salt)	10 (6M, 4F)

* Sham-dosed

Drug Administration: On Day 0, the ten dogs in the Credelio Quattro™ 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 28.6 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 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 Quattro™ group had 100% reduction in live tick counts (Table II.16) on Day 33. Mean live tick counts between the Credelio Quattro™ 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 Quattro™ 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 the 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 Quattro™ 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 (Tables II.17, II.18, and II.19). The proportion of dogs positive for *B. burgdorferi* in the Credelio Quattro™-treated group was significantly different than the placebo-treated 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 Quattro™ 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 Quattro™ 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 Quattro™ dogs Positive for *B. burgdorferi*
104 or 105	9/9	0/10

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

Conclusion: A single dose of Credelio Quattro™ 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.

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 141-581 dated October 7, 2024, 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 Quattro™:

Not for use in humans. Keep this and all drugs out of reach of children. Wash hands after handling. If accidentally ingested, seek medical attention immediately.

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 Quattro™, 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 order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because the product is indicated for the prevention of heartworm infections (*Dirofilaria immitis*) in dogs, which requires veterinary examination and testing to ensure dogs are negative for adult heartworm disease prior to administration of the product to dogs.

B. Exclusivity

This supplemental approval for Credelio Quattro™ 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 3.3 pounds or greater, and for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *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.