

Comparative Efficacy of Fipronil/(S)-Methoprene/Pyriproxyfen (FRONTLINE® Gold) and Sarolaner (SIMPARICA®) Against *Ctenocephalides felis* flea Infestations on Dogs

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ABSTRACT

A study was performed to compare the 6-hour efficacy of FRONTLINE® Gold (fipronil/(S)-methoprene/pyriproxyfen) with that of SIMPARICA® (sarolaner) against *Ctenocephalides felis* flea infestations on dogs. Twenty-four dogs were allocated to one of three groups, eight dogs in each group. On Day 0, each dog in Group B was treated with a dose of commercially available FRONTLINE Gold for dogs appropriate for its weight, and each dog in Group C was treated with a dose of commercially available SIMPARICA appropriate for its weight. Group A dogs remained untreated throughout the duration of the study. On each of Days 1, 7, 14, 21, and 28, all dogs were infested with 100 live, unfed *Ctenocephalides felis* fleas, and 6 hours later, all fleas were removed and counted. Us-

ing arithmetic means for all calculations, dogs treated with FRONTLINE Gold had significantly ($p < 0.01$) fewer live fleas than the controls at 6 hours post-infestation on all assessment days from Day 1 to Day 28. FRONTLINE Gold's 6-hour efficacies were 88.8%, 98.2%, 99.2%, 95.2%, and 83.0% on Days 1, 7, 14, 21, and 28, respectively. Dogs treated with SIMPARICA had significantly ($p < 0.01$) fewer live fleas than the controls at 6 hours post-infestation on the same days. SIMPARICA 6-hour efficacies were 100%, 100%, 98.8%, 86.6%, and 87.0% on the same days, respectively. There was no significant ($p > 0.05$) difference in flea count between the dogs treated with FRONTLINE Gold and those treated with SIMPARICA on any of the 6-hour post-infestation assessments.

INTRODUCTION

Ctenocephalides felis felis, also known as the cat flea, is a very common ectopara-

Table 1. Individual dog information and results of allocation (Day -4)

Treatment group	Dog ID	Age (years)	Sex	Weight (kg) Day -4	Dose given
Group A (untreated controls)	MC4692	2	M	13.5	N/A
	F0205	4	F	8.9	
	MC5208	2	F	12.6	
	MC1744	2	F	14.7	
	MC4581	3	M	10.0	
	NE1217	5	M	14.5	
	MC2256	4	F	10.3	
	F0187	4	F	8.4	
Group B (FRONT- LINE Gold-treated)	MC2983	3	M	9.0	0.67 mL
	MC5436	2	M	10.7	1.34 mL
	MC4645	2	M	11.0	1.34 mL
	MC4441	2	M	12.7	1.34 mL
	F0101	5	F	9.9	0.67 mL
	MC4195	4	M	10.3	1.34 mL
	MC4722	2	M	13.4	1.34 mL
	MC4172	3	M	12.2	1.34 mL
Group C (SIMPAR- ICA-treated)	F0121	5	F	12.5	40.0 mg
	MC4537	3	F	13.2	40.0 mg
	MC5599	2	F	9.9	20.0 mg
	MC4684	3	M	9.0	20.0 mg
	MC2844	2	F	9.9	20.0 mg
	MC4114	3	F	10.9	40.0 mg
	MC0365	3	M	11.3	40.0 mg
	F0194	4	F	10.7	40.0 mg

sitic insect that survives by feeding on the blood of dogs, cats, and other mammals. Flea infestations on pets can cause Flea Allergy Dermatitis, pruritus, tapeworms, and anemia.

In order to control such afflictions caused by the presence of fleas, many insecticidal formulations have been marketed in the past several decades to control flea infestations on pets, including selamectin, imidacloprid, pyrethroids/pyrethrins, isoxazolines, fipronil, and various insect growth regulators such as (S)-methoprene and pyriproxyfen. Two modes of action for flea control products currently exist: oral products, which are always systemically active, and topical products, which are typically

active by contact, and may, for some be systemically active. Each veterinarian and pet owner has a unique preference for the mode of action of the flea control product he/she selects for use.

The purpose of the present study was to assess the 6-hour efficacy of the topically applied FRONTLINE Gold for Dogs (fipronil/(S)-methoprene/pyriproxyfen) compared to that of orally-administered SIMPARICA (sarolaner) against *Ctenocephalides felis* flea infestations on dogs. A comparison of the capabilities of FRONTLINE Plus with those of SIMPARICA, including activity against fleas, is important to assist veterinarians and pet owners to decide which product is better

Table 2. Summary of arithmetic mean flea (*Ctenocephalides felis*) counts (with efficacies) for dogs treated with FRONTLINE Gold or SIMPARICA

Day	Control AM	FRONTLINE Gold AM (Efficacy)	SIMPARICA AM (Efficacy)
1	81.1	9.1 ^A (88.8%)	0.0 ^A (100%)
7	89.3	1.6 ^A (98.2%)	0.0 ^A (100%)
14	91.8	0.8 ^A (99.2%)	1.1 ^A (98.8%)
21	95.5	4.6 ^A (95.2%)	12.8 ^A (86.6%)
28	88.1	15.0 ^A (83.0%)	11.5 ^A (87.0%)

^A Significantly different from control ($p < 0.01$)

AM=Arithmetic mean

suiting for their pets, taking into account the efficacy of these products, as well as their modes of action.

MATERIALS AND METHODS

Animal Welfare

This study was conducted at BerTek, Inc., an experienced, independent contract research facility. All animals were managed similarly and with due regard for their welfare. All animals were handled in compliance with the Boehringer Ingelheim and BerTek, Inc. Institutional Animal Care and Use Committee (IACUC) approvals. The trial facility used for the study meets USDA-APHIS animal welfare requirements. The Investigator ensured that all personnel were appropriately trained, and that procedures were in compliance with the protocol. Concomitant veterinary care and therapy, as well as any adverse events, were recorded.

All dogs were allowed to

acclimate to the test facility for 7 days. All dogs were housed individually in accordance with the Animal Welfare Act. All dogs received one to two cups of commercial dry canine ration (Loyall, Adult Maintenance Formula, Nutrena) once daily, meeting their daily nutritional requirements, and fresh water was provided from the local city water supply ad libitum.

Animal Management and Study Inclusion

Twenty-four dogs (12 males and 12 females) were selected for study inclusion. The dogs were aged between approximately 2 to 5 years and weighed between 8.4 and 14.7 kilograms (as weighed on Day -4). No dogs younger than 8 weeks or weighing less than 5.0 kilograms were considered for use in this study. No animals which may have been debilitated, suffering from disease or injury, fractious, presenting abnormalities at the application sites, or otherwise unsuitable

Table 3. Results of the t-tests data comparing each treated group to the control group, and comparing FRONTLINE Gold to SIMPARICA

Day	Control vs. FRONTLINE Gold AM p-value	Control vs. SIMPARICA AM p-value	FRONTLINE Gold vs. SIMPARICA AM p-value
1	<0.0001 ^U	<0.0001 ^U	>0.10 ^U
7	<0.0001 ^U	<0.0001 ^U	>0.10 ^U
14	<0.0001 ^U	<0.0001 ^U	>0.10 ^E
21	<0.0001 ^E	<0.0001 ^U	>0.10 ^U
28	<0.0001 ^E	<0.0001 ^E	>0.10 ^E

^E Results from t-test for means with poolable variances

^U Results from t-test for means with unequal variances

AM=Arithmetic mean

for inclusion were considered for use. All dogs were in good health, and none had been treated with a monthly ectoparasiticide within 3 months prior to study initiation, nor had they been treated with a topical 3-month ectoparasiticide within 1 year of the study initiation. Individual dog information, as assessed before study inclusion, is listed in Table 1.

Allocation

Eight replicates of three dogs each were formed. Within replicates, each dog was randomly allocated to one of three treatment groups. Group A comprised untreated control dogs, Group B comprised FRONTLINE Gold-treated dogs, and Group C comprised SIMPARICA-treated dogs. Allocation was done with ticks, as the tick study took place concurrently with the present flea study, and the same dogs were used for these studies. Therefore, treatment groups formed during the allocation process for the tick study effectively randomized the dogs for the present flea study as well. The dogs remained in their assigned groups throughout the duration of the study. The results of the allocation process are shown in Table 1.

Study Design

This study was a well-controlled efficacy study using a randomized block design based on dog pre-treatment tick infestation counts, and all evaluations of efficacy were performed by personnel in blinded conditions. Each dog was an experimental unit.

The *Ctenocephalides felis* fleas used were from the BerTek, Inc. colony originating in 2004 from fleas purchased from Professional Laboratory and Research Services, Inc. The colony has been supplemented multiple times with new genetics from local, wild-caught fleas in Greenbrier, Arkansas, most recently on July 3, 2017. The colony is maintained on cats.

Treatment

All dogs were weighed on Day -4, and the appropriate product and dose were selected for each dog based on its weight. On Day 0, Group B dogs were treated with either 0.67 mL (for dogs 2.3 to 10.0 kg) or 1.34 mL (for

dogs 10.4 to 20.0 lbs) of FRONTLINE Gold for Dogs, which was applied according to label instructions: topically by parting the hair between the shoulder blades, applying the formulation directly to the skin at the base of the neck, and dragging it down the spine in a single line. Also on Day 0, Group C dogs were treated with either 20.0 mg (for dogs 5.0 to 10.0 kg) or 40.0 mg (for dogs 10.0 to 20.0 kg) of SIMPARICA, which was administered according to label instructions: by administering one whole chewable orally. Group A dogs remained untreated throughout the duration of the study.

Flea Counts

On each of Days 1, 7, 14, 21, and 28, all dogs were infested with 100 *Ctenocephalides felis* fleas, which were placed on the lateral aspect of the body to avoid potential direct contact with the product application site. At 6 hours following each infestation, all fleas were removed from all dogs, counted, and discarded.

STATISTICAL ANALYSIS

The statistician was responsible for the calculation of efficacy. The statistical unit was the individual dog, and the primary assessment variable in this study was the decrease in the number of live fleas. The average percent reduction in flea counts for each group was calculated using arithmetic means:

Efficacy (%) against fleas = $100 \times (\text{AMC} - \text{AMT}) / \text{AMC}$, where AMC = arithmetic mean number of live fleas in the control group, and AMT = arithmetic mean number of live fleas on dogs in the treated group.

The data were analyzed using t-tests for means with poolable variances or for means with unequal variances, as appropriate. Variances were compared using the Maximum-F test and Satterthwaite's Approximation was used to determine the degrees of freedom for the unequal-variance tests. When one group had zero variance, variances were declared unequal by definition. Each treated group was compared to the control group, and the two treated groups were compared to each other.

All analyses and calculations were performed using SAS Version 9.4, and statistical significance was declared at a two-sided p-value of 0.05.

The data and results of the t-tests are summarized in Tables 2 and 3.

RESULTS

Adverse Reactions

All dogs remained in apparent good health throughout the study, no adverse events were noted, and no dogs were removed from the study.

Flea Efficacy

Using arithmetic means for all calculations, dogs treated with FRONTLINE Gold had significantly ($p < 0.01$) fewer live fleas than the controls at 6 hours post-infestation on all assessment days from Day 1 to Day 28. Dogs treated with SIMPARICA had significantly ($P < 0.01$) fewer live fleas than the controls at 6 hours post-infestation on the same days.

FRONTLINE Gold 6-hour efficacies were 88.8%, 98.2%, 99.2%, 95.2%, and 83.0% on Days 1, 7, 14, 21, and 28, respectively. SIMPARICA 6-hour efficacies were 100%, 100%, 98.8%, 86.6%, and 87.0% on the same days, respectively. There was no significant ($p > 0.05$) difference in flea count between the dogs treated with FRONTLINE Gold and those treated with SIMPARICA on any of the 6-hour post-infestation assessments.

DISCUSSION AND CONCLUSIONS

Flea control products that are systemically active and administered orally, as well as products that are or are not systemically active and applied topically, can both be effective against fleas. Pet owners and veterinarians have different preferences for which type of flea control products to use for their pets. Additionally, each pet owner has his/her own unique preference for the mode of action of flea control products based on their prior experiences with pet products, the lifestyle and personal needs of their pets, and recommendations from their veterinarian.

The present study demonstrated that

treatment with a single dose of topically applied FRONTLINE Gold resulted in a rapid reduction in live flea numbers just 6 hours post-infestation throughout a 28-day period. There was no statistical ($p > 0.05$) difference in flea count between the dogs treated with FRONTLINE Gold and those treated with SIMPARICA throughout the study, making either product an effective flea control option for pet owners. For those who prefer topical products that are not systemically active, FRONTLINE Gold is an exceptional choice for flea control on pets.

CONFLICT OF INTEREST

These clinical studies were funded by Boehringer Ingelheim, of which Doug Carithers is an employee, and Jordan Crawford is a contractor. BerTek, Inc., of which William Russell Everett is an employee, is an independent contract research facility contracted to conduct the present study. Sheila Gross is an independent statistician.

All authors voluntarily publish this article and have no personal interest in these studies, other than publishing the scientific findings in which they have been involved via planning, initiating, monitoring, and conducting the investigations, as well as analyzing the results.

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