Date of Approval: October 7, 2024

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-581

Credelio Quattro™

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

Dogs

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 (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), 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.

Sponsored by:

Elanco US Inc.

Executive Summary

Credelio Quattro™ (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets) is approved 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 (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), 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 is given to dogs orally once a month.

Safety and Effectiveness

The sponsor conducted 15 laboratory dose confirmation studies and one clinical field study to demonstrate the effectiveness of Credelio Quattro™ against a variety of internal and external parasites in dogs. The studies, along with published literature and separate *in vitro* and *in vivo* studies, also demonstrated that each active ingredient contributes to the effectiveness of Credelio Quattro™ for the following indications:

- Lotilaner: to treat and prevent flea infestations and to treat and control tick infestations;
- Moxidectin: to prevent heartworm disease caused by *D. immitis*;
- Praziquantel: to treat and control cestode (tapeworm) infections; and
- Pyrantel: to treat and control nematode (roundworm and hookworm) infections.

Heartworm indication: The sponsor conducted two dose confirmation studies in beagles and one field study in client-owned dogs to show that Credelio Quattro™ is effective at preventing heartworm disease caused by *D. immitis*.

Gastrointestinal (GI) nematode indication: The sponsor conducted eight dose confirmation studies in beagles and mixed breed dogs to show that Credelio Quattro™ is effective at treating and controlling various nematode infections: roundworms (immature adult and adult *T. canis* and adult *T. leonina*) and hookworms (adult *U. stenocephala*).

GI cestode indication: Because of the public health implications of *E. granulosus*, the sponsor conducted two dose confirmation studies in beagles using *E. granulosus* as the representative cestode species to show that Credelio Quattro™ is effective at treating and controlling various tapeworm infections: *D. caninum, T. pisiformis*, and *E. granulosus*.

A praziquantel dose of 5 mg/kg was used in previous studies to support the effectiveness of this active ingredient for treating and controlling various tapeworm infections: *D. caninum*, *T. pisiformis*, *E. granulosus*, and *E. multilocularis*. These studies are described in the Freedom of Information (FOI) Summaries for the original and supplemental approvals of Droncit™ (praziquantel) Canine Cestocide Tablets under a different application (New Animal Drug Application (NADA) 111-798). However, for the current approval, the sponsor conducted a study using a non-final formulation that contained three of the active ingredients at the same doses as in Credelio Quattro™ (it did not contain pyrantel), and the formulation failed to demonstrate adequate effectiveness against *E. multilocularis*. Therefore, Credelio Quattro™ is not approved for treating and controlling *E. multilocularis*.

Flea and tick indications: The sponsor conducted one dose confirmation study in beagles to show that Credelio Quattro™ is effective at treating and preventing flea infestations (*C. felis*).

A minimum lotilaner dose of 20 mg/kg given orally once a month was used in previous studies to support the effectiveness of this active ingredient at treating and controlling tick infestations. These studies are described in the FOI Summary for the original approval of Credelio™ (lotilaner) Chewable Tablets under a different application (NADA 141-494). The data in NADA 141-494 identified *R. sanguineus* as the overall least susceptible tick to lotilaner. Therefore, the sponsor conducted two dose confirmation studies in beagles and mixed breed dogs using *R. sanguineus* as the representative tick species to show that Credelio Quattro™ is effective at treating and controlling various tick infestations: *A. americanum* (lone star tick), *D. variabilis* (American dog tick), *I. scapularis* (black-legged tick), and *R. sanguineus* (brown dog tick).

Common adverse reactions seen in the above studies were diarrhea (with or without blood or mucus), vomiting, lethargy, anorexia, weight loss, dermatitis, pruritus, alopecia, and neurologic signs.

The sponsor conducted a margin of safety study in young, healthy, male and female beagles. The dogs were given Credelio Quattro™ orally at 0X, 1X, 3X, and 5X the maximum intended dose for each of the four active ingredients every 28 days for nine treatments. All dogs completed the study and no serious adverse reactions occurred. Possible drug-related adverse reactions included hypersalivation, vomiting, discolored feces, diarrhea, and increased bile acids.

The sponsor conducted a safety study in young, healthy male and female beagles that were heartworm positive. The dogs were given Credelio Quattro™ orally at 0X, 1X, and 3X the maximum intended dose for each of the four active ingredients every 28 days for three treatments. The drug was well tolerated in dogs with pre-existing adult heartworm infections and circulating microfilariae. No serious adverse reactions occurred in any dogs. Vomiting was a possible drug-related adverse reaction.

The sponsor also conducted a safety study in avermectin-sensitive collies, which have a mutation at the multidrug resistance (MDR1) gene that makes them more sensitive to a variety of drugs, including macrocyclic lactones. Avermectin, ivermectin, and moxidectin are all macrocyclic lactones and structurally related. Healthy, male and female collies confirmed to have the MDR1 mutation (meaning they are MDR1 deficient) were given Credelio Quattro™ orally at 0X, 1X, 2X, and 5X the maximum intended dose for each of the four active ingredients for three treatments. The drug was well tolerated in MDR1-deficient, avermectin-sensitive collies. No dogs in any of the treatment groups had ataxia, seizures, mydriasis, or muscle tremors. Possible drug-related adverse reactions included diarrhea (with or without blood) and dose-dependent hypersalivation and vomiting.

In two foreign field studies in which dogs received Credelio Quattro™ monthly for various durations, reported adverse reactions included loose, soft, or dark feces, diarrhea, vomiting, lethargy, inappetence, and seizure-like activity. In two pilot studies in which dogs received a combination product containing either three or all four of the active ingredients at the same doses as in Credelio Quattro™ monthly for three to 11 treatments, reported adverse reactions included seizures, ataxia, and diarrhea with a duodenal ulcer.

Conclusions
Based on the data submitted by the sponsor for the approval of Credelio Quattro™, the Food and Drug Administration (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 141-581

B. Sponsor

Elanco US Inc.
2500 Innovation Way
Greenfield, IN 46140

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

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 (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), 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.

II. EFFECTIVENESS

A. Dosage Characterization

Lotilaner:
The minimum effective dosage of 20 mg/kg given orally once a month for the treatment and prevention of flea infestations and the treatment and control of tick infestations in dogs and puppies 8 weeks of age and older and weighing 3.3 pounds or greater is based on studies conducted in support of the approval of Credelio™ (lotilaner) Chewable Tablets under NADA 141-494. The FOI Summary for the original approval of NADA 141-494, dated January 19, 2018, contains dosage characterization information for lotilaner in dogs.

The bioavailability of lotilaner is lower and more variable in the fasted state. Laboratory studies previously conducted with lotilaner demonstrated reduced duration of effectiveness in fasted dogs compared to fed dogs and that administration of lotilaner in the fed state was required to achieve adequate oral bioavailability and effectiveness. Therefore, dose confirmation studies to support substantial evidence of effectiveness for Credelio Quattro™ were conducted under fed conditions.

Moxidectin:
The minimum effective dosage of 0.02 mg/kg given orally once a month for the prevention of canine heartworm disease caused by *Dirofilaria immitis* in dogs and puppies 8 weeks of age and older and weighing 3.3 pounds or greater was established by the results of pilot laboratory studies using a range of moxidectin doses and a pilot field study. Furthermore, based on the results of a pilot avermectin sensitive Collie safety study, a maximum oral moxidectin dose of 0.04 mg/kg was selected.

Praziquantel:
The minimum effective dosage of 5 mg/kg given orally once a month for the treatment and control of tapeworm (*Dipylidium caninum*, *Taenia pisiformis*, and *Echinococcus granulosus*) infections in dogs and puppies 8 weeks of age and older and weighing 3.3 pounds or greater is based on studies conducted in support of the approval of Droncit™ (praziquantel) Canine Cestocide Tablets under NADA 111-798. The FOI Summaries for the supplemental approvals of NADA 111-798, dated January 18, 1990, and July 16, 1993, contain dosage characterization information for praziquantel in dogs.

Pyrantel (as pamoate salt):
The minimum effective dosage of 5 mg/kg given orally once a month for the treatment and control of roundworm (immature adult and adult *Toxocara canis* and adult *Toxascaris leonina*) and hookworm (*Uncinaria stenocephala*) infections in dogs and puppies 8 weeks of age and older and weighing 3.3 pounds or greater is based on studies conducted in support of the approval of Drontal™ Plus (praziquantel/pyrantel pamoate/febantel) Taste Tabs for dogs under NADA 141-007. The FOI Summary for the original approval of NADA 141-007, dated May 19, 1994, contains dosage characterization information for pyrantel (as pamoate salt) in dogs.

B. Substantial Evidence

In accordance with 21 CFR 514.4(c)(3), the sponsor demonstrated by substantial evidence that Credelio Quattro™ is effective for the labeled conditions of use and that lotilaner, moxidectin, praziquantel, and pyrantel each contribute to the effectiveness of the combination new animal drug.

The 15 dose confirmation studies and one field study conducted to demonstrate the effectiveness of Credelio Quattro™, in addition to published literature and separate *in vitro* and/or *in vivo* studies, were used to demonstrate substantial evidence of the unique contribution of each active ingredient (lotilaner, moxidectin, praziquantel, and pyrantel) to the effectiveness of Credelio Quattro™ for the following indications:

- Lotilaner: for the treatment and prevention of flea infestations (*C. felis*) and the treatment and control of tick infestations (*R. sanguineus*).
- Moxidectin: for the prevention of heartworm disease caused by *D. immitis*.
- Praziquantel: for the treatment and control of *E. granulosus* infections.
- Pyrantel: for the treatment and control of adult *T. canis* infections.

Heartworm Indication:

The sponsor conducted two dose confirmation studies in laboratory dogs and one multi-site field safety and effectiveness study in client-owned dogs to demonstrate substantial evidence of effectiveness of Credelio Quattro™ for the prevention of heartworm disease caused by *D. immitis*.

Published literature[1,2] and a dose confirmation study that included a group treated with a combination of praziquantel, pyrantel pamoate, and febantel (Drontal® Plus, NADA 141-007) demonstrated that pyrantel and praziquantel failed to demonstrate effectiveness for the prevention of adult heartworm (*D. immitis*) infections. The lotilaner treatment group in a dose confirmation study (Study No. ELA210055) also failed to demonstrate effectiveness for the prevention of adult heartworm (*D. immitis*) infections. Therefore, because Credelio Quattro™ was effective against *D. immitis* infections, and lotilaner, praziquantel, and pyrantel failed to demonstrate effectiveness, moxidectin was established as the active ingredient responsible for the effectiveness of Credelio Quattro™ for the prevention of heartworm disease.

[1] Bradley and Conway (1970). Evaluation of Pyrantel Hydrochloride as an Anthelmintic in Dogs. Veterinary Medicine and Small Animal Clinic, 65 (8), 767-769.
[2] Kopp et al (2008). Pyrantel in small animal medicine: 30 years on. The Veterinary Journal, 178, 177-1844.

For the Prevention of Heartworm Disease:

1. Laboratory Dose Confirmation Study Against *Dirofilaria immitis*

Title: Dose Confirmation and Non-Interference Laboratory Study of Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel and Pyrantel Pamoate Administered Orally to Dogs for the Prevention of Heartworm Disease Caused by *Dirofilaria immitis.* (Study No. ELA210055)

Study Dates: May 24, 2021 to October 6, 2022

Study Location: Athens, GA

Study Design:

Objective: Confirm the effectiveness of Credelio Quattro™ for the prevention of heartworm disease caused by *D. immitis* when administered orally in dogs experimentally inoculated with *D. immitis* larvae (L3) and demonstrate the inclusion of moxidectin in the combination contributes to the effectiveness of Credelio Quattro™ against *D. immitis*.

Study Animals: Forty beagle dogs (20 male and 20 female), 6 to 8 months of age, weighing between 7.3 to 12 kg.

Experimental Design: Prior to allocation to treatment groups, dogs were subcutaneously inoculated in the inguinal region with 50 third-stage infective *D. immitis* larvae (L3) once on Day -30. On Day -1, 40 dogs, stratified by sex, were randomly allocated to one of five treatment groups. On Day 118, dogs in Groups 1, 2, and 5 were humanely euthanized and necropsied for recovery of adult heartworms. Dogs in Group 3 and 4 were not necropsied because no worms were found in any dog in Group 2. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Table II.1. Study ELA210055; Treatment Groups

Treatment Group	Treatment	Minimum Dose	Treatment Day(s)	Number and Sex of Dogs
1	Control	0 mg/kg	Day 0, 30, 60	8 (4M, 4F)
2	Credelio Quattro™	20 mg/kg lotilaner + 0.02 mg/kg moxidectin + 5 mg/kg praziquantel + 5 mg/kg pyrantel (as pamoate salt)	Day 0	8 (4M, 4F)
3	Credelio Quattro™	20 mg/kg lotilaner + 0.02 mg/kg moxidectin + 5 mg/kg praziquantel + 5 mg/kg pyrantel (as pamoate salt)	Day 0, 30	8 (4M, 4F)

Treatment Group	Treatment	Minimum Dose	Treatment Day(s)	Number and Sex of Dogs
4	Credelio Quattro™	20 mg/kg lotilaner + 0.02 mg/kg moxidectin + 5 mg/kg praziquantel + 5 mg/kg pyrantel (as pamoate salt)	Day 0, 30, 60	8 (4M, 4F)
5	Lotilaner	20 mg/kg	Day 0, 30, 60	8 (4M, 4F)

Drug Administration: On scheduled treatment days (Days 0, 30, and 60), dogs in Groups 2, 3, and 4 were administered one or more Credelio Quattro™ chewable tablets according to the treatment schedule (see Table II.1), at moxidectin doses as close as possible to 0.02 mg/kg without under-dosing. Moxidectin doses ranged from 0.02 to 0.03 mg/kg per dog. Dogs in the lotilaner only group received doses ranging from 20 to 25.2 mg/kg per dog. To ensure that dogs were handled similarly, and to maintain masking, dogs in the control group were administered a vehicle control on Days 0, 30, and 60, and dogs in Groups 2 and 3 received a vehicle control on days that they did not receive Credelio Quattro™. All dogs were administered tablets orally in a fed state.

Measurements and Observations: The primary variable for effectiveness was the adult *D. immitis* heartworm counts collected from the dogs. General health observations were conducted at least 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 -36. Dogs were weighed on Days -32, -2, 28, and 59. Worm counts and health observations were conducted masked to treatment.

A Knott's test was conducted on Day -32 and serum heartworm antigen tests were conducted on Days -32 and 90.

Statistical Methods: Percent effectiveness of the treated groups with respect to the control group was calculated using the formula [(C-T)/C] x 100, where C=the geometric mean worm counts for the control group and T=the geometric mean worm counts for the treated groups. Geometric means were obtained by back-transforming arithmetic means of the transformed worm counts (log(count + 1)).

Contribution of moxidectin to the effectiveness of the combination new animal drug was demonstrated if treatment with lotilaner was less than 100% effective against *D. immitis* while the treatment with Credelio Quattro™ was 100% effective.

Results: All of the eight dogs in the control group had an adequate infection, defined as ≥5 *D. immitis* heartworms present at necropsy.

Credelio Quattro™ was 100% effective against experimentally induced *D. immitis* infections in dogs (Table II.2).

Table II.2. Study ELA210055; Effectiveness Against *D. immitis*

Treatment	Worm Counts: Range	Worm Counts: Geometric Mean	Percent Effectiveness
Control	13-40	25.4	NA
Credelio Quattro™*	0	0	100%
Lotilaner	9-42	29.4	0%

*Results from Group 2 only

Adverse Reactions: Four dogs had diarrhea and two dogs vomited within 8 hours of dosing with Credelio Quattro™. One dog each in the control and lotilaner groups, respectively, had diarrhea and one dog in the control group vomited within 2 hours of dosing. All dogs fully recovered without treatment.

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ for the prevention of heartworm disease caused by *D. immitis* in dogs when administered 30 days after infection. Treatment with lotilaner alone was not effective against *D. immitis*, demonstrating the inclusion of moxidectin in the combination is necessary for effectiveness of Credelio Quattro™ against *D. immitis*. Self-limiting vomiting and diarrhea are considered possible drug-related adverse reactions.

2. Laboratory Dose Confirmation Against *Dirofilaria immitis*

Title: Dose Confirmation Efficacy Laboratory Study of Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel and Pyrantel Pamoate Administered Orally to Dogs for the Prevention of Heartworm Disease Caused by *Dirofilaria immitis.* (Study No. ELAVV200359)

Study Dates: May 24, 2021 to October 25, 2022

Study Location: Rockwood, TN

Study Design:

Objective: Confirm the effectiveness of Credelio Quattro™ for the prevention of heartworm disease caused by *D. immitis* when administered orally in dogs experimentally inoculated with *D. immitis* larvae (L3).

Study Animals: Thirty-two beagle dogs (16 male and 16 female), 7 to 11 months of age, weighing between 6.8 to 16.2 kg.

Experimental Design: Prior to allocation to treatment groups, dogs were subcutaneously inoculated in the inguinal region with 50 third-stage infective *D. immitis* larvae (L3) once on Day -30. On Day -1, 32 dogs, stratified by sex, were randomly allocated to one of four treatment groups. On Day 120, dogs in Groups 1 and 2 were humanely euthanized and necropsied for recovery of adult heartworms.

Dogs in Group 3 and 4 were not necropsied because no worms were found in any dog in Group 2. The study was conducted in accordance with GCP guidelines.

Table II.3. Study ELAVV200359; Treatment Groups

Treatment Group	Treatment	Minimum Dose	Days of Treatment	Number and Sex of Dogs
1	Control	0 mg/kg	Day 0, 30, 60	8 (4M, 4F)
2	Credelio Quattro™	20 mg/kg lotilaner + 0.02 mg/kg moxidectin+ 5 mg/kg praziquantel + 5 mg/kg pyrantel (as pamoate salt)	Day 0	8 (4M, 4F)
3	Credelio Quattro™	20 mg/kg lotilaner + 0.02 mg/kg moxidectin+ 5 mg/kg praziquantel + 5 mg/kg pyrantel (as pamoate salt)	Day 0, 30	8 (4M, 4F)
4	Credelio Quattro™	20 mg/kg lotilaner + 0.02 mg/kg moxidectin+ 5 mg/kg praziquantel + 5 mg/kg pyrantel (as pamoate salt)	Day 0, 30, 60	8 (4M, 4F)

Drug Administration: On scheduled treatment days (Days 0, 30, and 60), dogs in Groups 2, 3, and 4 were administered one or more Credelio Quattro™ chewable tablets according to the treatment schedule (see Table II.3), at moxidectin doses as close as possible to 0.02 mg/kg without under-dosing. Moxidectin doses ranged from 0.02 to 0.03 mg/kg per dog. To ensure that dogs were handled similarly and to maintain masking, dogs in the control group were administered a vehicle control on Days 0, 30, and 60, and dogs in Groups 2, and 3 received a vehicle control on days that they did not receive Credelio Quattro™. All dogs were administered tablets orally in a fed state.

Measurements and Observations: The primary variable for effectiveness was the adult *D. immitis* heartworm counts collected from the dogs. General health observations were conducted at least 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 -36. Dogs were weighed on Days -36, -1, 28, and 59. Worm counts and health observations were conducted masked to treatment.

A Knott's test was conducted on Day -36 and serum heartworm antigen tests were conducted on Days -35 and 88.

Statistical Methods: Percent effectiveness of the treated groups with respect to the control group was calculated using the formula [(C-T)/C] x 100, where C=the geometric mean worm counts for the control group and T=the geometric mean worm counts for the treated group. Geometric means were obtained by back-transforming arithmetic means of the transformed worm counts (log(count+1)).

Results: All of the eight dogs in the control group had an adequate infection, defined as ≥5 *D. immitis* heartworms present at necropsy.

Credelio Quattro™ was 100% effective against experimentally induced *D. immitis* infections in dogs (Table II.4).

Table II.4. Study ELAVV200359; Effectiveness Against *D. immitis*

Treatment	Worm Counts: Range	Worm Counts: Geometric Mean	Percent Effectiveness
Control	22-36	28.2	NA
Credelio Quattro™*	0	0	100%

*Results from Group 2 only

Adverse Reactions: Four dogs had feces with mucus, three dogs had feces with blood, four dogs had diarrhea, five dogs vomited, and two dogs regurgitated within 72 hours of dosing with Credelio Quattro™. One dog in the control group had feces with mucus within 8 hours of dosing. All dogs fully recovered without treatment.

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ for the prevention of heartworm disease caused by *D. immitis* in dogs when administered 30 days after infection. Self-limiting vomiting and diarrhea, including feces with mucus or blood, are considered possible drug-related adverse reactions.

3. Field Safety and Effectiveness Study

Title: A Field Study to Evaluate the Effectiveness and Safety of Orally Administered Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel and Pyrantel Pamoate for the Prevention of Heartworm Disease in Client-Owned Dogs. (Study No. ELA210049)

Study Dates: June 3, 2021 to June 26, 2023

Study Locations: Dogs were enrolled from thirteen veterinary clinics mainly located in heartworm-endemic regions of the United States (U.S.).

Decatur, IL
Dallas, TX
Franklin, IN
Jackson, MS
Memphis, TN
Navarre, FL
Quakertown, PA
Raleigh, NC
Springfield, MO
West Palm Beach, FL
Wichita Falls, TX (2 sites)

Zachary, LA

Study Design:

Objective: Evaluate the effectiveness and field safety of Credelio Quattro™ administered at monthly intervals for 11 consecutive months for the prevention of heartworm disease caused by *Dirofilaria immitis* in client-owned dogs.
Study Animals: Three hundred seventy-two (372) client-owned mixed breed and purebred intact and neutered male and female dogs, 2 months to 16 years of age, and weighing between 1.5 and 86.8 kg were enrolled in the study. There were no breed or sex restrictions, but dogs intended for breeding, and pregnant and lactating dogs were not eligible for enrollment. Dogs were confirmed healthy and negative for heartworm infection (by *D. immitis* antigen and blood microfilariae testing) prior to enrollment. Enrolled dogs that were 6 months of age or older had received a monthly commercial heartworm preventive for at least 2 consecutive months before enrollment with the last dose administered 21 to 30 days before Visit 1 (Day -1). Dogs that had received ProHeart® 6 within 365 days, or ProHeart® 12 within 730 days prior to Visit 1 (Day -1), or had a serious health condition that would interfere with the objectives of the study, were excluded from enrollment. Only one dog per household could enroll in the study. Other animals in the household could receive other approved oral or injectable heartworm preventives during the study (topical heartworm preventives were prohibited).

Dogs were included in the evaluation of field safety if they received at least one dose of Credelio Quattro™ or the active control product. One hundred ninety-one (191) dogs administered Credelio Quattro™ and 181 dogs administered the active control product were evaluated for safety.

One hundred fifty-six (156) dogs administered Credelio Quattro™ and 149 dogs administered the active control were included in the effectiveness evaluation.

Experimental Design: The study was a randomized, masked, multicenter, active control study. The study used a randomized block design based on the order of enrollment of the individual dogs on a per-site basis. The study compared Credelio Quattro™ to an orally administered active control containing sarolaner, moxidectin, and pyrantel (as pamoate salt). The clinical investigators and other personnel conducting safety assessments and effectiveness measurements were masked to treatment. The treatment dispensers and dog owners at each study location were not masked (due to product packaging, labeling, and instructions). The study was conducted in accordance with GCP guidelines.

Table II.5. Study ELA210049; Treatment Groups

Treatment	Minimum Dose	Approximate Days of Treatment	Total Dogs Per Group (Effectiveness Evaluable Dogs)	Approximate Days of Heartworm Testing
Credelio Quattro™	20 mg/kg lotilaner + 0.02 mg/kg moxidectin + 5 mg/kg praziquantel + 5 mg/kg pyrantel (as pamoate salt)	0, 30, 60, 90, 120, 150, 180, 210, 240, 270, and 300	191(156)	-1, 120, 240, and 330
Active Control	1.2 mg/kg sarolaner, + 0.024 mg/kg moxidectin, + 5 mg/kg pyrantel (as a pamoate salt)	0, 30, 60, 90, 120, 150, 180, 210, 240, 270, and 300	181(149)	-1, 120, 240, and 330

Drug Administration: Owners administered Credelio Quattro™ or the active control to the dog in the dog's home environment on approximately Days 0, 30, 60, 90, 120, 150, 180, 210, 240, 270, and 300. Treatments could be administered within 30 +/-5 days from the previous dose. All dogs received their first dose between July 19, 2021, and August 9, 2021. Owners were instructed to administer Credelio Quattro™ within 30 minutes of a meal (or with food), and the active control product with or without food according to the product label.

Measurements and Observations: The primary variable for effectiveness was success or failure of the treatment to prevent heartworm infection based on *D. immitis* antigen and blood microfilariae testing on Day 330. A treatment failure was defined as a positive result from either test, confirmed with repeat testing.

Physical examinations, including body weight measurements, were performed on all dogs prior to treatment on Day -1, and on Days 60, 120, 180, 240, and 330. Blood was collected for hematology and clinical chemistry at enrollment on Day -1, at premature study exit (if applicable), or scheduled study completion (Day 330). Blood was collected at enrollment (Day -1) and on Days 120, 240, and 330 for *D. immitis* antigen and microfilariae testing.

The acceptance of Credelio Quattro™ by dogs was assessed by the owners during the first three doses (Days 0, 30, and 60). Owners first offered the tablet(s) in an empty bowl or on the floor for one minute. If not consumed, they offered the tablet(s) by hand for one minute, then in food for one minute, and if not consumed, they placed the tablet(s) in the back of the dog's mouth.

Statistical Methods: The statistical analysis plan indicated that if 100% effectiveness was demonstrated for Credelio Quattro™, no statistical analysis would be performed. Because all heartworm antigen and microfilariae tests performed on Days 120, 240, and 330 were negative, no statistical analysis was required.

Results: None of the 156 dogs in the effectiveness population that were treated with Credelio Quattro™ tested positive for adult heartworms on Days 120, 240, or 330. Therefore, percent success of Credelio Quattro™ to prevent heartworm infection was 100%.

Owners recorded acceptance information for 552 of 561 doses of Credelio Quattro™, administered to 191 dogs. The administration method was not recorded for 9 doses.

Table II.6. Study ELA210049; Summary of Credelio Quattro™ Tablet Acceptance

Administration Method	Number of Doses (Percentage) N=552
Consumed from bowl/floor	280 (50.7%)
Consumed from hand	50 (9.1%)
Consumed with additional food	157 (28.4%)
Manually pilled	65 (11.8%)

Adverse Reactions: One hundred ninety-one (191) dogs administered Credelio Quattro™ and 181 dogs administered the active control product were evaluated for safety. Adverse reactions seen during the field study are summarized in Table II.7 (below).

Table II.7. Study ELA210049; Adverse Reactions

Clinical Sign	Credelio Quattro™ N=191 Number (Percentage)	Active Control N=181 Number (Percentage)
Diarrhea, with or without blood*	21 (11%)	15 (8.3%)
Vomiting	18 (9.4%)	8 (4.4%)
Lethargy	12 (6.3%)	1 (0.6%)
Anorexia	11 (5.8%)	5 (2.8%)
Dermatitis	10 (5.2%)	8 (4.4%)
Weight Loss	6 (3.1%)	3 (1.7%)
Pruritus (itching)	3 (1.6%)	1 (0.6%)
Alopecia (hair loss)	2 (1%)	4 (2.2%)

Clinical Sign	Credelio Quattro™ N=191 Number (Percentage)	Active Control N=181 Number (Percentage)
Seizure	1 (0.5%)	4 (2.2%)
Ataxia	1 (0.5%)	1 (0.6%)
Nystagmus	1 (0.5%)	0 (0.0%)
Anisocoria	1 (0.5%)	1 (0.6%)

*Four dogs administered Credelio Quattro™ and five dogs administered the active control had bloody diarrhea.

One geriatric dog receiving Credelio Quattro™ experienced two episodes of vomiting, ataxia, and nystagmus, 11 days apart, with the first episode occurring two days after the eighth dose. The dog recovered within 24 hours after the first episode and 1 hour after the second episode and completed the study.

One dog receiving Credelio Quattro™ was observed by the investigator to have anisocoria during scheduled physical examinations one month after the ninth dose and one month after the eleventh dose.

Conclusions: This study demonstrated that Credelio Quattro™ is safe and effective for the prevention of heartworm disease in dogs under field conditions. Diarrhea (with or without blood), vomiting, lethargy, anorexia, weight loss, dermatitis, pruritus, alopecia, and neurologic signs are considered possible drug-related adverse reactions.

Gastrointestinal Nematode Indications:

The sponsor conducted eight dose confirmation studies to demonstrate substantial evidence of effectiveness of Credelio Quattro™ for the treatment and control of roundworm (immature adult and adult *Toxocara canis* and adult *Toxascaris leonina*), and hookworm (adult *Uncinaria stenocephala*) infections.

The sponsor conducted adequate and well-controlled studies (Study No. ELA2000071 and Study No. ELA1900500) with a three-way combination of lotilaner, moxidectin, and praziquantel (administered at the same doses as in Credelio Quattro™) which failed to demonstrate effectiveness against experimentally induced adult *T. canis* infections. Therefore, because Credelio Quattro™ was effective against adult *T. canis* infections, and lotilaner, moxidectin, and praziquantel failed to demonstrate effectiveness, pyrantel was established as the active ingredient responsible for the effectiveness of Credelio Quattro™ for the treatment and control of adult *T. canis* infections.

For the Treatment and Control of Roundworm and Hookworm Infections:

4. Laboratory Dose Confirmation Study Against Immature Adult *Toxocara canis*

Title: Dose Confirmation Laboratory Study of Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel and Pyrantel Pamoate Administered Orally for the Treatment and Control of Immature Adult *Toxocara canis* in Experimentally Infected Dogs. (Study No. ELA220841)

Study Dates: June 30, 2022 to May 30, 2023

Study Location: Rockwood, TN

Study Design:

Objective: Confirm the effectiveness of a single oral dose of Credelio Quattro™ for the treatment and control of immature adult *T. canis* in experimentally infected dogs.

Study Animals: Twenty beagle dogs (10 male and 10 female), 14.7 to 15.6 weeks of age, weighing between 4.5 to 6.5 kg.

Experimental Design: On Day -24, each dog was orally inoculated with approximately 300 infective *T. canis* larvated eggs. On Day -1, dogs were randomized into treatment groups of ten dogs each using a completely randomized design. On Day 7 post-treatment, all dogs were humanely euthanized and necropsied for recovery and counting of *T. canis*. The study was conducted in accordance with GCP guidelines.

Table II.8. Study ELA220841; Treatment Groups

Treatment Group	Treatment	Minimum 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 (5M, 5F)

Drug Administration: On Day 0, the ten dogs in the Credelio Quattro™ group were administered one or more chewable tablets, at pyrantel doses as close as possible to 5 mg/kg without under-dosing. Pyrantel doses ranged from 5.2 to 7.6 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 *T. canis* worm counts collected from the dogs. General health observations were conducted at least once daily. Clinical observations were conducted prior to treatment and at approximately 1, 2, 4, and 8 hours after treatment. Physical examinations and fecal egg count examinations were conducted on Day -30. Dogs were weighed on Days -30 and -1. Worm counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog. The log-transformed *T. canis* worm counts were analyzed using a linear mixed model with treatment group as a fixed effect. The treatment effect was tested at a two-sided 5% significance level. Percent effectiveness was calculated by using the

geometric means obtained through back-transformation of the least squares (LS) means estimated from the model.

Percent Effectiveness = 100 × (C-T)/C
Where C=Geometric mean number of worms in the control group.
T=Geometric mean number of worms in the treatment group.

Results: Seven of the ten dogs in the control group had an adequate infection, defined as ≥5 *T. canis* worms present at necropsy.

Credelio Quattro™ was 97.9% effective against experimentally induced immature adult *T. canis* infections in dogs (Table II.9). Mean worm counts between the two groups were significantly different ($p<0.0001$).

Table II.9. Study ELA220841; Effectiveness Against Immature Adult *T. canis*

Treatment	Worm Counts: Range	Worm Counts: Geometric Mean	Percent Effectiveness
Control	0–45	9.4	NA
Credelio Quattro™	0–2	0.2	97.9%

Adverse Reactions: One dog treated with Credelio Quattro™ regurgitated on Day 1, and one dog treated with Credelio Quattro™ vomited on Day 2 and regurgitated on Day 4; both events resolved without treatment.

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ for the treatment and control of immature adult *T. canis* in dogs when administered at the labeled dose. Vomiting is considered a possible drug-related adverse reaction.

5. Laboratory Dose Confirmation Study Against Immature Adult *Toxocara canis*

Title: Dose Confirmation Laboratory Study of Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel and Pyrantel Pamoate Administered Orally for the Treatment and Control of Immature Adult *Toxocara canis* in Experimentally Infected Dogs. (Study No. ELA220842)

Study Dates: August 3, 2022 to June 26, 2023

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 immature adult *T. canis* in experimentally infected dogs.

Study Animals: Twenty beagle and mixed breed dogs (10 male and 10 female), 12 to 17.6 weeks of age, weighing between 4.6 to 8.4 kg.

Experimental Design: On Day -24, each dog was orally inoculated with approximately 300 infective *T. canis* larvated eggs. On Day -1, dogs were

randomized into treatment groups of ten dogs each using a completely randomized design. On Day 7 post-treatment, all dogs were humanely euthanized and necropsied for recovery and counting of *T. canis*. The study was conducted in accordance with GCP guidelines.

Table II.10. Study ELA220842; Treatment Groups

Treatment Group	Treatment	Minimum 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 (6M, 4F)

Drug Administration: On Day 0, the ten dogs in the Credelio Quattro™ group were administered one or more chewable tablets, at pyrantel doses as close as possible to 5 mg/kg without under-dosing. Pyrantel doses ranged from 5.2 to 7.3 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: The primary variable for effectiveness was the *T. canis* worm counts collected from the dogs. General health observations were conducted at least once 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 -30 and fecal egg count examinations were conducted on Day -29. Dogs were weighed on Days -30 and -1. Worm counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog. The log-transformed *T. canis* worm counts were analyzed using a linear mixed model with treatment group as a fixed effect. The treatment effect was tested at a two-sided 5% significance level. Percent effectiveness was calculated by using the geometric mean obtained through back-transformation of the LS mean estimated from the model.

Percent Effectiveness = 100 × (C-T)/C
Where C=Geometric mean number of worms in the control group.
T=Geometric mean number of worms in the treatment group.

Results: Six of the ten dogs in the control group had an adequate infection, defined as ≥5 *T. canis* worms present at necropsy.

Credelio Quattro™ was 100% effective against experimentally induced immature adult *T. canis* infections in dogs (Table II.11). Mean worm counts between the two groups were significantly different ($p<0.0001$).

Table II.11. Study ELA220842; Effectiveness Against Immature Adult *T. canis*

Treatment	Worm Counts: Range	Worm Counts: Geometric Mean	Percent Effectiveness
Control	0-43	6	NA
Credelio Quattro™	0	0	100%

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

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ for the treatment and control of immature adult *T. canis* in dogs when administered at the labeled dose.

6. Laboratory Dose Confirmation Study Against Adult *Toxocara canis*

Title: Dose Confirmation Laboratory Study of Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel and Pyrantel Pamoate when Administered Orally for the Treatment and Control of Adult *Toxocara canis* in Experimentally Infected Dogs. (Study No. ELA210278)

Study Dates: September 29, 2021 to October 5, 2022

Study Location: Rockwood, TN

Study Design:

Objective: Confirm the effectiveness of a single oral dose of Credelio Quattro™ for the treatment and control of adult *T. canis* in experimentally infected dogs.

Study Animals: Twenty beagle dogs (11 male and 9 female), 18.9 to 19.7 weeks of age, weighing between 5.2 to 7.6 kg.

Experimental Design: On Day -48, each dog was orally inoculated with approximately 300 infective *T. canis* larvated eggs. On Day -1, dogs were randomized into treatment groups of ten dogs each using a completely randomized design. On Day 10 post-treatment, all dogs were humanely euthanized and necropsied for recovery and counting of *T. canis*. The study was conducted in accordance with GCP guidelines.

Table II.12. Study ELA210278; Treatment Groups

Treatment Group	Treatment	Minimum 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 pyrantel doses as close as possible to 5 mg/kg without under-dosing. Pyrantel doses ranged from 5.6 to 7.6 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 *T. canis* worm counts collected from the dogs. General health observations were conducted at least once daily. Clinical observations were conducted prior to treatment and at approximately 1, 2, 4, and 8 hours after treatment. Physical examinations were conducted on Days -61 or -50. Fecal egg count examinations were performed on Days -2 and 10. Dogs were weighed on Days -61 or -50, and Day -1. Worm counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog. The log-transformed *T. canis* worm counts were analyzed using a linear mixed model with treatment group as a fixed effect. The treatment effect was tested at a two-sided 5% significance level. Percent effectiveness was calculated by using the geometric mean obtained through back-transformation of the LS mean estimated from the model.

Percent Effectiveness = 100 × (C-T)/C
Where C=Geometric mean number of worms in the control group.
T=Geometric mean number of worms in the treatment group.

Results: Seven of ten dogs in the control group had an adequate infection, defined as ≥5 *T. canis* worms present at necropsy.

Credelio Quattro™ was 97% effective against experimentally induced adult *T. canis* infections in dogs (Table II.13). Mean worm counts between the two groups were significantly different ($p<0.0001$).

Table II.13. Study ELA210278; Effectiveness Against Adult *T. canis*

Treatment	Worm Counts: Range	Worm Counts: Geometric Mean	Percent Effectiveness
Control	2-18	7.7	NA
Credelio Quattro™	0-1	0.2	97%

Adverse Reactions: One treated dog vomited within 8 hours of dosing. In the Credelio Quattro™ group, six dogs had feces with blood and/or mucus from 3 to 6 days post-dosing. In the control group, four dogs had feces with blood and/or mucus from 1 to 6 days of post-dosing.

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ for the treatment and control of adult *T. canis* in dogs. Vomiting and feces with blood and/or mucus are considered possible drug-related adverse reactions to Credelio Quattro™.

7. Laboratory Dose Confirmation Study Against Adult *Toxocara canis*

Title: Dose Confirmation Laboratory Efficacy Study using Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel and Pyrantel Pamoate Administered Orally to Dogs for the Treatment and Control of Adult *Toxocara canis* in Naturally Infected Dogs. (Study No. ELA210217)

Study Dates: October 19, 2022 to August 29, 2023

Study Location: Mohammedia, Morocco

Study Design:

Objective: Confirm the effectiveness of a single oral dose of Credelio Quattro™ for the treatment and control of adult *T. canis* in naturally infected dogs.

Study Animals: Twenty-seven mixed breed dogs (22 male and 5 female), 3 months to 10 years of age, weighing between 4.6 to 22.4 kg.

Experimental Design: Dogs positive for *T. canis, T. leonina,* or *U. stenocephala* infection by fecal egg count between Days -7 and -1 were included in studies ELA210217, ELA210219 (see below), and ELA220985 (see below), respectively, and were randomized into treatment groups using a randomized block design on Day -1. Dogs could be enrolled in one, two, or all three studies, depending on the parasite(s) present. Dogs were enrolled in cohorts in complete blocks of two dogs based on time of entry into the study. On Day 10 post-treatment, all dogs were humanely euthanized and necropsied for recovery and counting of *T. canis, T. leonina,* and *U. stenocephala*. This study was conducted in accordance with GCP guidelines.

Table II.14. Study ELA210217; Treatment Groups

Treatment Group	Treatment	Minimum Dose	Number and Sex of Dogs
1	Control	0 mg/kg	14 (11M, 3F)
2	Credelio Quattro™	20 mg/kg lotilaner + 0.02 mg/kg moxidectin + 5 mg/kg praziquantel + 5 mg/kg pyrantel (as pamoate salt)	13 (11M, 2F)

Drug Administration: On Day 0, the 13 dogs in the Credelio Quattro™ group were administered one or more chewable tablets, at pyrantel doses as close as possible to 5 mg/kg without under-dosing. Pyrantel doses ranged from 5.1 to 6.8 mg/kg per dog. The 14 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 *T. canis* worm counts collected from the dogs. General health observations were conducted at least once 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 -7. Fecal egg counts were performed three times between Days -7 and -1, and once on Day 10. Dogs were weighed on Day -1. Worm counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog. Dogs that were positive for *T. canis* at the start of the study were included in the statistical analysis for Study ELA210217 independent of their enrollment status in the other two studies (ELA210219 and ELA220985). The log-transformed *T. canis* worm counts were analyzed using a linear mixed model with treatment group as a fixed effect and cohort as a random effect. The treatment effect was tested at a two-sided 5% significance level. Percent effectiveness was calculated by using the geometric mean obtained through back-transformation of the LS mean estimated from the model.

Percent Effectiveness = 100 × (C-T)/C
Where C=Geometric mean number of worms in the control group.
T=Geometric mean number of worms in the treatment group.

Results: Seven of the 14 dogs in the control group had an adequate infection, defined as ≥5 *T. canis* worms present at necropsy.

Credelio Quattro™ was 99% effective against natural adult *T. canis* infections in dogs (Table II.15). Mean worm counts between the two groups were significantly different ($p<0.0001$).

Table II.15. Study ELA210217; Effectiveness Against Adult *T. canis*

Treatment	Worm Counts: Range	Worm Counts: Geometric Mean	Percent Effectiveness
Control	0-36	4.31	NA
Credelio Quattro™	0	0.04*	99%

*No worms were recovered from any of the Credelio Quattro™ group dogs; however, due to cohort-to-cohort variability in the control group, the model estimates affected the overall geometric mean of both groups.

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

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ for the treatment and control of adult *T. canis* in dogs.

8. Laboratory Dose Confirmation Study Against Adult *Toxascaris leonina*

Title: Dose Confirmation Laboratory Study of Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel and Pyrantel Pamoate when Administered Orally for the Treatment and Control of Adult *Toxascaris leonina* in Experimentally Infected Dogs. (Study No. ELA210701)

Study Dates: April 3, 2023 to August 22, 2023

Study Location: Rockwood, TN

Study Design:

Objective: Confirm the effectiveness of a single oral dose of Credelio Quattro™ for the treatment and control of adult *T. leonina* in experimentally infected dogs.

Study Animals: Twenty beagle dogs (14 male and 6 female), approximately 5 months of age, weighing between 4.3 to 5.9 kg.

Experimental Design: On Day -63, each dog was orally inoculated with approximately 500 infective *T. leonina* eggs. On Day -1, dogs were randomized into treatment groups of ten dogs each using a completely randomized design. On Day 10 post-treatment, all dogs were humanely euthanized and necropsied for recovery and counting of *T. leonina*. The study was conducted in accordance with GCP guidelines.

Table II.16. Study ELA210701; Treatment Groups

Treatment Group	Treatment	Minimum Dose	Number and Sex of Dogs
1	Control	0 mg/kg	10 (7M, 3F)
2	Credelio Quattro™	20 mg/kg lotilaner + 0.02 mg/kg moxidectin + 5 mg/kg praziquantel + 5 mg/kg pyrantel (as pamoate salt)	10 (7M, 3F)

Drug Administration: On Day 0, the ten dogs in the Credelio Quattro™ group were administered one or more chewable tablets, at pyrantel doses as close as possible to 5 mg/kg without under-dosing. Pyrantel doses ranged from 5.2 to 7.3 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: The primary variable for effectiveness was the *T. leonina* worm counts collected from the dogs. General health observations were conducted at least once daily. Clinical observations were conducted prior to treatment and at 1, 2, 4, and 8 hours after treatment. Physical examinations and fecal examinations were conducted on Day -67. Fecal egg counts were conducted on Days -16, -9, -4, -2, -1, and 10. Dogs were weighed on Days -67 and -1. Worm counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog. The log-transformed *T. leonina* worm counts were analyzed using a linear mixed model with treatment group as a fixed effect. The treatment effect was tested at a two-sided 5% significance level. Percent effectiveness was calculated by using the geometric mean obtained through back-transformation of the LS mean estimated from the model.

Percent Effectiveness = 100 × (C-T)/C
Where C=Geometric mean number of worms in the control group.
T=Geometric mean number of worms in the treatment group.

Results: Nine of the ten dogs in the control group had an adequate infection, defined as ≥5 *T. leonina* worms present at necropsy.

Credelio Quattro™ was 100% effective against experimentally induced adult *T. leonina* infections in dogs (Table II.17). Mean worm counts between the two groups were significantly different ($p<0.0001$).

Table II.17. Study ELA210701; Effectiveness Against Adult *T. leonina*

Treatment	Worm Counts: Range	Worm Counts: Geometric Mean	Percent Effectiveness
Control	4-62	17.2	NA
Credelio Quattro™	0	0	100%

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

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ for the treatment and control of adult *T. leonina* in dogs.

9. Laboratory Dose Confirmation Study Against Adult *Toxascaris leonina*

Title: Dose Confirmation Laboratory Efficacy Study using Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel and Pyrantel Pamoate Administered Orally to Dogs for the Treatment and Control of Adult *Toxascaris leonina* in Naturally Infected Dogs. (Study No. ELA210219)

Study Dates: October 19, 2022 to August 29, 2023

Study Location: Mohammedia, Morocco

Study Design:

Objective: Confirm the effectiveness of a single oral dose of Credelio Quattro™ for the treatment and control of adult *T. leonina* in naturally infected dogs.

Study Animals: Twenty-two mixed breed dogs (11 male and 11 female), 4 months to 10 years of age, weighing between 6.5 to 20.8 kg.

Experimental Design: Dogs positive for *T. canis, T. leonina,* or *U. stenocephala* infection by fecal egg count between Days -7 and -1 were included in studies ELA210217 (see above), ELA210219, and ELA220985 (see below), respectively, and were randomized into treatment groups using a randomized block design on Day -1. Dogs could be enrolled in one, two, or all three studies, depending on the parasite(s) present. Dogs were enrolled in cohorts in complete blocks of two dogs based on time of entry into the study. On Day 10 post-treatment, all dogs were humanely euthanized and necropsied for recovery and counting of *T. canis, T. leonina,* and *U. stenocephala*. This study was conducted in accordance with GCP guidelines.

Table II.18. Study ELA210219; Treatment Groups

Treatment Group	Treatment	Minimum Dose	Number and Sex of Dogs
1	Control	0 mg/kg	12 (6M, 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 (5M, 5F)

Drug Administration: On Day 0, the ten dogs in the Credelio Quattro™ group were administered one or more chewable tablets, at pyrantel doses as close as possible to 5 mg/kg without under-dosing. Pyrantel doses ranged from 5.1 to 6.8 mg/kg per dog. The 12 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 *T. leonina* worm counts collected from the dogs. General health observations were conducted at least once 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 -7. Fecal egg counts were performed three times between Days -7 and -1, and once on Day 10. Dogs were weighed on Day -1. Worm counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog. Dogs that were positive for *T. leonina* at the start of the study were included in the statistical analysis for Study ELA210219 independent of their enrollment status in the other two studies (ELA210217 and ELA220985). The log-transformed *T. leonina* worm counts were analyzed using a linear mixed model with treatment group as a fixed effect and cohort as a random effect. The treatment effect was tested at a two-sided 5% significance level. Percent effectiveness was calculated by using the geometric mean obtained through back-transformation of the LS mean estimated from the model.

Percent Effectiveness = 100 × (C-T)/C
Where C=Geometric mean number of worms in the control group.
T=Geometric mean number of worms in the treatment group.

Results: Nine of the 12 dogs in the control group had an adequate infection, defined as ≥5 *T. leonina* worms present at necropsy.

Credelio Quattro™ was 100% effective against natural adult *T. leonina* infections in dogs (Table II.19). Mean worm counts between the two groups were significantly different ($p<0.0001$).

Table II.19. Study ELA210219; Effectiveness Against Adult *T. leonina*

Treatment	Worm Counts: Range	Worm Counts: Geometric Mean	Percent Effectiveness
Control	0-18	5.7	NA
Credelio Quattro™	0	0	100%

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

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ for the treatment and control of adult *T. leonina* in dogs.

10. Laboratory Dose Confirmation Study Against Adult *Uncinaria stenocephala*

Title: Dose Confirmation Laboratory Study of Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel and Pyrantel Pamoate when Administered Orally for the Treatment and Control of Adult *Uncinaria stenocephala* in Experimentally Infected Dogs. (Study No. ELA220819)

Study Dates: June 22, 2022 to May 2, 2023

Study Location: Rockwood, TN

Study Design:

Objective: Confirm the effectiveness of a single oral dose of Credelio Quattro™ for the treatment and control of adult *U. stenocephala* in experimentally infected dogs.

Study Animals: Twenty beagle dogs (9 male and 11 female), 18.1 to 19.1 weeks of age, weighing between 5.4 to 7.6 kg.

Experimental Design: On Day -28, each dog was orally inoculated with approximately 1,000 infective *U. stenocephala* larvae. On Day -1, dogs were randomized into treatment groups of ten dogs each using a completely randomized design. On Day 10 post-treatment, all dogs were humanely euthanized and necropsied for recovery and counting of *U. stenocephala*. The study was conducted in accordance with GCP guidelines.

Table II.20. Study ELA220819; Treatment Groups

Treatment Group	Treatment	Minimum 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 (5M, 5F)

Drug Administration: On Day 0, the ten dogs in the Credelio Quattro™ group were administered one or more chewable tablets, at pyrantel doses as close as possible to 5 mg/kg without under-dosing. Pyrantel doses ranged from 5.3 to 7.4 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 *U. stenocephala* worm counts collected from the dogs. General health observations were conducted at least once daily. Clinical observations were conducted prior to treatment and at 1, 2, 4, and 8 hours after treatment. Physical examinations were conducted on Day -32 and fecal examinations were conducted on Day -31. Fecal egg counts were conducted on Days -4, -2, -1, and 10. Dogs were weighed on Days -32 and -1. Worm counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog. The log-transformed *U. stenocephala* worm counts were analyzed using a linear mixed model with treatment group as a fixed effect. The treatment effect was tested at a two-sided 5% significance level. Percent effectiveness was calculated by using the geometric mean obtained through back-transformation of LS mean estimated from the model.

Percent Effectiveness = 100 × (C-T)/C
Where C=Geometric mean number of worms in the control group.
T=Geometric mean number of worms in the treatment group.

Results: All ten dogs in the control group had an adequate infection, defined as ≥5 *U. stenocephala* worms present at necropsy.

Credelio Quattro™ was 99.6% effective against experimentally induced adult *U. stenocephala* infections in dogs (Table II.21). Mean worm counts between the two groups were significantly different ($p<0.0001$).

Table II.21. Study ELA220819; Effectiveness Against Adult *U. stenocephala*

Treatment	Worm Counts: Range	Worm Counts: Geometric Mean	Percent Effectiveness
Control	289-578	478.5	NA
Credelio Quattro™	0-8	1.8	99.6%

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

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ for the treatment and control of adult *U. stenocephala* in dogs.

11. Laboratory Dose Confirmation Study Against Adult *Uncinaria stenocephala*

Title: Dose Confirmation Laboratory Efficacy Study using Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel and Pyrantel Pamoate Administered Orally to Dogs for the Treatment and Control of Adult *Uncinaria stenocephala* in Naturally Infected Dogs. (Study No. ELA220985)

Study Dates: October 19, 2022 to August 29, 2023

Study Location: Mohammedia, Morocco

Study Design:

Objective: Confirm the effectiveness of a single oral dose of Credelio Quattro™ for the treatment and control of adult *U. stenocephala* in naturally infected dogs.

Study Animals: Thirty-one mixed breed dogs (18 male and 13 female), 3 months to 10 years of age, weighing between 9 to 22.4 kg.

Experimental Design: Dogs positive for *T. canis, T. leonina,* or *U. stenocephala* infection by fecal egg count between Days -7 and -1 were included in studies ELA210217 (see above), ELA210219 (see above), and ELA220985, respectively, and were randomized into treatment groups using a randomized block design on Day 1. Dogs could be enrolled in one, two, or all three studies, depending on the parasite(s) present. Dogs were enrolled in cohorts in complete blocks of two dogs based on time of entry into the study. On Day 10 post-treatment, all dogs were humanely euthanized and necropsied for recovery and counting of *T. canis, T. leonina,* and *U. stenocephala*. This study was conducted in accordance with GCP guidelines.

Table II.22. Study ELA220985; Treatment Groups

Treatment Group	Treatment	Minimum Dose	Number and Sex of Dogs
1	Control	0 mg/kg	13 (8M, 5F)
2	Credelio Quattro™	20 mg/kg lotilaner + 0.02 mg/kg moxidectin + 5 mg/kg praziquantel + 5 mg/kg pyrantel (as pamoate salt)	18 (10M, 8F)

Drug Administration: On Day 0, the 18 dogs in the Credelio Quattro™ group were administered one or more chewable tablets, at pyrantel doses as close as possible to 5 mg/kg without under-dosing. Pyrantel doses ranged from 5.1 to 6.8 mg/kg per dog. The 13 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 *U. stenocephala* worm counts collected from the dogs. General health observations were conducted at least once 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 -7 except one dog on Day -6. Fecal egg counts were performed three times between Days -7 and -1, and once on Day 10. Dogs were weighed on Day -1. Worm counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog. Dogs that were positive for *U. stenocephala* at the start of the study were included in the statistical analysis for Study ELA220985 independent of their enrollment status in the other two studies (ELA210217 and ELA210219). The log-transformed *U. stenocephala* worm counts were analyzed using a linear mixed model with treatment group as a fixed effect and cohort as a random effect. The treatment effect was tested at a two-sided 5% significance level. Percent effectiveness was calculated by using the geometric mean obtained through back-transformation of the LS mean estimated from the model.

Percent Effectiveness = 100 × (C-T)/C
Where C=Geometric mean number of worms in the control group.
T=Geometric mean number of worms in the treatment group.

Results: Nine of the 13 dogs in the control group had an adequate infection, defined as ≥5 *U. stenocephala* worms present at necropsy.

Credelio Quattro™ was 100% effective against natural adult *U. stenocephala* infections in dogs (Table II.23). Mean worm counts between the two groups were significantly different ($p<0.0001$).

Table II.23. Study ELA220985; Effectiveness Against Adult *U. stenocephala*

Treatment	Worm Counts: Range	Worm Counts: Geometric Mean	Percent Effectiveness
Control	0–263	7.3	NA
Credelio Quattro™	0	0	100%

Adverse Reactions: One dog treated with Credelio Quattro™ had diarrhea 5.5 hours after administration on Day 0, which resolved without treatment.

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ for the treatment and control of adult *U. stenocephala* in dogs. Self-limiting diarrhea is considered a possible drug-related adverse reaction.

Gastrointestinal Cestode Indications:

The sponsor owns data to support substantial evidence of effectiveness of a minimum oral praziquantel dose of 5 mg/kg for the removal of *Dipylidium caninum*, *Taenia pisiformis*, and *Echinococcus granulosus* and the removal and control of *Echinococcus multilocularis* in the original and supplemental approvals of Droncit™ (praziquantel) Canine Cestocide Tablets (NADA 111-798) dated January 23, 1990, and July 16, 1993. The data in the supplemental approvals for Droncit™ Canine Cestocide Tablets demonstrated that praziquantel was 100% effective against *Dipylidium caninum*, *Taenia pisiformis*, *Echinococcus granulosus*, and *Echinococcus multilocularis.* Although the studies to support the approval of Droncit™ demonstrated that praziquantel was 100% effective against *E. multilocularis*, one of three studies conducted with two formulations containing minimum doses of 20 mg/kg lotilaner, 0.02 mg/kg moxidectin, and 5 mg/kg praziquantel, with or without pyrantel at doses of 5 mg/kg, failed to demonstrate adequate effectiveness against *E. multilocularis*. Therefore, the sponsor conducted two dose confirmation studies to demonstrate effectiveness for *Echinococcus granulosus* only as the representative species to demonstrate that Credelio Quattro™ is effective for the treatment and control of *Dipylidium caninum*, *Taenia pisiformis*, and *Echinococcus granulosus*.

Evidence demonstrating that moxidectin and pyrantel consistently lack effectiveness against gastrointestinal cestodes has been established.[3,4,5] One of the two *E. granulosus* dose confirmation studies (Study No. ELA210571) included a treatment group administered lotilaner alone, which failed to demonstrate effectiveness against *E. granulosus.* Therefore, because Credelio Quattro™ was effective against *E. granulosus* infections, and lotilaner, moxidectin, and pyrantel failed to demonstrate effectiveness, praziquantel was established as the active ingredient responsible for the effectiveness of Credelio Quattro™ for the treatment and control of *E. granulosus* infections.

For the Treatment and Control of Cestode Infections:

12. Laboratory Dose Confirmation Study Against *Echinococcus granulosus*

Title: Dose Confirmation Laboratory Efficacy Study Using Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel and Pyrantel Pamoate Administered Orally to Dogs for the Treatment and Control of *Echinococcus granulosus* in Experimentally Infected Dogs. (Study No. ELA210218)

Study Dates: October 28, 2021 to October 16, 2022

Study Location: Stanwood, MI

Study Design:

Objective: Confirm the effectiveness of a single oral dose of Credelio Quattro™ for the treatment and control of *E. granulosus* in experimentally infected dogs.

Study Animals: Sixteen beagle dogs (9 male and 7 female), 7 to 10 months of age, weighing between 7.6 to 11.9 kg.

Experimental Design: On Day -28, each dog was orally inoculated with approximately 10,000 infective *E. granulosus* protoscolices. On Day -1, dogs were randomized into treatment groups of eight dogs each using a completely randomized design. On Day 5 post-treatment, all dogs were humanely euthanized and necropsied for recovery and counting of *E. granulosus*. The study was conducted in accordance with GCP guidelines.

[3] Kopp et al (2008). Pyrantel in small animal medicine: 30 years on. *Vet J*, 178: 177-184
[4] Papich M (2016). Saunders Handbook of Veterinary Drugs (Fourth Edition). Moxidectin, 545-548. W.B. Saunders.
[5] Howes and Lynch (1967). Anthelmintic Studies with Pyrantel. I. Therapeutic and prophylactic efficacy against the enteral stages of various helminths in mice and dogs. *J Parasitol*. 53(5):1085-1091.

Table II.24. Study ELA210218; Treatment Groups

Treatment Group	Treatment	Minimum Dose	Number and Sex of Dogs
1	Control	0 mg/kg	8 (4M, 4F)
2	Credelio Quattro™	20 mg/kg lotilaner + 0.02 mg/kg moxidectin + 5 mg/kg praziquantel + 5 mg/kg pyrantel (as pamoate salt)	8 (5M, 3F)

Drug Administration: On Day 0, the eight dogs in the Credelio Quattro™ group were administered one or more chewable tablets, at praziquantel doses as close as possible to 5 mg/kg without under-dosing. Praziquantel doses ranged from 5.1 to 6 mg/kg per dog. The eight 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 *E. granulosus* worm counts collected from the dogs. General health observations were conducted at least once 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 -34. Dogs were weighed on Days -34 and -1. Worm counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog. The log-transformed *E. granulosus* worm counts were analyzed using a linear mixed model with treatment group as a fixed effect. The treatment effect was tested at a two-sided 5% significance level. Percent effectiveness was calculated by using the geometric mean obtained through back-transformation of the LS mean estimated from the model.

Percent Effectiveness = 100 × (C-T)/C
Where C=Geometric mean number of worms in the control group.
T=Geometric mean number of worms in the treatment group.

Results: All eight dogs in the control group had an adequate infection, defined as ≥5 *E. granulosus* tapeworms present at necropsy.

Credelio Quattro™ was 100% effective against experimentally induced *E. granulosus* infections in dogs (Table II.25). Mean worm counts between the two groups were significant different ($p<0.0001$).

Table II.25. Study ELA210218; Effectiveness Against *E. granulosus*

Treatment	Worm Counts: Range	Worm Counts: Geometric Mean	Percent Effectiveness
Control	930-2,530	1,543	NA
Credelio Quattro™	0	0	100%

Adverse Reactions: One dog treated with Credelio Quattro™ had diarrhea one hour after administration on Day 0, which resolved without treatment.

Conclusions: This study demonstrated the effectiveness of Credelio Quattro™ for the treatment and control of *E. granulosus* in dogs. Self-limiting diarrhea is considered a possible drug-related adverse reaction.

13. Laboratory Dose Confirmation and Study Against *Echinococcus granulosus*

Title: Non-Interference Dose Confirmation Efficacy Laboratory Study Using Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel and Pyrantel Pamoate Administered Orally to Dogs for the Treatment and Control of *Echinococcus granulosus* in Experimentally Infected Dogs. (Study No. ELA210571)

Study Dates: November 11, 2021 to December 6, 2022

Study Location: Stanwood, MI

Study Design:

Objective: Confirm the effectiveness of a single oral dose of Credelio Quattro™ for the treatment and control of *E. granulosus* in experimentally infected dogs and demonstrate the inclusion of praziquantel in the combination contributes to the effectiveness of Credelio Quattro™ against *E. granulosus*.

Study Animals: Twenty-four beagle dogs (12 male and 12 female), 7 to 8 months of age, weighing between 6.5 to 10.7 kg.

Experimental Design: On Day -28, each dog was orally inoculated with approximately 10,000 infective *E. granulosus* protoscolices. On Day -1, dogs were randomized into treatment groups of eight dogs each using a completely randomized design. On Day 5 post-treatment, all dogs were humanely euthanized and necropsied for recovery and counting of *E. granulosus*. The study was conducted in accordance with GCP guidelines.

Table II.26. Study ELA210571; Treatment Groups

Treatment Group	Treatment	Minimum Dose	Number and Sex of Dogs
1	Control	0 mg/kg	8 (4M, 4F)
2	Credelio Quattro™	20 mg/kg lotilaner + 0.02 mg/kg moxidectin + 5 mg/kg praziquantel + 5 mg/kg pyrantel (as pamoate salt)	8 (3M, 5F)
3	Lotilaner	20 mg/kg	8 (5M, 3F)

Drug Administration: On Day 0, the eight dogs in the Credelio Quattro™ group were administered one or more chewable tablets, at praziquantel doses as close as possible to 5 mg/kg without under-dosing. Praziquantel doses ranged from 5.4 to 6.4 mg/kg per dog. Dogs in the lotilaner only group received doses ranging from 21.4 to 24.7 mg/kg per dog. The eight 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 *E. granulosus* worm counts collected from the dogs. General health observations were conducted at least once 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 -31. Dogs were weighed on Days -31 and -1. Worm counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog. The log-transformed *E. granulosus* worm counts were analyzed using a linear mixed model with treatment group as a fixed effect. Separate models were used for each treated group compared to the control group. The treatment effect was tested at a two-sided 5% significance level. Percent effectiveness was calculated by using the geometric mean obtained through back-transformation of the LS mean estimated from the model.

Percent Effectiveness = 100 × (C-T)/C
Where C=Geometric mean number of worms in the control group.
T=Geometric mean number of worms in the treatment group.

Contribution of praziquantel to the effectiveness of the combination new animal drug was demonstrated if treatment with lotilaner was less than 100% effective against *E. granulosus* while the treatment with Credelio Quattro™ was 100% effective.

Results: All eight dogs in the control group had an adequate infection, defined as ≥5 *E. granulosus* tapeworms present at necropsy.

Credelio Quattro™ was 100% effective against experimentally induced *E. granulosus* infections in dogs (Table II.27). Mean worm counts between the control group and the Credelio Quattro™ group were significantly different ($p<0.0001$). There was no significant difference ($p=0.2269$) in worm counts between the lotilaner and control groups.

Table II.27. Study ELA210571; Effectiveness Against *E. granulosus*

Treatment	Worm Counts: Range	Worm Counts: Geometric Mean	Percent Effectiveness
Control	1,210-3,830	2,118	NA
Credelio Quattro™	0	0	100%
Lotilaner	500-3,910	1,492	29.6%

Adverse Reactions: One dog treated with lotilaner only had diarrhea one hour after administration on Day 0, which resolved without treatment.

Conclusions: This study demonstrated the effectiveness of Credelio Quattro™ for the treatment and control of *E. granulosus* in dogs. Treatment with lotilaner alone was not effective against *E. granulosus*, demonstrating the inclusion of praziquantel in the combination is necessary for effectiveness of Credelio Quattro™ against *E. granulosus*. Because lotilaner is a component of Credelio Quattro™, self-limiting diarrhea is considered a possible drug-related adverse reaction to Credelio Quattro™.

Flea and Tick Indications:

The sponsor conducted one dose confirmation study to demonstrate substantial evidence of effectiveness of Credelio Quattro™ for the treatment and prevention of flea infestations (*Ctenocephalides felis*).

The sponsor owns the data to support substantial evidence of effectiveness of a minimum lotilaner dose of 20 mg/kg given orally once a month for 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 the original approval of Credelio™ (lotilaner) Chewable Tablets (NADA 141-494) dated January 19, 2018. The data in the original approval for Credelio™ (lotilaner) Chewable Tablets identified *Rhipicephalus sanguineus* as the overall least susceptible tick to lotilaner. Therefore, the sponsor conducted two dose confirmation studies to demonstrate effectiveness for *Rhipicephalus sanguineus* only as the representative species to demonstrate that Credelio Quattro™ is effective for the treatment and control of *Amblyomma americanum*, *Dermacentor variabilis*, *Ixodes scapularis,* and *Rhipicephalus sanguineus*.

An *in vitro* study (Study No. ELA3388162) demonstrated that praziquantel has no activity against *C. felis* and *R. sanguineus*. In two *in vivo* studies (Study No. ELA1900470 and Study No. ELA1900474) moxidectin failed to demonstrate effectiveness against *C. felis* and *R. sanguineus*. Data from published literature[6] also demonstrated that moxidectin and pyrantel pamoate each consistently failed to demonstrate effectiveness against *C. felis*. One of the two *R. sanguineus* dose confirmation studies (Study No. ELA210285) included a treatment group administered pyrantel (as pamoate salt) alone, which failed to demonstrate effectiveness against *R. sanguineus*. Therefore, because Credelio Quattro™ was effective against *C. felis* and *R. sanguineus* infestations, and moxidectin, praziquantel, and pyrantel failed to demonstrate effectiveness, lotilaner was established as the active ingredient responsible for the effectiveness of Credelio Quattro™ for the treatment and prevention of flea infestations (*C. felis*) and the treatment and control of tick infestations (*R. sanguineus*).

[6] Kryda, et al (2020). Laboratory studies evaluating the efficacy of a novel orally administered combination product containing sarolaner, moxidectin, and pyrantel for the treatment and control of flea infestations on dogs. Parasites and Vectors, 13, 57.

For the Treatment and Prevention of Flea Infestations:

14. Laboratory Dose Confirmation Study (24 hours) Against *Ctenocephalides felis*

Title: Dose Confirmation Laboratory Study of Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel and Pyrantel Pamoate Administered Orally in Dogs Experimentally Infested with Fleas (*Ctenocephalides felis*). (Study No. ELA220912)

Study Dates: March 29, 2022 to September 19, 2022

Study Location: Athens, GA

Study Design:

Objective: Confirm the effectiveness of a single oral dose of Credelio Quattro™ for the treatment of adult *C. felis* infestations on dogs at 24 hours after treatment or experimental infestation for 36 days.

Study Animals: Twenty beagle dogs (10 male and 10 female), 11 months of age, weighing between 5.5 to 9.4 kg.

Experimental Design: Prior to allocation to treatment groups on Day -5, an initial flea infestation and count was conducted to evaluate susceptibility of each dog to experimental infestation (host suitability). Dogs were ranked by live flea count and randomly allocated within blocks to two groups. Flea infestations were conducted on Days -1, 6, 13, 20, 29, and 35. At each infestation, each dog was infested with approximately 100 unfed, adult *C. felis* fleas.

Flea counts were performed at 24 hours after drug administration or flea infestation. Fleas were not returned to the dog after counting. The study was conducted in accordance with GCP guidelines.

Table II.28. Study ELA220912; Treatment Groups

Treatment Group	Treatment	Minimum 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 (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 20.3 to 27.7 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 live flea counts collected from the dogs. At each flea count, the fleas were removed, and the numbers of live fleas were counted. 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 -9. Dogs were weighed on Day -5. Flea counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog. 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 flea counts for the control group and T=the LS mean of live flea counts for the treated group. The comparisons were tested using the two-sided 5% significance level. Untransformed live flea counts were compared at each time point using mixed linear models, including treatment as a fixed effect and block as a random effect.

Results: At each flea count, a minimum of six dogs in the control group had an adequate flea infestation, defined as a retention rate of at least 50% (i.e., ≥50 live fleas). Credelio Quattro™ was 100% effective at 24 hours post-treatment or infestation through Day 36 (Table II.29). On all flea count days following drug administration, mean live flea counts between the two groups were significantly different ($p<0.0001$).

Table II.29. Study ELA220912; Effectiveness Against *C. felis* at 24 hours After Infestation

Days After Treatment	Control Group LS Mean	Credelio Quattro™ Group LS Mean	Percent Effectiveness
1	89.8	0	100%
7	93.9	0	100%
14	90.1	0	100%
21	85.9	0	100%
30	79.7	0	100%
36	83.2	0	100%

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

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ for the treatment of existing flea infestations for 36 days when assessed 24 hours after drug administration or infestation.

For the Treatment and Control of Tick Infestations:

15. Laboratory Dose Confirmation Study Against *Rhipicephalus sanguineus*

Title: Non-Interference Dose Confirmation Laboratory Study of Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel and Pyrantel Pamoate Administered Orally for the Treatment and Control of *Rhipicephalus sanguineus* in Experimentally Infested Dogs. (Study No. ELA210285)

Study Dates: December 2, 2021 to August 16, 2022

Study Location: Greenbrier, AR

Study Design:

Objective: Confirm the effectiveness of a single oral dose of Credelio Quattro™ for the treatment and control of adult *R. sanguineus* infestations on dogs at 48 hours after treatment or experimental infestation for 32 days and demonstrate the inclusion of lotilaner in the combination contributes to the effectiveness of Credelio Quattro™ against *R. sanguineus*.

Study Animals: Thirty mixed breed and beagle dogs (15 male and 15 female), approximately 11 months to 8 years of age, weighing between 6.7 to 12.7 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 three groups. Tick infestations were conducted on Days -2, 5, 12, 19, and 30. At each infestation, each dog was infested with approximately 50±5 unfed, adult *R. sanguineus* ticks.

Tick counts were performed at 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.30. Study ELA210285; Treatment Groups

Treatment Group	Treatment	Minimum Dose	Number and Sex of Dogs
1	Control	0 mg/kg	10 (7M, 3F)
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)
3	Pyrantel (as pamoate salt)	5 mg/kg	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 20.3 to 24.9 mg/kg per dog. Dogs in the pyrantel only group received doses ranging from 5.2 to 6.1 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 *R. sanguineus* 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 -14. 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 groups with respect to the control groups 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 groups.

On each tick count day, untransformed live tick counts were analyzed using linear mixed models, including treatment as a fixed effect and block nested within room and room as random effects. Separate models were used for each treated group compared to the control group. 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 groups compared to the control group. Effectiveness for the treatment indication was determined on the basis of a numerically higher value of the arithmetic mean of dead ticks in the treated groups compared to the control group.

Contribution of lotilaner to the effectiveness of the combination new animal drug was demonstrated if treatment with pyrantel was less than 90% effective against *R. sanguineus* while the treatment with Credelio Quattro™ was ≥90% effective.

Results: At each tick count, 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 ≥97.1% reduction in live tick counts at 48 hours (Table II.31) 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 ($p \leq 0.0007$).

The pyrantel group was less than 90% effective against *R. sanguineus* ticks at 48 hours following drug administration or infestation through Day 32. On all count days following drug administration, live tick counts between the pyrantel and control group were not significantly different (p≥0.0601).

The Credelio Quattro™ and pyrantel groups had increased numbers of dead ticks compared to the control group 48 hours (Table II.32) following treatment or infestation through Day 32. On all count days following drug administration, mean dead tick counts between Credelio Quattro™ and the control group were significantly different (p≤0.0107). On all count days following drug administration, mean dead tick counts between the pyrantel and control groups were not significantly different (p≥0.0726).

Table II.31. Study ELA210285; *R. sanguineus* Live Tick Counts 48 Hours After Administration or Infestation (Percent Effectiveness)

Days After Treatment	Control Group LS Mean	Credelio Quattro™ Group LS Mean	Pyrantel Group LS Mean
2	20.4	0.1 (99.5%)	19.9 (2.5%)
7	20.4	0.1 (99.5%)	10.9 (46.6%)
14	21.2	0.2 (99.1%)	13.7 (35.4%)
21	21.8	0.1 (99.5%)	18.6 (14.7%)
32	24.4	0.7 (97.1%)	15.7 (35.7%)

Table II.32. Study ELA210285; *R. sanguineus* Dead Tick Counts 48 Hours After Administration or Infestation

Days After Treatment	Control Group AM* Mean	Credelio Quattro™ Group AM* Mean	Pyrantel Group AM* Mean
2	3.3	21.4	4.1
7	7.6	20.3	9
14	10.5	22.6	14.1
21	8.6	25.1	10.4
32	4	22.2	8.8

*AM=arithmetic mean

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 *R. sanguineus* ticks for 32 days when assessed 48 hours after drug administration or infestation. Treatment with pyrantel alone was not effective against *R. sanguineus*, demonstrating the inclusion of lotilaner in the combination is necessary for effectiveness of Credelio Quattro™ against *R. sanguineus*.

16. Laboratory Dose Confirmation Study Against *Rhipicephalus sanguineus* Ticks

Title: Dose Confirmation Laboratory Study of Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel and Pyrantel Pamoate Administered Orally for the Treatment and Control of *Rhipicephalus sanguineus* in Experimentally Infested Dogs. (Study No. ELA220892)

Study Dates: March 17, 2022 to September 22, 2022

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 *R. sanguineus* infestations on dogs at 48 hours after treatment or experimental infestation for 32 days.

Study Animals: Twenty beagle dogs (7 male and 13 female), approximately 14 to 26 months of age, weighing between 6.3 to 12.3 kg.

Experimental Design: Prior to allocation to treatment groups on Day -3, an initial tick infestation and count was conducted to evaluate susceptibility of each dog to experimental infestation (host suitability). Dogs were ranked by live tick count and randomly allocated within blocks to two groups. Tick infestations were conducted on Days -2, 5, 12, 19, and 30. At each infestation, each dog was infested with approximately 50±5 unfed, adult *R. sanguineus* ticks.

Tick counts were performed at 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.33. Study ELA220892; Treatment Groups

Treatment Group	Treatment	Minimum 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 (3M, 7F)

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 21.9 to 25.2 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 *R. sanguineus* 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 -8. 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 groups with respect to the control groups 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 groups.

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 arithmetic mean of dead ticks in the treated group compared to the control group.

Results: At each tick count, 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 99.7% reduction in live tick counts at 48 hours (Table II.34) 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 ($p<0.0001$).

The Credelio Quattro™ group had increased numbers of dead ticks compared to the control group 48 hours (Table II.35) following treatment or infestation through Day 32. On all count days following drug administration, mean dead tick counts between Credelio Quattro™ group and the control group were significantly different ($p\leq0.0015$).

Table II.34. Study ELA220892; *R. sanguineus* 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	34	0.1	99.7%
7	31.8	0	100%
14	26.5	0	100%
21	23.6	0	100%
32	24.7	0	100%

Table II.35. Study ELA220892; *R. sanguineus* Dead Tick Counts 48 Hours After Administration or Infestation

Days After Treatment	Control Group AM* Mean	Credelio Quattro™ Group AM* Mean
2	1.9	16.2
7	0.3	28.9
14	0.3	6.8
21	0.3	18.5
32	1.2	18.2

*AM=arithmetic mean

Adverse Reactions: One dog vomited once, 3 days post-treatment with Credelio Quattro™, and had subsequent bloody diarrhea for 3 days. The dog fully recovered.

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ for the control (reduced live ticks) and treatment (increased dead ticks) of *R. sanguineus* ticks for 32 days when assessed 48 hours after drug administration or infestation. Vomiting and bloody diarrhea are considered possible drug-related adverse reactions.

III. TARGET ANIMAL SAFETY

A. Margin of Safety Study

Title: A Good Laboratory Practice (GLP) Margin of Safety Study of Lotilaner, Moxidectin, Praziquantel, and Pyrantel Co-Administered Orally to 8-Week-Old Beagle Dogs. (Study No. ELA210202)

Study Dates: August 24, 2021 to August 22, 2023

Study Location: Mattawan, MI

Study Design:

Objective: Evaluate the safety of Credelio Quattro™ following oral administration at one (1X), three (3X), and five times (5X) the maximum labeled dose administered nine times, once every 28 days, to beagle dogs starting approximately 8 weeks of age.

Study Animals: Thirty-two beagle dogs (16 male and 16 female), 7.9 to 8.4 weeks of age, weighing between 2 kg to 2.9 kg.

Experimental Design: Dogs were randomized to one of four groups (0X, 1X, 3X, and 5X) of eight dogs per group (four per sex). From Days 1 to 27, dogs were pair housed by treatment group and sex. On Day 0, dogs were separated prior to moist food offering and not re-paired until 24 hours post-dosing for post-dose observations. On Day 28 and for the remainder of the study, the dogs were individually housed. The study was conducted in accordance with GLP regulations.

Table III.1. Study ELA210202; Treatment Groups

Treatment Group	Treatment	Maximum Dose	Treatment Days	Number and Sex of Dogs
1 (0X)	Control	0 mg/kg	Day 0, 28, 56, 84, 112, 140, 168, 196, 224	8 (4M, 4F)
2 (1X)	Credelio Quattro™	40 mg/kg lotilaner + 0.04 mg/kg moxidectin + 10 mg/kg praziquantel + 10 mg/kg pyrantel (as pamoate salt)	Day 0, 28, 56, 84, 112, 140, 168, 196, 224	8 (4M, 4F)
3 (3X)	Credelio Quattro™	120 mg/kg lotilaner + 0.12 mg/kg moxidectin + 30 mg/kg praziquantel + 30 mg/kg pyrantel (as pamoate salt)	Day 0, 28, 56, 84, 112, 140, 168, 196, 224	8 (4M, 4F)
4 (5X)	Credelio Quattro™	200 mg/kg lotilaner + 0.20 mg/kg moxidectin + 50 mg/kg praziquantel + 50 mg/kg pyrantel (as pamoate salt)	Day 0, 28, 56, 84, 112, 140, 168, 196, 224	8 (4 M, 4 F)

Drug Administration: All treatments were administered orally. Dogs were fed approximately 30 to 45 minutes prior to dosing. Dogs in the control group (0X) received a vehicle control at the same number of tablets as the 5X treatment group dogs.

Measurements and Observations: General health observations were performed twice daily on all dogs. Detailed clinical observations (Day -1, then once weekly), veterinary physical examinations (Days -8, -2, 26, 54, 82, 110, 138, 166, 194, 222, and 251), and ophthalmoscopic examinations (Days -5, 83, 167, and 251) were conducted. Dogs were continuously observed for 4 hours post-dosing and at 10 hours post-dosing. Dogs were re-dosed if vomiting occurred within 2 hours of dosing. Body weight (daily during acclimation, twice weekly through Day 55, then once weekly) and daily food consumption were measured. Samples for hematology, coagulation, serum chemistry, urinalysis, fecal assay evaluation, and C-reactive protein (CRP) assessment were collected on Days -8, 63, 83, 147, 167, 231, and 251. Blood samples for lotilaner, moxidectin, praziquantel, and pyrantel drug concentrations were collected at pretreatment and at 4, 10, 24,168, 336, and 672 hours post-dosing on Days 0, 28, 56, 84, 112, 140, 168, 196, and 224. A complete necropsy with organ weights and histopathologic examinations were performed on all dogs on Day 252.

Statistical Methods: The cage was the experimental unit from Days 0 through 27 because the dogs were pair housed by treatment group and sex. After the second dose (Day 28), the individual dog was the experimental unit because the dogs were individually housed. The data collected after Day 28 was used for the statistical analysis. The data collected while the dogs were pair-housed (Day 0 through Day 27) such as food consumption, body weights, body weight gain, and vital signs, were summarized through descriptive statistics or frequency counts separately from the data collected on and after Day 28.

Organ weight variables were analyzed using analysis of variance (ANOVA) with treatment group, sex, and the sex-by-treatment group interaction as fixed effects, and block within sex as a random effect.

Body weights and clinical pathology data were analyzed using repeated measures analysis of covariance (RMANCOVA) with treatment group, sex, time, and the 2-way and 3-way interactions as fixed effects, pre-treatment value as the covariate, and block within sex as a random effect.

All fixed model effects were tested at a 2-sided significance level of $\alpha=0.10$ except the 3-way treatment-by-sex-by-treatment day interaction, which was tested at $\alpha=0.05$. No adjustment was made for pairwise mean comparisons between each treatment against the control group. Descriptive statistics (mean, standard deviation, minimum, maximum, median, frequency of findings) were also used to summarize variables by treatment group, and time (where variables are measured at multiple time points).

Results: All dogs completed the study and no serious adverse events occurred.

Credelio Quattro™-related clinical observations included a dose-dependent increase in the frequency of discolored feces, diarrhea, and vomiting. All dogs recovered without treatment. Hypersalivation associated with vomiting on the day of dosing occurred in two of the 5X dogs. Increased bile acids occurred in two of the 3X dogs. Minimal mononuclear cell infiltration of the liver was noted microscopically in five control dogs, two 1X dogs, three 3X dogs, and five 5X dogs. One control dog, one 1X dog, two 3X dogs, and none of the 5X dogs also had minimal extramedullary hematopoiesis. All other results in the groups administered Credelio Quattro™ were similar to the control group.

Following nine oral administrations of Credelio Quattro™ at 1, 3, and 5X the maximum labeled dose of 40 mg/kg of lotilaner, 0.04 mg/kg of moxidectin, 10 mg/kg of praziquantel, and 10 mg/kg of pyrantel, every 28 days in 8-week-old beagle dogs, moxidectin and lotilaner area under the curve from time of dosing to the time of the last measurable concentration (AUC_{last}) was estimated to increase in a less than proportional manner, whereas praziquantel AUC_{last} was estimated to increase in a more than proportional manner from 1X to 5X after most study doses. Pyrantel AUC_{last} was estimated to increase in a proportional manner from 1X to 5X observed after first, sixth, and last doses. Within the 1X group, accumulation was observed between Days 0 and 224 with geometric mean accumulation ratios for AUC_{last} of 6.2 and 7.9 for lotilaner and moxidectin, respectively. Concentrations of praziquantel and pyrantel prior to each dose were below the limit of quantification.

Table III.2. Geometric Mean (95% Confidence Interval) Plasma Pharmacokinetic Parameters (First 1X Dose) of Lotilaner, Moxidectin, Praziquantel, and Pyrantel in Study ELA210202.

Parameter	Lotilaner	Moxidectin	Praziquantel	Pyrantel
C_{max}* (ng/mL)	6,470 (4,880-8,590)	14.9 (11.9-18.8)	136 (89.5-206)	42.1 (30.3-58.6)
AUC_{last}ł (h*ng/mL)	1,320,000 (1,120,000-1,570,000)	468 (344-636)	486 (291-814)	184 (128-263)

*C_{max}=maximum observed plasma concentration
łAUC_{last}=area under the curve from the time of dosing to the last quantifiable plasma concentration

Conclusion: The study supports the safe use of Credelio Quattro™ in dogs 8 weeks of age and older when used at the labeled dose. Credelio Quattro™ demonstrated an adequate margin of safety when administered orally nine times, once every 28 days, to fed beagles dogs at 1X, 3X, and 5X the maximum exposure dose. Hypersalivation associated with vomiting, vomiting, discolored feces, diarrhea, and increased bile acids are considered possible drug-related adverse reactions.

B. Safety Study in Heartworm Positive Dogs

Title: A GLP Safety Evaluation of a Lotilaner, Moxidectin, Praziquantel and Pyrantel Fixed Combination Tablet Administered Orally to Dogs Infected with Adult Heartworms (*Dirofilaria immitis*). (Study No. ELA210157)

Study Dates: March 17, 2022 to June 5, 2023

Study Location: Athens, GA

Study Design:

Objective: Evaluate the safety of Credelio Quattro™ following oral administration at one (1X) and three times (3X) the maximum labeled dose administered three times, once every 28 days, to beagle dogs infected with adult *Dirofilaria immitis*.

Study Animals: Twenty-four beagle dogs (12 male and 12 female), 8 months of age, weighing between 6.7 to 11.5 kg.

Experimental Design: Twenty-four dogs with pre-existing heartworm infections resulting from surgical transplantation of adult *D. immitis* (10 male and 10 female worms) were used in this study. Implantations were >2 months prior to study initiation and dogs were verified to be microfilaremic (>300 microfilaria/mL) and *D. immitis* antigen positive prior to study initiation. The study was conducted in accordance with GLP regulations.

Table III.3. Study ELA210157; Treatment Groups

Treatment Group	Treatment	Maximum Dose	Treatment Days	Number and Sex of Dogs
1 (0X)	Control	0 mg/kg	Day 1, 29, 57	8 (4M, 4F)
2 (1X)	Credelio Quattro™	40 mg/kg lotilaner + 0.04 mg/kg moxidectin + 10 mg/kg praziquantel + 10 mg/kg pyrantel (as pamoate salt)	Day 1, 29, 57	8 (4M, 4F)
3 (3X)	Credelio Quattro™	120 mg/kg lotilaner + 0.12 mg/kg moxidectin + 30 mg/kg praziquantel + 30 mg/kg pyrantel (as pamoate salt)	Day 1, 29, 57	8 (4M, 4F)

Drug Administration: All treatments were administered orally. Dogs were fed approximately 30 to 45 minutes prior to dosing. Dogs in the control group (0X) received a vehicle control at the same number of tablets as the 3X treatment group dogs.

Measurements and Observations: General health observations were performed twice daily. Body weight and physical exams were conducted prior to each dosing day. Clinical observations were performed on all dogs prior to dosing and at 1, 2, 4, 6, 8, 12, and 24 hours post-dosing on Days 0, 28, and 56. Dogs were monitored for vomiting for 2 hours after dosing, and re-dosed if needed. Microfilaria counts were conducted pre-dose and on Days 1, 27, 29, 55, and 57. *D. immitis* antigen testing was conducted pre-dose and on Day 57. A necropsy with examination for adult *D. immitis* worms was completed at the end of the study on Day 85.

Statistical Methods: Descriptive statistics (mean, standard deviation, minimum, maximum, frequency of findings) were used to summarize variables by sex, treatment group, and time (where variables were measured at multiple time points). The number of adult heartworms from necropsy was summarized with descriptive statistics by treatment group.

Results: There were no treatment related effects on body weight. Vomiting was observed in all eight of the 3X dogs within 12 hours post-dosing although not all eight dogs vomited at each of the three dosing time points. Diarrhea occurred in all groups up to 4 hours post-dosing in 2 of the control dogs, 2 of the 1X dogs, and 3 of the 3X dogs. The dogs experiencing post-dose vomiting/diarrhea recovered without treatment.

On Day 57, the microfilaria (MF) count was lower in both the 1X and 3X groups (means of 261.1 MF/mL and 151.5 MF/mL, respectively) compared with the control group (mean of 21881.3 MF/mL). There were no associated abnormalities due to death of microfilariae or dead worms and no hypersensitivity reactions (e.g., anaphylaxis, shock, collapse, respiratory distress, or depression). Adult heartworms were recovered at necropsy with mean live worm counts of 16.6 (83% of 20 worms implanted), 17.5 (87.5%), and 15.3 (76.3%) in the control, 1X, and 3X groups, respectively.

Conclusions: The oral administration of Credelio Quattro™ at 1X and 3X the maximum labeled dose to dogs with pre-existing adult heartworm infections and circulating microfilaria was well tolerated and did not cause severe adverse reactions in any dogs. Vomiting is considered a possible drug-related adverse reaction.

C. Safety Study in Avermectin-Sensitive Collie Dogs

Title: A GLP Safety Study of Lotilaner, Moxidectin, Praziquantel, and Pyrantel in a Fixed Combination Tablet Administered Orally to Avermectin Sensitive Collies. (Study No. ELA210751)

Study Dates: July 7, 2022 to June 21, 2023

Study Location: Stanwood, MI

Study Design:

Objective: Evaluate the safety of Credelio Quattro™ following oral administration at one (1X), two (2X), and five times (5X) the maximum labeled dose administered three times, once every 28 days, to avermectin-sensitive Collie dogs.

Study Animals: Thirty-two phenotypic (pre-screened to sensitivity to ivermectin at a dose of 120 µg/kg) and genotypic (homozygous MDR1 negative) avermectin-sensitive Collie dogs (15 male and 17 female), 1.6 to 8.4 years of age, weighing between 15.7 and 34.6 kg.

Experimental Design: Dogs were randomized to treatment group, cohort (A or B), and cage on Day -3. The study was conducted in accordance with GLP regulations.

Table III.4. Study ELA210751; Treatment Groups

Treatment Group	Treatment	Maximum Dose	Treatment Days	Number of Dogs
0X	Control	0 mg/kg	Cohort A: Day 0, 28, 56 Cohort B: Day 1, 29, 57	8 (1M, 7F)
1X	Credelio Quattro™	40 mg/kg lotilaner + 0.04 mg/kg moxidectin + 10 mg/kg praziquantel + 10 mg/kg pyrantel (as pamoate salt)	Cohort A: Day 0, 28, 56 Cohort B: Day 1, 29, 57	8 (6M, 2F)
2X	Credelio Quattro™	80 mg/kg lotilaner + 0.08 mg/kg moxidectin + 20 mg/kg praziquantel + 20 mg/kg pyrantel (as pamoate salt)	Cohort A: Day 0, 28, 56 Cohort B: Day 1, 29, 57	8 (4M, 4F)
5X	Credelio Quattro™	200 mg/kg lotilaner + 0.20 mg/kg moxidectin + 50 mg/kg praziquantel + 50 mg/kg pyrantel (as pamoate salt)	Cohort A: Day 0, 28, 56 Cohort B: Day 1, 29, 57	8 (4M, 4F)

Drug Administration: All treatments were administered orally. Dogs were fed approximately 30 to 45 minutes prior to dosing. Dogs in the control group (0X) received a vehicle control at the same number of tablets as the 5X treatment group dogs.

Measurements and Observations: General health observations were performed twice daily on all dogs on non-dosing days. Body weight and physical exams were conducted prior to each cohort's dosing day. Clinical observations were performed by a veterinarian on all dogs prior to dosing and at 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48, 60, and 72 hours post-dosing. Dogs were monitored for vomiting for 2 hours after dosing, and re-dosed if needed.

Statistical Methods: For the data from individual animals, descriptive statistics (mean, standard deviation, minimum, maximum, median, frequency of findings) were used to summarize variables by treatment group and time (where variables are measured at multiple time points).

Results: No dogs in any treatment group were observed with ataxia, seizures, mydriasis, or muscle tremors. One dog in each of the control, 2X, and 5X groups was observed with transient, mild depression, resolving without treatment by 24 hours. Hypersalivation and drooling associated with avermectin sensitivity was observed in the 1X, 2X, and 5X treatment groups and tended to increase with dose.

Vomiting was observed in all groups and increased with dose. The number of animals observed vomiting in the 2X and 5X groups (1 to 3 animals in 2X group and 5 to 8 animals in 5X group) tended to increase with time, with all 8 dogs in the 5X treatment group experiencing vomiting in the third dose cycle (Tables III.5, III.6, and III.7).

Table III.5. Number of Events (Number of Affected Animals) of Clinical Observations by Treatment Group: Dosed on Day 0 or 1

Clinical Observation	0X	1X	2X	5X
Depression	0	0	5 (1)	0
Salivation	0	8 (1)	7 (1)	16 (4)
Vomiting	1 (1)	1 (1)	1 (1)	9 (5)

Table III.6. Number of Events (Number of Affected Animals) of Clinical Observations by Treatment Group: Dosed on Day 28 or 29

Clinical Observation	0X	1X	2X	5X
Depression	0	0	0	1 (1)
Salivation	0	6 (2)	5 (1)	12 (3)
Vomiting	1 (1)	1 (1)	1 (1)	11 (7)

Table III.7. Number of Events (Number of Affected Animals) of Clinical Observations by Treatment Group: Dosed on Day 56 or 57

Clinical Observation	0X	1X	2X	5X
Depression	2 (1)	0	0	0
Salivation	0	10 (2)	5 (2)	15 (2)
Vomiting	1 (1)	1 (1)	3 (3)	10 (8)

Diarrhea was observed in some dogs in all groups and resolved without treatment. A single instance of dark colored diarrhea (melena) was observed in 1 dog in the 5X group. A majority of observations were noted on the day of or day following dosing.

Conclusion: Oral administration of Credelio Quattro™ was well tolerated in avermectin-sensitive Collies (MDR1 negative) up to 5X the maximum labeled dose. Dose-dependent salivation and vomiting are considered drug-related adverse reactions. Diarrhea, with or without blood, is considered a possible drug-related adverse reaction.

D. Foreign or Pilot Experience

In a single arm field study of 36 dogs with flea infestations conducted in Australia, one dog receiving Credelio Quattro™ had loose or dark feces, one dog was lethargic, and one dog vomited within 72 hours of dosing. All dogs fully recovered without treatment.

In a U.S. field study, 165 dogs received a combination of lotilaner, moxidectin, and praziquantel, three of the active ingredients at the same doses as in Credelio Quattro™, monthly for up to 11 months. Two dogs with no history of seizures experienced seizures during the study. One of the dogs developed cluster seizures and was removed from the study. Ataxia was also observed in one other dog three days after the first dose.

In a pilot margin of safety study, 24 dogs received a combination product containing lotilaner, moxidectin, praziquantel, and pyrantel at the same doses as in Credelio Quattro™, monthly for three consecutive months (3 doses). One dog had diarrhea on the day of dosing. The dog was then euthanized on Day 9 due to declining physical condition and a duodenal ulcer was found on necropsy.

In a single arm field study of 28 dogs with flea infestations conducted in Australia, dogs received Credelio Quattro™ once monthly for 3 months. Nine dogs had soft feces/diarrhea. Three dogs vomited, two dogs were lethargic, and two dogs were inappetent. All dogs recovered except one 12-year-old, neutered male chihuahua, weighing approximately 8 kg, which continued to have diarrhea, vomiting, and inappetence for four days after the first dose. Eleven days after the first dose, the dog had a seizure-like episode and was hospitalized and treated for acute gastritis. Approximately one month after the second dose, the dog was again inappetent with notable borborygmus, but the symptoms resolved the next day. Approximately one month after the third dose, the dog had seizure-like activity and recovered without intervention.

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 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 conditions of use 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

Credelio Quattro™, 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 Credelio Quattro™.

C. Patent Information

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