Date of Approval: February 24, 2016

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-452

SIMPARICA

Sarolaner

Chewable tablets

Dog

SIMPARICA 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), *Amblyomma maculatum* (Gulf Coast tick), *Dermacentor variabilis* (American dog tick), and *Rhipicephalus sanguineus* (brown dog tick)] for one month in dogs 6 months of age or older and weighing 2.8 pounds or more.

Sponsored by:

Zoetis Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-452

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

SIMPARICA

D. Product Established Name

Sarolaner

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Chewable tablet

G. Amount of Active Ingredient

Six tablet sizes 5 mg, 10 mg, 20 mg, 40 mg, 80 mg, and 120 mg.

H. How Supplied

Each tablet size is available in color-coded packages of one, three, or six tablets.

I. Dispensing Status

Rx

J. Dosage Regimen

2 mg/kg body weight, once per month

K. Route of Administration

Oral

L. Species/Class

Dog

M. Indication

SIMPARICA 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), *Amblyomma maculatum* (Gulf Coast tick), *Dermacentor variabilis* (American dog tick), and *Rhipicephalus sanguineus* (brown dog tick)] for one month in dogs 6 months of age or older and weighing 2.8 pounds or more.

II. EFFECTIVENESS

A. Dosage Characterization

Laboratory effectiveness studies demonstrated that fleas were more susceptible to sarolaner than ticks, and that *Amblyomma* was the least susceptible tick genus. A laboratory dose determination study evaluating the effectiveness of a single oral dose of 1.0, 2.0, or 4.0 mg/kg sarolaner against *Amblyomma maculatum* demonstrated that 2.0 mg/kg provided greater than 90% effectiveness for 35 days. Therefore a monthly oral dosage of 2.0 mg/kg was selected as the minimum dosage for sarolaner.

B. Substantial Evidence

1. For the Treatment and Control of Tick Infestations

   a. Laboratory Dose Confirmation Study A166C-US-12-130: Dose Confirmation of sarolaner Administered Orally Against Induced Infestations of *Amblyomma americanum* on Dogs

      (i) Location of Study:

      Turlock, CA

      (ii) Study Design:

      (a) Study Objective: Confirm the effectiveness of a single oral dose of 2.0 mg/kg sarolaner against induced infestations of *Amblyomma americanum* for up to 35 days on dogs.

      (b) Study Animals:

      16 mixed-breed dogs (8 male and 8 female), 2-13 years of age, weighing between 8.8-34.9 kg.

(c) Treatment Groups:

Table 1: Treatment groups for Study A166C-US-12-130

Group	Treatment	Days of Treatment	Dogs per Group	Days of Tick Infestation	Days of Tick Count
T01	Vehicle control	Day 0	8	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35
T02	Sarolaner	Day 0	8	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35

(d) Drug Administration:

All treatments were administered orally. Food was withheld overnight and tablets were administered within 20 minutes after food had been offered, followed by administration of a small volume of water.

(e) Measurements and Observations:

Each dog was infested with approximately 50 unfed adult *A. americanum* (approximately equal numbers of males and females) on Days -2, 5, 12, 19, 26, and 33. At each tick count on Days 2, 7, 14, 21, 28, and 35, the numbers of live and dead ticks were counted, and the ticks were removed from the dog. Clinical observations were conducted 1, 3, 6, and 24 hours after treatment. General health observations were conducted at least once daily. Tick counts and health observations were conducted masked to treatment.

(f) Statistical Methods:

For live tick counts, percent effectiveness of the treated group with respect to the control group was calculated using the formula $[(C - T)/C] \times 100$, where C = geometric mean for the control group and T = geometric mean for the treated group for each time point. The comparisons were tested using the (two-sided) 5% significance level. The mixed model analysis was used to analyze log-counts, with treatment group as a fixed effect and the allocation blocks as a random effect.

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

(iii) Results:

The sarolaner-treated group had a 100% reduction in the initial live tick counts 48 hours after treatment, and ≥96.9% reduction in live tick counts 48 hours after weekly re-infestations for 35 days.

Live tick counts for the sarolaner group were significantly reduced following each of the infestation time points in comparison to the control group ($P<0.0001$). Total dead tick counts were significantly increased ($P\leq0.0004$, Table 3) in comparison with the control group following each tick infestation.

A minimum of 25% of the original ticks used to infest the animal at each time point evaluated was considered to be an adequate infestation, and a minimum of six adequately infested control dogs was required for the study to be considered valid. An adequate infestation was achieved for all time points evaluated.

Table 2: Geometric mean live tick counts and percent effectiveness of sarolaner for the control of induced *A. americanum* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Live Tick Count	Sarolaner Geometric Mean Live Tick Count	Percent Effectiveness
2	23.3	0.0	100
7	19.2	0.2	99.0
14	15.6	0.0	100
21	22.3	0.1	99.6
28	26.1	0.1	100
35	24.7	0.8	96.9

Table 3: Geometric mean dead tick counts and percent effectiveness of sarolaner for the treatment of induced *A. americanum* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Dead Tick Count	Sarolaner Geometric Mean Dead Tick Count
2	0.0	13.6
7	0.3	10.3
14	0.6	8.4
21	0.0	10.2
28	0.0	14.7
35	0.0	10.9

(iv) Adverse Reactions:

There were no adverse reactions during this study.

(v) Conclusions:

Sarolaner was effective against adult *A. americanum* at 48 hours after treatment of an existing infestation and after weekly re-infestation for 35 days.

The increased number of dead ticks and the reduction of live ticks support the treatment and control indication for *A. americanum*, respectively.

b. Laboratory Dose Confirmation Study A166C-US-12-131: Dose Confirmation of sarolaner Administered Orally Against Induced Infestations of *Amblyomma americanum* on Dogs

(i) Location of Study:

Greenbrier, AR

(ii) Study Design:

(a) Study Objective: Confirm the effectiveness of a single oral dose of 2.0 mg/kg sarolaner against induced infestations of *Amblyomma americanum* for up to 35 days on dogs.

(b) Study Animals:

Sixteen Beagle dogs (8 male and 8 female), 7-70 months of age, weighing between 8.0-14.2 kg.

(c) Treatment Groups:

Table 4: Treatment groups for Study A166C-US-12-131

Group	Treatment	Days of Treatment	Dogs per Group	Days of Tick Infestation	Days of Tick Count
T01	Vehicle control	Day 0	8	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35
T02	Sarolaner	Day 0	8	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35

(d) Drug Administration:

All treatments were administered orally. Food was withheld overnight and tablets were administered within 20 minutes after food had been offered, followed by administration of a small volume of water.

(e) Measurements and Observations:

Each dog was infested with approximately 50 unfed adult *A. americanum* (approximately equal numbers of males and females) at each infestation. At each tick count the numbers of live and dead ticks were counted, and the ticks were removed from the dog. Clinical observations were conducted 1, 3, 6, and 24 hours after treatment. General health observations were conducted at least once daily. Tick counts and health observations were conducted masked to treatment.

(f) Statistical Methods:

For live tick counts, percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C – T)/C] x 100, where C = geometric mean for the control group and T = geometric mean for the treated group for each time point. The comparisons were tested using the (two-sided) 5% significance level. The mixed model analysis was used to analyze log-counts, with treatment group as a fixed effect and the allocation blocks as a random effect.

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

(iii) Results:

The sarolaner-treated group had a 99.6% reduction in initial live tick counts 48 hours after treatment, and 100% reduction in live tick counts 48 hours after weekly re-infestations for 35 days.

Live tick counts for the sarolaner group were significantly reduced following each of the infestation time points in comparison to the control group ($P<0.0001$). Total dead tick counts were significantly increased ($P\leq0.0004$, Table 6) in comparison with the control group following each tick infestation.

A minimum of 25% of the original ticks used to infest the animal at each time point evaluated was considered to be an adequate infestation, and a minimum of six adequately infested control dogs was required for the study to be considered valid. An adequate infestation was achieved for all time points evaluated.

Table 5: Geometric mean live tick counts and percent effectiveness of sarolaner for the control of induced *A. americanum* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Live Tick Count	Sarolaner Geometric Mean Live Tick Count	Percent Effectiveness
2	23.7	0.1	99.6
7	14.3	0.0	100
14	18.8	0.0	100
21	13.2	0.0	100
28	17.3	0.0	100
35	15.1	0.0	100

Table 6: Geometric mean dead tick counts and percent effectiveness of sarolaner for the treatment of induced *A. americanum* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Live Tick Count	Sarolaner Geometric Mean Dead Tick Count
2	0.0	7.1
7	0.3	5.5
14	0.1	10.0
21	0.0	8.9
28	0.0	11.4
35	0.0	11.0

(iv)Adverse Reactions:

There were no adverse reactions during this study.

(v) Conclusions:

Sarolaner was effective against adult *A. americanum* at 48 hours after treatment of an existing infestation and after weekly re-infestation for 35 days.

The increased number of dead ticks and the reduction of live ticks support the treatment and control indication for *A. americanum*, respectively.

c. Laboratory Dose Confirmation Study A166C-US-12-128: Dose Confirmation of sarolaner Administered Orally Against Induced Infestations of *Amblyomma maculatum* on Dogs

(i) Location of Study:

Greenbrier, AR

(ii) Study Design:

(a) Study Objective: Confirm the effectiveness of a single oral dose of 2.0 mg/kg sarolaner against induced infestations of *Amblyomma maculatum* for up to 35 days on dogs.

(b) Study Animals:

16 Beagle dogs (8 male and 8 female), 7-42 months of age, weighing between 7.9-15.9 kg.

(c) Treatment Groups:

Table 7: Treatment groups for Study A166C-US-12-128

Group	Treatment	Days of Treatment	Dogs per Group	Days of Tick Infestation	Days of Tick Count
T01	Vehicle control	Day 0	8	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35
T02	Sarolaner	Day 0	8	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35

(d) Drug Administration:

All treatments were administered orally. Food was withheld overnight and tablets were administered within 20 minutes after food had been offered, followed by administration of a small volume of water.

(e) Measurements and Observations:

Each dog was infested with approximately 50 unfed adult *A. maculatum* (approximately equal numbers of males and females) at each infestation. At each tick count the numbers of live and dead ticks were counted, and the ticks were removed from the dog. Clinical observations were conducted 1, 3, 6, and 24 hours after treatment. General health observations were conducted at least once daily. Tick counts and health observations were conducted masked to treatment.

(f) Statistical Methods:

For live tick counts, percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C – T)/C] x 100, where C = geometric mean for the control group and T = geometric mean for the treated group for each time point. The comparisons were tested using the (two-sided) 5% significance level. The mixed model analysis was used to analyze log-counts, with treatment group as a fixed effect and the allocation blocks as a random effect.

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

(iii) Results:

The sarolaner-treated group had a 100% reduction in initial live tick counts 48 hours after treatment, and ≥99.7% reduction in live tick counts 48 hours after weekly re-infestations for 35 days.

Live tick counts for the sarolaner group were significantly reduced following each of the infestation time points in comparison to the control group ($P<0.0001$). Total dead tick counts were significantly increased ($P\leq0.0015$, Table 9) in comparison with the control group following each tick infestation.

A minimum of 25% of the original ticks used to infest the animal at each time point evaluated was considered to be an adequate infestation, and a minimum of six adequately infested control dogs was required for the study to be considered valid. An adequate infestation was achieved for all time points evaluated.

Table 8: Geometric mean live tick counts and percent effectiveness of sarolaner for the control of induced *A. maculatum* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Live Tick Count	Sarolaner Geometric Mean Live Tick Count	Percent Effectiveness
2	30.1	0.0	100
7	31.1	0.0	100
14	26.6	0.1	99.7
21	25.8	0.0	100
28	28.0	0.0	100
35	20.6	0.0	100

Table 9: Geometric mean dead tick counts and percent effectiveness of sarolaner for the treatment of induced *A. maculatum* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Dead Tick Count	Sarolaner Geometric Mean Dead Tick Count
2	0.0	12.4
7	0.0	4.5
14	0.0	5.8
21	0.0	5.7
28	0.0	9.9
35	0.0	5.7

(iv)Adverse Reactions:

There were no adverse reactions in this study.

(v) Conclusions:

Sarolaner was effective against adult *A. maculatum* at 48 hours after treatment of an existing infestation and after weekly re-infestation for 35 days.

The increased number of dead ticks and the reduction of live ticks support the treatment and control indication for *A. maculatum*, respectively.

d. Laboratory Dose Confirmation Study A166C-US-12-129: Dose Confirmation of sarolaner Administered Orally Against Induced Infestations of *Amblyomma maculatum* on Dogs

(i) Location of Study:

Sugar Land, TX

(ii) Study Design:

(a) Study Objective: Confirm the effectiveness of a single oral dose of 2.0 mg/kg sarolaner against induced infestations of *Amblyomma maculatum* for up to 35 days on dogs.

(b) Study Animals:

16 Beagles and mixed breed dogs (8 male and 8 female), 34-63 months of age, weighing between 8.3-21.8 kg.

(c) Treatment Groups:

Table 10: Treatment groups for Study A166C-US-12-129

Group	Treatment	Days of Treatment	Dogs per Group	Days of Tick Infestation	Days of Tick Count
T01	Vehicle control	Day 0	8	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35
T02	Sarolaner	Day 0	8	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35

(d) Drug Administration

All treatments were administered orally. Food was withheld overnight and tablets were administered within 20 minutes after food had been offered, followed by administration of a small volume of water.

(e) Measurements and Observations:

Each dog was infested with approximately 50 unfed adult *A. maculatum* (approximately equal numbers of males and females) at each infestation. At each tick count the numbers of live and dead ticks were counted, and the ticks were removed from the dog. Clinical observations were conducted 1, 3, 6, and 24 hours after treatment. General health observations were conducted at least once daily. Tick counts and health observations were conducted masked to treatment.

(f) Statistical Methods:

For live tick counts, percent effectiveness of the treated group with respect to the control group was calculated using the formula $[(C - T)/C] \times 100$, where C = geometric mean for the control group and T = geometric mean for the treated group for each time point. The comparisons were tested using the (two-sided) 5% significance level. The mixed model analysis was used to analyze log-counts, with treatment group as a fixed effect and the allocation blocks as a random effect.

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

(iii) Results:

The sarolaner-treated group had a 100% reduction in initial live tick counts 48 hours after treatment, and ≥99.3% reduction in live tick counts 48 hours after weekly re-infestations for 35 days.

Live tick counts for the sarolaner group were significantly reduced following each of the infestation time points in comparison to the control group ($P<0.0001$). Total dead tick counts were significantly increased ($P\leq0.0001$, Table 12) in comparison with the control group following each tick infestation.

A minimum of 25% of the original ticks used to infest the animal at each time point evaluated was considered to be an adequate infestation, and a minimum of six adequately infested control dogs was required for the study to be considered valid. An adequate infestation was achieved for all time points evaluated.

Table 11: Geometric mean live tick counts and percent effectiveness of sarolaner for the control of induced *A. maculatum* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Live Tick Count	Sarolaner Geometric Mean Live Tick Count	Percent Effectiveness
2	21.5	0.0	100
7	25.0	0.0	100
14	32.5	0.1	99.5
21	28.6	0.0	100
28	30.6	0.1	99.5
35	26.1	0.2	99.3

Table 12: Geometric mean dead tick counts and percent effectiveness of sarolaner for the treatment of induced *A. maculatum* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Dead Tick Count	Sarolaner Geometric Mean Dead Tick Count
2	0.3	15.0
7	0.1	9.2
14	0.4	7.4
21	0.0	5.8
28	0.3	4.7
35	0.3	9.1

(iv)Adverse Reactions:

There were no adverse reactions in this study.

(v) Conclusions:

Sarolaner was effective against adult *A. maculatum* at 48 hours after treatment of an existing infestation and after weekly re-infestation for 35 days.

The increased number of dead ticks and the reduction of live ticks support the treatment and control indication for *A. maculatum*, respectively.

e. Laboratory Dose Confirmation Study A166C-US-12-133: Dose Confirmation of sarolaner Administered Orally Against Induced Infestations of *Dermacentor variabilis* on Dogs

(i) Location of Study:

Turlock, CA

(ii) Study Design:

(a) Study Objective: Confirm the effectiveness of a single oral dose of 2.0 mg/kg sarolaner against induced infestations of *Dermacentor variabilis* for up to 35 days on dogs.

(b) Study Animals:

16 Beagle dogs (8 male and 8 female), 32-33 months of age, weighing between 8.8-14.8 kg.

(c) Treatment Groups:

Table 13: Treatment groups for Study A166C-US-12-133

Group	Treatment	Days of Treatment	Dogs per Group	Days of Tick Infestation	Days of Tick Count
T01	Vehicle control	Day 0	8	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35
T02	Sarolaner	Day 0	8	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35

(d) Drug Administration:

All treatments were administered orally. Food was withheld overnight and tablets were administered within 20 minutes after food had been offered, followed by administration of a small volume of water.

(e) Measurements and Observations:

Each dog was infested with approximately 50 unfed adult *D. variabilis* (approximately equal numbers of males and females) at each infestation. At each tick count the numbers of live and dead ticks were counted, and the ticks were removed from the dog. Clinical observations were conducted 1, 3, 6, and 24 hours after treatment. General health observations were conducted at least once daily. Tick counts and health observations were conducted masked to treatment.

(f) Statistical Methods:

For live tick counts, percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C – T)/C] x 100, where C = geometric mean for the control group and T = geometric mean for the treated group for each time point. The comparisons were tested using the (two-sided) 5% significance level. The mixed model analysis was used to analyze log-counts, with treatment group as a fixed effect and the allocation blocks as a random effect.

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

(iii) Results:

The sarolaner-treated group had a 99.7% reduction in initial live tick counts 48 hours after treatment, and ≥98.5% reduction in live tick counts 48 hours after weekly re-infestations for 35 days.

Live tick counts for the sarolaner group were significantly reduced following each of the infestation time points in comparison to the control group ($P<0.0001$). Total dead tick counts were significantly increased ($P\leq0.0012$, Table 15) in comparison with the control group following each tick infestation.

A minimum of 25% of the original ticks used to infest the animal at each time point evaluated was considered to be an adequate infestation, and a minimum of six adequately infested control dogs was required for the study to be considered valid. An adequate infestation was achieved for all time points evaluated.

Table 14: Geometric mean live tick counts and percent effectiveness of sarolaner for the control of induced *D. variabilis* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Live Tick Count	Sarolaner Geometric Mean Live Tick Count	Percent Effectiveness
2	33.4	0.1	99.7
7	35.2	0.2	99.5
14	28.0	0.4	98.5
21	32.4	0.1	99.7
28	22.4	0.2	99.2
35	22.6	0.1	99.3

Table 15: Geometric mean dead tick counts and percent effectiveness of sarolaner for the treatment of induced *D. variabilis* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Dead Tick Count	Sarolaner Geometric Mean Dead Tick Count
2	0.0	7.6
7	0.0	10.1
14	0.0	6.4
21	0.0	3.8
28	0.1	3.3
35	0.0	2.6

(iv)Adverse Reactions:

There were no adverse reactions during this study.

(v) Conclusions:

Sarolaner was effective against adult *D. variabilis* at 48 hours after treatment of an existing infestation and after weekly re-infestation for 35 days.

The increased number of dead ticks and the reduction of live ticks support the treatment and control indication for *D. variabilis*, respectively.

f. Laboratory Dose Confirmation Study A166C-US-12-132: Dose Confirmation of Sarolaner Administered Orally Against Induced Infestations of *Dermacentor variabilis* on Dogs

(i) Location of Study:

Greenbrier, AR

(ii) Study Design:

(a) Study Objective: Confirm the effectiveness of a single oral dose of 2.0 mg/kg sarolaner against induced infestations of *Dermacentor variabilis* for up to 35 days on dogs.

(b) Study Animals:

16 Beagle and mixed breed dogs (8 male and 8 female), 14 - 84 months of age, weighing between 5.6 - 18.3 kg.

(c) Treatment Groups:

Table 16: Treatment groups for Study A166C-US-12-132

Group	Treatment	Days of Treatment	Dogs per Group	Days of Tick Infestation	Days of Tick Count
T01	Vehicle control	Day 0	8	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35
T02	Sarolaner	Day 0	8	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35

(d) Drug Administration:

All treatments were administered orally. Food was withheld overnight and tablets were administered within 20 minutes after food had been offered, followed by administration of a small volume of water.

(e) Measurements and Observations:

Each dog was infested with approximately 50 unfed adult *D. variabilis* (approximately equal numbers of males and females) at each infestation. At each tick count the numbers of live and dead ticks were counted, and the ticks were removed from the dog. Clinical observations were conducted 1, 3, 6, and 24 hours after treatment. General health observations were conducted at least once daily. Tick counts and health observations were conducted masked to treatment.

(f) Statistical Methods:

For live tick counts, percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C – T)/C] x 100, where C = geometric mean for the control group and T = geometric mean for the treated group for each time point. The comparisons were tested using the (two-sided) 5% significance level. The mixed model analysis was used to analyze log-counts, with treatment group as a fixed effect and the allocation blocks as a random effect.

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

(iii) Results:

The sarolaner-treated group had a 100% reduction in initial live tick counts 48 hours after treatment, and ≥99.3% reduction in live tick counts 48 hours after weekly re-infestations for 35 days.

Live tick counts for the sarolaner group were significantly reduced following each of the infestation time points in comparison to the control group ($P<0.0001$). Total dead tick counts were significantly increased ($P\leq0.0095$, Table 18) in comparison with the control group following each tick infestation, except Day 28 ($P=0.0578$).

A minimum of 25% of the original ticks used to infest the animal at each time point evaluated was considered to be an adequate infestation, and a minimum of six adequately infested control dogs was required for the study to be considered valid. An adequate infestation was achieved for all time points evaluated.

Table 17: Geometric mean live tick counts and percent effectiveness of sarolaner for the control of induced *D. variabilis* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Live Tick Count	Sarolaner Geometric Mean Live Tick Count	Percent Effectiveness
2	21.3	0.0	100
7	18.6	0.1	99.5
14	20.8	0.1	99.3
21	15.6	0.0	100
28	16.2	0.0	100
35	17.9	0.0	100

Table 18: Geometric mean dead tick counts and percent effectiveness of sarolaner for the treatment of induced *D. variabilis* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Dead Tick Count	Sarolaner Geometric Mean Dead Tick Count
2	0.1	3.2
7	0.0	3.0
14	0.0	2.5
21	0.0	4.4
28	0.0	1.4
35	0.0	2.0

(iv)Adverse Reactions:

No adverse reactions were reported in this study.

(v) Conclusions:

Sarolaner was effective against adult *D. variabilis* at 48 hours after treatment of an existing infestation and after weekly re-infestation for 35 days.

The increased number of dead ticks and the reduction of live ticks support the treatment and control indication for *D. variabilis*, respectively.

g. Laboratory Dose Confirmation Study A166C-US-13-303: Dose Confirmation of Sarolaner Administered Orally Against Induced Infestations of *Rhipicephalus sanguineus* on Dogs

(i) Location of Study:

Greenbrier, AR

(ii) Study Design:

(a) Study Objective: Confirm the effectiveness of a single oral dose of 2.0 mg/kg sarolaner against induced infestations of *Rhipicephalus sanguineus* for up to 35 days on dogs.

(b) Study Animals:

16 Beagle dogs (8 male and 8 female), 13-37 months of age, and weighing 6.9-11.6 kg.

(c) Treatment Groups:

Table 19: Treatment groups for Study A166C-US-13-303

Group	Treatment	Days of Treatment	Dogs per Group	Days of Tick Infestation	Days of Tick Count
T01	Vehicle control	Day 0	8	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35
T02	Sarolaner	Day 0	8	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35

(d) Drug Administration:

All treatments were administered orally. Food was withheld overnight and tablets were administered within 20 minutes after food had been offered, followed by administration of a small volume of water.

(e) Measurements and Observations:

Each dog was infested with approximately 50 unfed adult *R. sanguineus* (approximately equal numbers of males and females) at each infestation. At each tick count the numbers of live and dead ticks were counted, and the ticks were removed from the dog. Clinical observations were conducted 1, 3, 6, and 24 hours after treatment. General health observations were conducted at least once daily.

(f) Statistical Methods:

For live tick counts, percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C – T)/C]x100, where C = geometric mean for the control group and T = geometric mean for the treated group for each time point. The comparisons were tested using the (two-sided) 5% significance level. The mixed model analysis was used to analyze log-counts, with treatment group as a fixed effect and the allocation blocks as a random effect.

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

(iii) Results:

The sarolaner-treated group had a 100% reduction in initial live tick counts 48 hours after treatment, and 100% reduction in live tick counts 48 hours after weekly re-infestations for 35 days.

Live tick counts for the sarolaner group were significantly reduced following each of the infestation time points in comparison to the control group ($P<0.0001$). Total dead tick counts were significantly increased ($P\leq0.0008$, Table 21) in comparison with the control group following each tick infestation.

A minimum of 25% of the original ticks used to infest the animal at each time point evaluated was considered to be an adequate infestation, and a minimum of six adequately infested control dogs was required for the study to be considered valid. An adequate infestation was achieved for all time points evaluated.

Table 20: Geometric mean live tick counts and percent effectiveness of sarolaner for the control of induced *R. sanguineus* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Live Tick Count	Sarolaner Geometric Mean Live Tick Count	Percent Effectiveness
2	24.3	0.0	100
7	17.9	0.0	100
14	18.0	0.0	100
21	19.0	0.0	100
28	19.1	0.0	100
35	20.7	0.0	100

Table 21: Geometric mean dead tick counts and percent effectiveness of sarolaner for the treatment of induced *R. sanguineus* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Dead Tick Count	Sarolaner Geometric Mean Dead Tick Count
2	0.0	4.9
7	0.0	4.4
14	0.0	7.8
21	0.0	6.3
28	0.0	6.8
35	0.0	4.7

(iv)Adverse Reactions:

No adverse reactions were reported in this study.

(v) Conclusions:

Sarolaner was effective against adult *R. sanguineus* at 48 hours after treatment of an existing infestation and after weekly re-infestation for 35 days.

The increased number of dead ticks and the reduction of live ticks support the treatment and control indication for *R. sanguineus*, respectively.

h. Laboratory Dose Confirmation Study A166C-US-12-135: Dose Confirmation of sarolaner Administered Orally Against Induced Infestations of *Rhipicephalus sanguineus* on Dogs

(i) Location of Study:

Turlock, CA

(ii) Study Design:

(a) Study Objective: Confirm the effectiveness of a single oral dose of 2.0 mg/kg sarolaner against induced infestations of Rhipicephalus sanguineus for up to 35 days on dogs.

(b) Study Animals:

16 pure- and mixed-breed dogs (8 male and 8 female), 46-145 months of age, weighing between 7.3-35 kg

(c) Treatment Groups:

Table 22: Treatment groups for Study A166C-US-12-135

Group	Treatment	Days of Treatment	Dogs per Group	Days of Tick Infestation	Days of Tick Count
T01	Vehicle control	Day 0	8	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35
T02	Sarolaner	Day 0	8	-2, 5, 12, 19, 26, and 33	2, 7, 14, 21, 28, and 35

(d) Drug Administration:

All treatments were administered orally. Food was withheld overnight and tablets were administered within 20 minutes after food had been offered, followed by administration of a small volume of water.

(e) Measurements and Observations:

Each dog was infested with approximately 50 unfed adult *R. sanguineus* (approximately equal numbers of males and females) at each infestation. At each tick count the numbers of live and dead ticks were counted, and the ticks were removed from the dog. Clinical observations were conducted 1, 3, 6, and 24 hours after treatment. General health observations were conducted at least once daily.

(f) Statistical Methods:

For live tick counts, percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C – T)/C] x 100, where C = geometric mean for the control group and T = geometric mean for the treated group for each time point. The comparisons were tested using the (two-sided) 5% significance level. The mixed model analysis was used to analyze log-counts, with treatment group as a fixed effect and the allocation blocks as a random effect.

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

(iii) Results:

The sarolaner-treated group had a 100% reduction in initial live tick counts 48 hours after treatment, and ≥97.1% reduction in live tick counts 48 hours after weekly re-infestations for 35 days.

Live tick counts for the sarolaner group were significantly reduced following each of the infestation time points in comparison to the control group ($P<0.0001$). Total dead tick counts were significantly increased ($P\leq0.0064$, Table 24) in comparison with the control group following each tick infestation, except Day 14 ($P=0.0529$).

A minimum of 25% of the original ticks used to infest the animal at each time point evaluated was considered to be an adequate infestation, and a minimum of six adequately infested control dogs was required for the study to be considered valid. An adequate infestation was achieved for all time points evaluated.

Table 23: Geometric mean live tick counts and percent effectiveness of sarolaner for the control of induced *R. sanguineus* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Live Tick Count	Sarolaner Geometric Mean Live Tick Count	Percent Effectiveness
2	32.7	0.0	100
7	30.4	0.1	99.7
14	26.9	0.0	100
21	27.9	0.0	100
28	24.2	0.1	99.6
35	26.1	0.8	97.1

Table 24: Geometric mean dead tick counts and percent effectiveness of sarolaner for the treatment of *induced R. sanguineus* infestations of dogs, 48 hours after treatment of the initial infestation and weekly re-infestation

Day of Tick Count	Control Group Geometric Mean Dead Tick Count	Sarolaner Geometric Mean Dead Tick Count
2	0.0	8.1
7	0.0	3.1
14	0.0	1.2
21	0.0	2.3
28	0.0	2.4
35	0.0	2.9

(iv)Adverse Reactions:

There were no adverse reactions during this study.

(v) Conclusions:

Sarolaner was effective against adult *R. sanguineus* at 48 hours after treatment of an existing infestation and after weekly re-infestation for 35 days.

The increased number of dead ticks and the reduction of live ticks support the treatment and control indication for *R. sanguineus*, respectively.

2. For the Treatment and Prevention of Flea Infestations

a. Laboratory Dose Confirmation Study A166C-US-12-107: Dose Confirmation of sarolaner Administered Orally Against Induced Infestations of *Ctenocephalides felis* on Dogs

(i) Location of Study:

Greenbrier, AR

(ii) Study Design:

(a) Study Objective: Confirm the effectiveness of a single oral dose of 2.0 mg/kg sarolaner against induced infestations of *Ctenocephalides felis* for up to 35 days on dogs.

(b) Study Animals:

16 mixed breed dogs (8 male and 8 female), 9-66 months of age, weighing between 6.0-14.6 kg.

(c) Treatment Groups:

Table 25: Treatment Group for Study A166C-US-12-107

Group	Treatment	Days of Treatment	Dogs per Group	Days of Flea Infestation	Days of Flea Count
T01	Vehicle control	Day 0	8	-1, 6, 13, 20, 27, and 34	1, 7, 14, 21, 28, and 35
T02	Sarolaner	Day 0	8	-1, 6, 13, 20, 27, and 34	1, 7, 14, 21, 28, and 35

(d) Drug Administration:

All treatments were administered orally. Food was withheld overnight and tablets were administered within 20 minutes after food had been offered, followed by administration of a small volume of water.

(e) Measurements and Observations:

Each dog was infested with approximately 100 unfed adult *C. felis* at each infestation. At each flea count the numbers of live and dead fleas were counted, and the fl*eas* were removed from the dog. Clinical observations were conducted 1, 3, 6, and 24 hours after treatment. General health observations were conducted at least once daily. Flea counts and health assessments were conducted masked to treatment allocation.

(f) Statistical Methods:

For flea counts, percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C – T)/C] x 100, where C = geometric mean for the control group and T = geometric mean for the treated group for each time poin*t.* The comparisons were tested using the (two-sided) 5% significance

level. The mixed model analysis was used to analyze log-counts, with treatment group as a fixed effect and the allocation blocks as a random effect.

(iii) Results:

Control dogs maintained adequate flea infestations throughout the study with at least six of the eight dogs having 50 or more live fleas on each counting day.

The sarolaner-treated group had a 100% reduction in initial live flea counts 24 hours after treatment, and 100% reduction in live flea counts 24 hours after weekly re-infestations for 35 days.

Live flea counts for the sarolaner group were significantly different than the control group ($P \leq 0.0001$) on all post-treatment count days.

Table 26: Effectiveness Against Adult *C. felis*

Day of Flea Count	Control Group Geometric Mean Live Flea Count	Sarolaner Geometric Mean Live Flea Count	Percent Effectiveness
1	92.6	0.0	100
7	96.4	0.0	100
14	85.4	0.0	100
21	83.3	0.0	100
28	68.8	0.0	100
35	83.0	0.0	100

(iv) Adverse Reactions:

One dog in the sarolaner group vomited 6 hours after dosing.

(v) Conclusion:

This study demonstrated the effectiveness of sarolaner for the treatment of *C. felis* when assessed 24 hours after treatment of an existing infestation and 24 hours after weekly re-infestation for 35 days.

b. Laboratory Dose Confirmation Study A166C-US-12-110: Efficacy of sarolaner Administered Orally Against Induced Infestations of *Ctenocephalides felis* on Dogs in a Simulated Home Environment

(i) Location of Study:

Sugar Land, TX

(ii) Study Design:

(a) Study Objective: Demonstrate the effectiveness of repeated monthly oral doses of sarolaner at a minimum dosage of 2.0 mg/kg

to dogs for the treatment and prevention of infestations of *Ctenocephalides felis* in a simulated home environment.

(b) Study Animals:

24 Beagle dogs (12 male and 12 female), 6-8 months of age, weighing between 6.1-9.2 kg.

(c) Treatment Groups:

Table 27: Treatment groups for Study A166C-US-12-110

Group	Treatment	Days of Treatment	Dogs per Group	Days of Flea Infestation	Days of Flea Count
T01	Vehicle control	0, 30, and 60	12	-42, -35, 7, 37, and 67	-20, -6, 0, 14, 30, 44, 60, 74, and 90
T02	Sarolaner	0, 30, and 60	12	-42, -35, 7, 37, and 67	-20, -6, 0, 14, 30, 44, 60, 74, and 90

(d) Drug Administration:

All treatments were administered orally. Food was withheld overnight and tablets were administered within 20 minutes after food had been offered, followed by administration of a small volume of water.

(e) Measurements and Observations:

Each dog was infested with approximately 100 unfed adult *C. felis* at each infestation. The primary efficacy parameter was the live flea count. On Day 0 fleas were not replaced after counting. At all other counts up to 100 viable adult fleas were returned to the dog after counting. Clinical observations were conducted 1, 3, 6, and 24 hours after treatment. General health observations were conducted at least once daily. Flea counts and health assessments were conducted masked to treatment allocation.

(f) Statistical Methods:

For flea counts, percent effectiveness of the treated group with respect to the control group was calculated using the formula $[(C - T)/C]x100$, where C = geometric mean for the control group and T = geometric mean for the treated group for each time point. The comparisons were tested using the (two-sided) 5% significance level. The mixed model analysis was used to analyze log-counts, with treatment group as a fixed effect and the allocation blocks as a random effect.

(iii) Results:

Prior to treatment, nine of 12 dogs in each treatment group had 50 or more live fleas, and the mean live flea counts for the two groups were not statistically different, indicating that adequate environmental infestation had been established in all pens. After initiation of treatment, control dogs maintained adequate flea infestations with at least six of the 12 dogs having 50 or more live fleas through Day 60. After Day 60, an adequate infestation was not present in the control group.

The sarolaner-treated group had a ≥95.6% reduction in live flea counts within 14 days after the first treatment administration, and 100% effectiveness was reached on Day 60.

Live flea counts for the sarolaner group were significantly different than the control group ($P \leq 0.0001$) on all post-treatment count days.

Table 28: Effectiveness Against *C. felis* In Simulated Home Environment

Day of Flea Count	Control Group Geometric Mean Live Flea Count	Sarolaner Geometric Mean Live Flea Count	Percent Effectiveness
0	92.5	102.2	NA
14	99.6	4.4	95.6
30	54.6	0.8	98.6
44	65.4	0.2	99.6
60	40.9	0.0	100

(iv) Adverse Reactions:

No adverse reactions related to treatment with sarolaner were reported in this study.

(v) Conclusion:

This study demonstrated the effectiveness of sarolaner for the treatment and prevention of *C. felis* infestations in a simulated home environment.

c. Field Effectiveness and Safety Study A161C-US12-074: A Clinical Effectiveness and Safety Study of Orally Administered Sarolaner in the Treatment and Prevention of Natural Flea Infestations on Dogs Presented as Veterinary Patients

(i) Investigators:

Dickson Bain, DVM, Dallas, TX
Susan Baker, DVM, West Palm Beach, FL
Angela Bentley, DVM, Pensacola, FL
Brett Berryhill, DVM, Baton Rouge, LA
Justin Bruening, DVM, Seguin, TX
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Philip VanVranken, DVM, Battle Creek, MI
Phillip Waguespack, DVM, Baton Rouge, LA
Elizabeth Wynn, DVM Tampa, FL

Of the 19 sites, one site did not screen or enroll any cases. Two sites did not enroll adequate cases; therefore, these sites were removed from the effectiveness evaluation but remained in the safety database.

(ii) Study Design:

This was a masked, multi-center, field safety and effectiveness study using a randomized block design based on order of enrollment of households comparing sarolaner to an active control, spinosad. Dogs were recruited from 19 different sites in three distinct geographical regions across the United States. Due to the age restriction for the control product, eligible dogs less than 14 weeks of age and randomized to the control product were not enrolled in the study. The use of medications or products with flea treatment or control activity in any household dogs or household premises prior to or during the study period was not permitted. Treatments were administered on Days 0, 30, and 60. On or within one day prior to Day 0, each dog underwent a physical examination, flea counts were performed, clinical assessments of the severity of clinical signs of flea allergy dermatitis were made, body weight was measured, and blood and urine were collected for clinical pathology.

For primary dogs only, post-treatment flea counts and clinical assessments of the severity of clinical signs of flea allergy dermatitis were performed on Days 14, 30, 60, and 90.

For all dogs, post-treatment physical examination and body weight measurement were performed on Days 30, 60, and 90, and blood and urine were collected for clinical pathology on Day 90.

With the exception of Day 0, procedures were allowed to occur within three days of the scheduled Day.

Any ticks present on the dog during flea counts were counted, removed, and stored for later speciation.

(a) Study Objective: Evaluate the effectiveness and safety of sarolaner against natural infestations of fleas on dogs under field conditions. Secondary objectives were to evaluate improvement in the clinical signs of flea allergy dermatitis and to evaluate tick counts.

(b) Study Animals:

315 sarolaner-treated dogs and 164 spinosad-treated dogs were evaluated for safety. The effectiveness analysis for Day 30 was performed on 186 sarolaner-treated dogs and 96 spinosad-treated dogs.

Enrollment was limited to those households with a maximum of three dogs; there was no restriction on the type or number of other pets in the household. There were no breed or gender restrictions, but dogs intended for breeding, and pregnant or lactating dogs were not eligible for enrollment.

For a household to be included, at least one dog (the primary dog) had to have 10 or more live fleas. In households where more than one dog met this requirement, the primary dog was selected randomly, and the other dogs were designated as supplementary dogs. All dogs in a household received the same treatment as the primary dog and were included in safety evaluations. Only primary dogs were included effectiveness evaluations.

(c) Treatment Groups:

Table 29: Treatment Groups for Study A161C-US12-074

Group	Treatment	Days of Treatment	Dogs per Group (Primary Dogs)	Days of Flea Counts and Clinical Assessments	Days of Clinical Pathology
T01	Sarolaner	Day 0, 30, and 60	315 (195)	0, 14, 30, 60, and 90	0 and 90
T02	Spinosad	Day 0, 30, and 60	164 (98)	0, 14, 30, 60, and 90	0 and 90

(d) Drug Administration:

Owners administered sarolaner or the active control to their dogs in the dog's home environment. Owners were instructed to administer sarolaner with or without food, or to administer the spinosad with food.

(e) Measurements and Observations:

The primary effectiveness variable was the difference in mean live flea counts on primary dogs on Days 14, 30, 60, and 90 compared to pre-treatment on Day 0. Secondary variables included palatability, summaries of the severity of clinical signs of flea allergy dermatitis, physical examination, clinical pathology, dosing, and abnormal health. The number of dogs that voluntarily consumed sarolaner or vehicle without food (free choice) on each occasion was tabulated.

(f) Statistical Methods:

For flea counts, percent effectiveness of each treated group with respect to the baseline was calculated using the formula $[(B - T)/B] \times 100$, where B = baseline (pre-treatment) geometric mean and T = post-treatment geometric mean for each treated group at each time point.

(iii) Results:

The sarolaner-treated group had a 99.2% reduction in live flea counts 14 days after the first treatment administration, and >99.4% effectiveness was reached and maintained from Day 30 through the end of the study. The spinosad-treated group had a 97.1% reduction in live flea counts 14 days after the first treatment administration, and >94.9% effectiveness was maintained from Day 30 through the end of the study.

Table 30: Field Effectiveness Against Fleas- Geometric Mean Live Flea Count (Percent Reduction Compared to Pre-Treatment)

Group	Treatment	Day 0 (Pre-Treatment)	Day 14	Day 30	Day 60	Day 90
T01	Sarolaner	49.0	0.4 (99.2%)	0.3 (99.4%)	0.1 (99.8%)	0.0 (100%)
T02	Spinosad	48.0	1.4 (97.1%)	2.5 (94.9%)	0.3 (99.3%)	0.2 (99.6%)

Of those sarolaner-treated dogs that had clinical signs of flea allergy dermatitis prior to treatment, 87.7%-100% had improvement of the clinical signs by Day 90. Of the spinosad-treated dogs, 85.7% – 100% had improvement of the clinical signs of flea allergy dermatitis by Day 90.

Table 31: Field Effectiveness Against Fleas – Improvement in Clinical Signs of Flea Allergy Dermatitis- Percentage of Dogs with Improvement in Clinical Signs of Flea Allergy Dermatitis on Day 90

Clinical Sign	Sarolaner	Spinosad
Pruritus	93.6% (73 of 78)	93.5% (29 of 31)
Papules	100% (40 of 40)	100% (12 of 12)
Erythema	91.3% (73 of 80)	85.7% (30 of 35)
Scaling	87.7% (50 of 57)	89.3% (25 of 28)
Alopecia (from self-trauma)	92.2% (47 of 51)	91.7% (22 of 24)
Dermatitis / Pyodermatitis	96.2 (50 of 52)	91.3% (21 of 23)

On Day 90 there were no ticks on any dog in either treatment group. However, there were an insufficient number of dogs with pre-existing tick infestations to derive any conclusions.

Of the total of 884 doses administered in this study, 59.5% of dogs voluntarily consumed SIMPARICA, an additional 32.01% voluntarily consumed the product when offered with food, and 8.5% were pilled. Re-dosing was required for one dog that voluntary consumed the product.

(iv)Adverse Reactions:

Evaluation of safety was completed over the 90-day period through in-clinic physical examinations or through reporting of abnormalities by the owner for both primary and supplementary dogs. The safety database included 315 dogs administered sarolaner and 164 dogs administered spinosad.

Table 32: Dogs with adverse reactions

Adverse Reaction	Sarolaner	Spinosad
-	N (%)	N (%)
Vomiting	3 (0.95)	9 (5.5)
Diarrhea	2 (0.63)	2 (1.2)
Lethargy	1 (0.32)	2 (1.2)
Inappetence	0 (0)	3 (1.8)

One dog exhibited lethargy, ataxia while posturing to eliminate, elevated third eyelids, and inappetence one day after receiving sarolaner concurrently with a heartworm preventative (ivermectin/pyrantel pamoate). The signs resolved one day later. After the day 14 visit, the owner elected to withdraw the dog from the study.

(v) Clinical Pathology:

Mean results for hematology and serum chemistry in both treatment groups were within the normal reference range prior to initiation of treatment and on Day 90. Results of urinalyses were unremarkable for both treatment groups.

(vi)Conclusion:

The results of this study demonstrate that sarolaner, when used monthly at the minimum labeled dose of 2.0 mg/kg, is safe and effective for the treatment and prevention of flea infestations in dogs under field conditions.

3. Onset of Activity and Speed of Kill Against Fleas

a. Laboratory Dose Confirmation Study A166C-US-12-113: Knock-down and Speed of Kill of sarolaner Administered Orally Against Induced Infestations of *Ctenocephalides felis* on Dogs

(i) Location of Study:

Turlock, CA

(ii) Study Design:

(a) Study Objective: To confirm the knock-down and speed of kill of a single oral administration of 2 mg/kg sarolaner for a period of 35 days against *Ctenocephalides felis*.

(b) Study Animals:

64 Beagle dogs (32 male and 32 female), 10 - 142 months of age, weighing 8.0 - 18.6 kg.

(c) Treatment Groups:

Table 33: Treatment groups for Study A166C-US-12-113; Flea infestations on Days -1, 7, 14, 21, 28, and 35

Group	Treatment	Days of Treatment	Dogs per Group	Time of Flea Count After Treatment/ Infestation
T01	Vehicle control	Day 0	8	3 Hours
T02	Sarolaner	Day 0	8	3 Hours
T03	Vehicle control	Day 0	8	4 Hours
T04	Sarolaner	Day 0	8	4 Hours
T05	Vehicle control	Day 0	8	8 Hours
T06	Sarolaner	Day 0	8	8 Hours
T07	Vehicle control	Day 0	8	12 Hours
T08	Sarolaner	Day 0	8	12 Hours

(d) Drug Administration:

All treatments were administered orally. Food was withheld overnight and tablets were administered within 20 minutes after food had been offered, followed by administration of a small volume of water.

(e) Measurements and Observations:

Each dog was infested with approximately 100 unfed adult *C. felis*. The primary effectiveness parameter was the live flea count. Fleas were removed from the dog after each count. Clinical observations were conducted 1, 3, 6, and 24 hours after treatment. General health observations were conducted at least once daily. Flea counts and health assessments were conducted masked to treatment allocation.

(f) Statistical Methods:

For flea counts, percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C – T)/C] x 100, where C = geometric mean for the control group and T = geometric mean for the treated group for each time point. The comparisons were tested using the (two-sided) 5% significance

level. The mixed model analysis was used to analyze log-counts, with treatment group as a fixed effect and the allocation blocks as a random effect.

(iii) Results:

Control group dogs maintained adequate flea infestations throughout the study with at least six of the eight dogs having 50 or more live fleas at each counting time on all days.

Against an existing flea infestation and five weekly re-infestations, sarolaner provided ≥2.9%, ≥26.6%, ≥96.2%, and ≥95.7% reduction in live flea counts at 3, 4, 8, and 12 hours after treatment/infestation. Live flea counts in the sarolaner group were significantly different than control on all study days for the 8 and 12 hour time points (P≤0.0017)

Table 34: *C. felis* Onset of Activity and Speed of Kill

Day of Flea Infestation	Time of Flea Count	Control Group Geometric Mean Live Flea Count	Sarolaner Geometric Mean Live Flea Count	Percent Effectiveness
-1	3 Hours	63.7	27.8	56.3
-1	4 Hours	67.1	6.4	90.4
-1	8 Hours	69.9	0.0	100
-1	12 Hours	60.7	0.0	100
7	3 Hours	76.4	6.9	91.0
7	4 Hours	81.0	12.6	84.4
7	8 Hours	90.9	0.0	100
7	12 Hours	87.9	0.0	100
14	3 Hours	66.8	52.6	21.3
14	4 Hours	72.2	14.1	80.4
14	8 Hours	73.5	0.2	99.7
14	12 Hours	81.9	0.1	99.9
21	3 Hours	77.6	25.5	67.2
21	4 Hours	82.1	36.6	55.4
21	8 Hours	83.3	0.3	99.6
21	12 Hours	83.3	0.0	100
28	3 Hours	69.4	61.1	12.0
28	4 Hours	74.5	44.3	40.5
28	8 Hours	84.3	1.7	98.0
28	12 Hours	86.2	0.8	99.1
35	3 Hours	76.7	74.5	2.9
35	4 Hours	79.4	58.3	26.6
35	8 Hours	81.9	3.1	96.1
35	12 Hours	80.7	3.5	95.7

(iv) Adverse Reactions:

There were no adverse reactions during this study.

(v) Conclusion:

This study demonstrated that sarolaner reduced the number of live fleas by ≥96.2% within 8 hours after flea infestation through Day 35. At 12 hours after infestation, sarolaner reduced the number of live fleas by ≥95.7% through Day 35.

b. Laboratory Dose Confirmation Study A166C-US-13-268: Dose Confirmation of sarolaner Administered Orally Against *Ctenocephalides felis* Egg Production, Egg Hatch, and Adult Flea Emergence

(i) Location of Study:

Turlock, CA

(ii) Study Design

(a) Study Objective: To confirm the effectiveness of a single oral administration of 2.0 mg/kg sarolaner in the prevention of pre-adult stages of *C. felis*.

(b) Study Animals:

20 Beagle dogs (10 male and 10 female), 1 - 3 years of age, weighing 8.4 - 12.4 kg.

(c) Treatment Groups:

Table 35: Treatment groups for Study A166C-US-13-268

Group	Treatment	Days of Treatment	Dogs per Group	Days of Flea Infestation	Days of Flea Egg Collection
T01	Vehicle control	Day 0	10	-1, 5, 12, 19, 26, and 33	1, 7, 14, 21, 28, and 35
T02	Sarolaner	Day 0	10	-1, 5, 12, 19, 26, and 33	1, 7, 14, 21, 28, and 35

(d) Drug Administration:

All treatments were administered orally. Food was withheld overnight and tablets were administered within 20 minutes after food had been offered, followed by administration of a small volume of water.

(e) Measurements and Observations:

Each dog was infested with approximately 100 unfed adult *C. felis* at each infestation. The primary effectiveness parameter was the flea egg count. Flea eggs were collected for a 20 hour period beginning 48 hours after each infestation. After each egg collection

dogs were combed to remove adult fleas, but fleas were not counted. Up to 100 eggs from each dog were incubated for five days and evaluated for larval emergence, and up to 100 eggs from each dog were incubated for 35 days and evaluated for adult flea emergence. Clinical observations were conducted 1, 3, 6, and 24 hours after treatment. General health observations were conducted at least once daily. Study participants making assessments of efficacy and safety were masked to treatment allocation.

(f) Statistical Methods:

Log-transformed flea egg counts for treated and control dogs were compared using a mixed linear model with treatment group as a fixed effect and block and error as random effects at each time. Testing was two-sided at the 5% significance level. Percent effectiveness against control was calculated based on geometric means.

(iii) Results:

No flea eggs were collected from any sarolaner-treated dog on any post-treatment collection day, through Day 35.

Flea egg counts for the sarolaner group were significantly different than the control group ($P<0.0002$) on all post-treatment egg collection days.

Table 36: Effectiveness Against *C. felis* Egg Production

Day of Flea Egg Collection	Control Group Geometric Mean Flea Egg Count (range)	Sarolaner Geometric Mean Flea Egg Count	Percent Effectiveness
1	229.9 (10-735)	0.0	100
7	159.4 (0-710)	0.0	100
14	78.5 (10-582)	0.0	100
21	61.6 (0-933)	0.0	100
28	59.3 (0-597)	0.0	100
35	153.9 (12-812)	0.0	100

(iv) Adverse Reactions:

No adverse reactions were reported in this study.

(v) Conclusion:

This study demonstrated the effectiveness of sarolaner in killing adult *C. felis* in an existing infestation, and against weekly re-infestation, before they can lay eggs, thus contributing to the prevention of flea infestations.

III. TARGET ANIMAL SAFETY

A. Margin of Safety Study A362N-US-12-115 (WIL-344084)

1. Title: Margin of Safety of sarolaner (sarolaner) in Young Beagle Dogs Administered in 10 Consecutive Monthly Doses

2. Location and Dates:

   Ashland, OH
   Study dates: April 22, 2013 to July 28, 2014

3. Study Design:

   a. Objective:

      Study A362N-US-12-115 evaluated the margin of safety of sarolaner chewable tablets following oral administration to puppies 8 weeks old at initiation of the study at doses of 0, 1, 3, and 5X the maximum label dose (0, 4, 12, and 20 mg/kg) dosed 10 times at 28 day intervals.

   b. Study Animals:

      32 healthy beagle puppies (16 male and 16 female), age 56-59 days at Day 0. Body weight on Day 0 ranged for females from 1.6-2.5 kg and for males from 1.6-2.6 kg.

   c. Treatment Groups:

      Table 37: Treatment Groups for Study A362N-US-12-115

Treatment	Dogs	Dose (mg/kg) PO
Vehicle control	8 (4M/4F)	0
1X	8 (4M/4F)	4
3X	8 (4M/4F)	12
5X	8 (4M/4F)	20

   d. Drug Administration:

      All treatments were administered orally on Days 0, 28, 56, 84, 112, 140, 168, 196, 224, and 252, for a total of 10 treatments per dog. Dogs were fasted overnight prior to dosing and at least 4 hours post-dosing with sarolaner chewable tablets, except on Day 0. The control group received the number of vehicle control tablets (same excipients as test formulation minus the active ingredient) corresponding to the 5X treatment group dogs.

   e. Measurements and Observations:

      In-life assessments included measurements of body weight twice weekly, food consumption daily, ophthalmic examinations pre-treatment and prior to necropsy, twice daily technician-conducted daily general health observations, and veterinary physical examinations before pre-treatment and prior to necropsy. Directed veterinary clinical observations were

performed prior to each dose, and at 2 and 6 hours post-dosing, and then daily for 6 days following each dose. Veterinary Neurologic Examinations were performed prior to dosing, at 2 and 6 hours post-dosing, and once daily on the day following each dosing day. Blood samples were collected for clinical pathology (hematology, coagulation, and serum chemistry) and pharmacokinetic evaluation at pre-treatment, prior to each dose, and prior to necropsy. Urine was collected for analysis. All dogs were euthanized one week after the final dose (Day 259) and a complete necropsy was performed. Macroscopic and microscopic examination of tissues was conducted by a board-certified veterinary pathologist.

4. Statistical Methods:

   Body weight, temperature, average daily feed consumption, and numerical clinical pathology data were analyzed by using a general linear mixed model for repeated measures. The most recent pre-treatment clinical pathology data were used as covariates for their respective analyses.

   For organs collected, organ weight and organ weight relative to final body weight and brain weight were analyzed using a mixed linear model.

5. Results:

   There were no test article related findings in veterinary physical examinations, ophthalmic, macroscopic or microscopic evaluations. There were no effects on survival, body weights, food consumption, hematology, coagulation, serum chemistry, urinalysis parameters, or organ weights.

   Test article related neurological signs were noted during daily general health observations and directed veterinary clinical observations in the 3X and 5X groups, primarily during the first half of the 10 dose study. Directed observations were conducted 2 and 6 hours after dosing and then daily for 7 days.

   The most severe test article-related clinical sign was seizures, observed in 2 female 5X dogs, #3640 and #3646.

   - Dog #3640 exhibited seizures within approximately 24 hours of both Dose 2 (at 12 weeks of age) and Dose 4 (at 20 weeks of age) which were accompanied by typical ictal and post-ictal signs (tremors, hypersalivation, decreased activity, mild dyspnea, equilibrium impairment, mentation change, abnormal head posture). No treatment was required and recovery was complete. The dog also exhibited tremors associated with Dose 2 six hours post-dose and intermittent tremors associated with Dose 3.

   - A seizure was recorded in dog #3646 five days after the third dose (at 16 weeks of age). This dog recovered without treatment and did not have any other neurological signs through the rest of the study

Test article-related neurologic events were observed in several dogs at various time points during the first half of the study:

- Following Dose 1, one 3X male (#3628) exhibited tremors and ataxia at 2 hours post-dose; one 3X female (#3636) exhibited tremors on Days 1, 2, 3, and 5; one 3X female (#3650) exhibited tremors on Day 1; and one 5X female (#3654) exhibited tremors 6 hours post-dose.

- Following Dose 3, one 5X dog (#3640) exhibited intermittent tremors (as described above, this dog had seizures after Dose 2 and 4).

The only other test article-related neurological sign was observed on a directed neurological exam after dose 6. Female 5X dog #3654 exhibited "abnormal head coordination" on neurological examination that was considered to be test article-related.

Following oral dosing at 1X, 3X, and 5X the maximum intended dose of 4 mg/kg, sarolaner was determined to be dose-proportional with regards to AUC_{o-t}. Upon visual inspection and statistical analysis of the plasma concentration-time profiles, it appeared that steady state was reached following 6 - 7 consecutive monthly doses.

6. Conclusion:

Due to the number, severity, and dose dependent manner in which the abnormal neurologic observations occurred, an adequate margin of safety was not demonstrated in 8 week old Beagle puppies. Based on the absence of abnormal neurologic observations at 6 months of age and older, and the extensive effectiveness safety database, it was determined that sarolaner was well tolerated when administered orally once monthly in dogs 6 months of age and older with a bodyweight of 2.8 pounds or more.

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, 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 SIMPARICA:

Not for use in humans. Keep this and all drugs out of reach of children.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that SIMPARICA, when used according to the label, 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), *Amblyomma maculatum* (Gulf Coast tick), *Dermacentor variabilis* (American Dog tick), and *Rhipicephalus sanguineus* (brown dog tick)] for one month in dogs 6 months of age or older and weighing 2.8 pounds or more.

A. Marketing Status

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to monitor for and respond to adverse reactions.

B. Exclusivity

SIMPARICA, as approved in our letter, qualifies for FIVE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(i) of the FD&C Act because this is the first time we are approving this active ingredient in a new animal drug application submitted under section 512(b)(1) of the FD&C Act.

C. Patent Information:

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