**COMPARATIVE EFFICACY ON DOGS OF A SINGLE TOPICAL TREATMENT WITH THE PIONEER FIPRONIL/(S)-METHOPRENE AND AN ORAL TREATMENT WITH SPINOSAD AGAINST Ctenocephalides felis**

BEUGNET F.*, DOYLE V.**, MURRAY M.*** & CHALVET-MONFRAY K.****

Summary:
In the study reported here, the pioneer fipronil/(S)-methoprene topical product (FRONTLINE® PLUS, Merial Limited, Duluth, GA) was compared to the oral spinosad product (COMFORTIS® Elanco, Greenfield, IN) for efficacy against adult fleas and preventing egg production. The product presentations, doses and labelling were the same applicable in the USA. Using a standard protocol, 200 cat fleas of mixed sex were applied to dogs on Days 1, 7, 14, 21, 28, 35, and 42. Dogs were combed to remove fleas 24 hours post-infestation, the fleas were counted, collected, and then reapplied to each dog following completion of their respective count. At 48 hours post-infestation, comb counts were performed and fleas were removed. No fleas were collected from any dog in the fipronil/(S)-methoprene group at any 24 or 48 hours post-infestation assessment throughout the six weeks study, yielding a preventive efficacy of 100%. For the spinosad treatment, efficacy was 100% at 24 hours and 48 hours through Day 16, and thereafter declined. The results observed in the spinosad-treated dogs were highly variable between animals. At the 24 and 48 hours counts following the Day 21 infestation, only five of eight spinosad-treated dogs (62.5%) were flea-free. Following the Day 28 infestation, spinosad efficacy fell to 85% and 89%, for the 24 and 48 hours counts, and only two dogs (25%) were flea free, compared to 100% flea-free dogs in the fipronil/(S)-methoprene group. No fleas were collected from the fipronil/(S)-methoprene treated dogs throughout the entire study, therefore, no eggs were collected at any time from any dog in the group. However, in the spinosad group adult fleas were found on dogs starting on Day 21 and by Day 30, 42 eggs were collected from one dog that had 107 adult fleas counted at 48 hours. At Day 37 and Day 49, more than 100 eggs were collected from each dog in the spinosad-treated and control groups.

**KEY WORDS:** fipronil/(S)-methoprene, spinosad, Ctenocephalides felis felis, duration of efficacy, flea egg, FRONTLINE® PLUS, COMFORTIS®.

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**Dogs are infested by two flea species: the cat flea, Ctenocephalides felis felis, which is considered to be the predominant flea species found on dogs and cats worldwide (Durden et al., 2005; Farkas et al., 2009; Gracia et al., 2007), and the dog flea, Ctenocephalides canis, generally regarded as less important (Beck et al., 2006; Dryden & Rust, 1994; Franc et al., 1998). Fleas are responsible for various clinical signs, including pruritus, alopecia, anaemia, seborrhoea, and development of an allergies (Flea Allergy Dermatitis). Fleas are also the carrier of pathogens, including Rickettsia felis, Bartonella henselae, and Mycoplasma-Haemoplasma and the parasite, Diphylidium caninum. Due to their low host-specificity, fleas easily infest numerous species of wild animals, feral dogs and cats, pets***
and will feed on pet owners. The goals of effective flea control are to provide relief to the pet and eliminate infestation of the premises (Dryden, 2009). Controlling flea infestations is mainly based on the regular administration of flea adulticides on pets, and the use of insect growth regulators (IGR) (Franc & Cadiergues, 1995; Jacobs et al., 2001). Available insecticides are represented by many classes with various modes of action (IRAC, 2010). The majority of available treatments for dogs and/or cats are topical spot-on applications (Barnett et al., 2008; Cadiergues et al., 2001; Rust et al., 2007; Young et al., 2004). The active molecules of these topical preparations are absorbed and act systemically, or spread on the skin and act by direct contact with the arthropods (Cochet et al., 1997). A few products are given orally like lufenuron, nitenpyram, and more recently spinosad (Dobson et al., 2000; Kirst, 2010; Robertson-Plouch et al., 2008).

The most effective animal-based flea control strategies need to provide: 1 – a sustained activity and speed of kill on adult fleas during a known period (at least a month); and 2 – the control of immature stages by inhibiting the production of eggs and/or the development of flea eggs into larvae, pupae and newly emerged fleas (Dryden, 2009; Dryden et al., 2000; Beugnet & Franc, 2010). Failure to kill all fleas before they can reproduce in the absence of an insect growth regulator can permit the persistence of a premise flea infestation.

The aim of this trial was to study and compare the level and duration of efficacy of the topical formulation of fipronil/(S)-methoprene (FRONTLINE® PLUS, Merial Limited, Duluth, GA) and the oral formulation of spinosad (COMFORTIS® Elanco, Greenfield, IN) against adult fleas on dogs, and to assess their respective efficacy for controlling flea egg production. Fipronil is a phenylpyrazole acting by contact on arthropods, binding and blocking GABA and glutamate-gated chloride channels on the arthropod nerve cells and inducing the parasite death. Spinosad is a mixture of spinosyns A and D, belonging to the spinosyn macrocyclic lactone group, and acting on insects through ingestion by stimulating the nicotinic acetylcholine receptors of insect nerve cells.

### MATERIALS AND METHODS

#### STUDY DESIGN

This study was a negative controlled efficacy study using a randomized block design where blocks were based on pre-treatment flea counts. Three groups of eight dogs were formed: untreated control, fipronil/(S)-methoprene treated group and spinosad treated group. 30 healthy Beagle dogs were used, 15 males and 15 females, between eight to 12 months old. To qualify for inclusion, dogs could not have been treated with an ectoparasiticide within three months prior to the start of the study. Animals were managed similarly and with due regard for their well-being. Animals were handled in compliance with the relevant Institutional Animal Care and Use Committee approvals and any other, e.g. national or local, applicable regulations and requirements.

All dogs were shampooed, according to the Schedule of Operations, with a non-insecticidal shampoo for approximately five minutes each prior to or on Day -20. Dogs were pre-infested with 200 (± 5) adult unfed *C. felis* once, on Day -16, for selection purposes. Three dogs of each sex with lowest flea counts were removed. Dogs were treated on Day 0, and post treatment, infestations were performed on Days 1, 7, 14, 21, 28, 35, and 42 using 200 (± 5) adult unfed *C. felis*, and counts were performed at 24 and 48 hours post-infestation.

Adult unfed *C. felis* belonging to the CRL strain (Charles River Laboratories, Ireland) were used for infestations. These fleas are not known to be tolerant to any ectoparasiticide. The study was conducted such that all personnel involved in parasite infestation counting and evaluation of results were blinded to the treatment.

#### TREATMENT ADMINISTRATION (Table I)

Dogs were weighed between Day -3 and Day -1 for dosage determinations. When the weights were not a whole kg, they were rounded up to the next whole kg. Dogs in Treatment Group 1, negative control, were untreated.

| Bodyweight range – kg (lbs) | Pipette size | Pipette volumes – ml. | Tablet size – mg |
|-----------------------------|-------------|----------------------|-----------------|
| Frontline® Plus treated dogs | Up to 10 (22 lbs) | S | 0.67 |
| 10.1-20 (23-44 lbs) | M | 1.34 |
| Comfortis® treated dogs | 9.1-18.1 (20.1-40 lbs) | | 560 |

Table I. – Dosage of dogs in the treated groups.
Dogs in Treatment Group 2 were treated with the appropriate pipette size of FRONTLINE® PLUS spot-on. For treatment administration, the total volume was applied on one spot placed on the midline of the neck. The hair was parted at the base of the neck, between the shoulder blades, until the skin was visible. The tip of the pipette was placed on the skin and squeezed to empty its contents directly onto the skin. The dogs treated with FRONTLINE® PLUS weighed from 10 to 13.3 kg. They were all treated with the 1.34 mL pipette except the 10 kg dog with the 0.67 mL pipette.

Dogs in Treatment Group 3 were treated with the appropriate chewable tablet of COMFORTIS®, using the US presentations and labeling. The tablet was administered with food as recommended by the manufacturer. Following treatment on Day 0, all dogs were observed hourly (± 30 minutes) for four hours after the last animal was treated. The dogs treated with COMFORTIS® weighed from 10.4 to 15.8 kg. They were all treated with the 560 mg tablet. The minimal treatment dose is 30 mg/kg in the USA and 45 mg/kg in Europe. Except two dogs treated at 35.44 mg/kg and 38.55 mg/kg, all the others received a dose over the minimum European recommended dose of 45 mg/kg.

SPECIFICATION OF STUDY VARIABLES

• Adult flea count

Fleas were comb-counted initially at 24 hours post-infestation, then replaced on the dog, and then counted and removed at 48 hours post-infestation on all dogs.

• Egg count

Flea eggs were collected overnight for a 12 hours period from 36 to 48 hours post infestation. The dogs were placed in a cage with a grille at the bottom and a dark plate below the grille. The flea eggs are small, oval and white, measuring 0.4 × 0.6 mm. When the 24 hours adult flea counts were found to be positive, those dogs were subsequently placed in cages for flea egg collection. It was predetermined that egg counts at or higher than 100 eggs per dog within a 12 hours period would be sufficient enough to ensure the animal's environment would be continuously contaminated. Egg totals less than 100 were recorded, but when the egg counts reached or exceeded the threshold of 100 flea eggs within a 12 hours period, the count was entered as a maximum of 100 eggs.

DATA ANALYSIS

• Adulticidal efficacy

Counts of live adult fleas were transformed to the natural logarithm of (count + 1) for calculation of geometric means by treatment group at each time point. Percent reduction from the negative control mean was calculated using the formula [(C - T) / C] × 100, where C = geometric mean for the control group and T = geometric mean for the treated group. Arithmetic means were also calculated.

• Statistical analysis

The three treatment groups were initially tested using the Kruskal-Wallis rank sum test. Because all Kruskal-Wallis rank tests were significant, a non parametric multiple comparison test (Pairwise Wilcoxon Rank Sum Test) was done at each date. Thus for each date, the test compared Control vs FRONTLINE® PLUS, Control vs COMFORTIS®, and COMFORTIS® vs FRONTLINE® PLUS.

RESULTS

ADULTICIDAL EFFICACY (Tables II and III)

No fleas were collected in the fipronil/(S)-methoprene treated group on any dog at any time during the six weeks of the trial. The preventive efficacy was 100 %, and all dogs remained free of fleas (Tables II and III).

In the group treated with spinosad, efficacy was 100 % during the first two weeks (from Day 1 to Day 14 challenge), but for the Day 28 infestation efficacy fell to 85 % at the 24 hours count and to 89 % at the 48 hours count (Table III, Fig. 1). The geometric and arithmetic means were significantly different between the spinosad and the fipronil/(S)-methoprene groups following the weekly infestations on Day 28, Day 35 and Day 42 at both 24 hours and 48 hours (p < 0.01 at each time counts). There was no significant difference between the spinosad group and the untreated control group at the 48 hours count following the Day 42 infestation.

Moreover, the results in the spinosad treated group were highly variable between dogs (Table II; Figs 2 and 3). Following the Day 21 infestation, only 5/8 (62.5 %) dogs remained free of fleas at 24 and 48 hours in the spinosad group, and only 2/8 (25 %) of them were still free of fleas following the Day 28 infestation.

EGG COLLECTIONS (Table IV)

No eggs were collected from the fipronil/(S)-methoprene group at any time on any dog. A single application of the fipronil/(S)-methoprene topical controlled all flea stages during the entire six weeks. For the infested dogs that produced flea eggs, eggs were randomly collected until a target number of 100
### Table II. – Number of fleas counted at 24 hours and 48 hours post-infestation, from Day 21 infestation to Day 42 infestation. Calculation of the % of flea free dogs and comparison between the two treated groups.

| Groups          | Dog tag number | Day 22** | Day 23 | Day 29 | Day 30 | Day 36 | Day 37 | Day 43 | Day 44 |
|-----------------|----------------|----------|--------|--------|--------|--------|--------|--------|--------|
| Untreated       | 58091          | 133      | 124    | 149    | 127    | 128    | 135    | 137    | 126    |
|                 | 27351          | 125      | 103    | 71     | 87     | 119    | 126    | 147    | 155    |
|                 | 40061          | 135      | 138    | 118    | 124    | 155    | 159    | 121    | 141    |
|                 | 43861          | 156      | 164    | 132    | 114    | 107    | 141    | 150    | 132    |
|                 | 22774          | 137      | 121    | 133    | 116    | 118    | 106    | 138    | 133    |
|                 | 39545          | 117      | 111    | 104    | 106    | 111    | 123    | 152    | 143    |
|                 | 94289          | 161      | 125    | 132    | 130    | 142    | 128    | 153    | 147    |
|                 | 28632          | 133      | 154    | 102    | 102    | 141    | 132    | 136    | 144    |
| Frontline® Plus | 38603          | 0        | 0      | 0      | 0      | 0      | 0      | 0      | 0      |
|                 | 38793          | 0        | 0      | 0      | 0      | 0      | 0      | 0      | 0      |
|                 | 35092          | 0        | 0      | 0      | 0      | 0      | 0      | 0      | 0      |
|                 | 67804          | 0        | 0      | 0      | 0      | 0      | 0      | 0      | 0      |
|                 | 38257          | 0        | 0      | 0      | 0      | 0      | 0      | 0      | 0      |

| % Flea free dogs | 100 %* | 100 %* | 100 %* | 100 %* | 100 %* | 100 %* | 100 %* | 100 %* | 100 %* |
|------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Comfortis®       | 89565  | 0      | 0      | 0      | 0      | 59     | 48     | 118    | 112    |
|                  | 41363  | 13     | 11     | 87     | 79     | 75     | 89     | 180    | 179    |
|                  | 33824  | 0      | 0      | 0      | 0      | 74     | 67     | 94     | 77     |
|                  | 02777  | 0      | 0      | 32     | 22     | 90     | 73     | 127    | 125    |
|                  | 44355  | 17     | 6      | 57     | 56     | 116    | 113    | 105    | 107    |
|                  | 44799  | 0      | 0      | 19     | 3      | 0      | 0      | 122    | 112    |
|                  | 02352  | 0      | 0      | 31     | 22     | 23     | 42     | 134    | 141    |
|                  | 27347  | 48     | 15     | 115    | 107    | 106    | 104    | 125    | 168    |

* Significant difference between the two treatment groups at Day 29, Day 36 and Day 43 at p < 0.01.

### Table III. – Compared killing efficacies of the two treatments on adult fleas at 24 and 48 hours counts.

| Day of flea count (48 hours post-infestation) | Day 2 | Day 8 | Day 15 | Day 22 | Day 29 | Day 36 | Day 43 |
|----------------------------------------------|-------|-------|--------|--------|--------|--------|--------|
| Frontline® Plus                              | 100   | 100   | 100    | 98.4   | 85.0*  | 67.8*  | 12.6*  |
| Comfortis®                                   | 100   | 100   | 100    | 100    | 100    | 100    | 100    |

* Significant difference between the two treatment groups at Day 29, Day 36 and Day 43 at p < 0.01.

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**Fig 1.** – Comparative % of adult flea efficacy in the two treated groups at 24 hours counts.

**Fig 2.** – Comparative number of flea free dogs in the two treated groups at 48 hours counts.
per each dog. In the control group, 100 eggs were collected from each dog at every collect time.

In the spinosad group, 42 eggs were collected from one dog following the Day 28 infestation. That same dog had 107 adult fleas counted at 48 hours. Following the Day 35 and Day 42 infestations, the maximum threshold of 100 eggs collected was exceeded on all dogs in the spinosad treated group.

**DISCUSSION**

This well controlled study confirmed both the high efficacy and the long duration of efficacy of the pioneer fipronil/(S)-methoprene (FRONTLINE® COMBO/FRONTLINE® PLUS, Merial Limited, Duluth, GA) topical formulation on dogs with at least six weeks of 100% efficacy. Similar
results were previously obtained in other trials on both dogs and cats (Cadiergues et al., 2001; Franc et al., 2007; Schenker et al., 2003; Young et al., 2004). The results of this study and those of previous studies also demonstrate the consistency of control provided by this formulation from one dog to the next. Due to the high level of efficacy and speed of kill of the fipronil, no eggs were collected on the dogs at any time of the study. It was previously shown that if any newly acquired fleas survive long enough to produce eggs, the eggs laid would be sterilized by (S)-methoprene (Young et al., 2004).

In this study, the treatment with spinosad provided complete flea control for only 16 days after treatment. After the D21 infestation, only five of the eight (62.5 %) spinosad-treated dogs were flea-free at both the 24 hours and 48 hours counts, and after the Day 28 infestation only two of the eight dogs (25 %) remained flea-free at both the 24 hours and 48 hours counts.

Every effort was made in the study design to ensure consistency of the animals; dogs were selected from the same breed, same age and similar weight ranges and were maintained under essentially identical management conditions for assessments, feeding, watering and handling. The consistency of the flea burdens observed on the control dogs attests to both the consistency of animals and management practices.

The variable and declining flea-killing efficacy of orally administered spinosad were observed in other post-approval laboratory studies. In one report (Blagburn et al., 2010), efficacy studies using the oral spinosad formulation were conducted at research laboratories in the United States and in Ireland, with each site using its own flea strain. Purpose-bred Beagle dogs that were 14 to 16 weeks old were used. Data combined from the three study sites revealed that 48 hours pulicidal efficacies for oral spinosad were 100 % through Day 9, thereafter declining to 85 % (Day 16), 63 % (Day 23), and 2 % (Day 30).

There were no statistical differences (p > 0.05) in the number of live fleas recovered from the dogs treated with oral spinosad compared to untreated control dogs on study Days 22 and 29 for two study sites and on Day 29 for the third site.

In a study conducted at another research laboratory, purpose-bred mongrel dogs that were eight to 11 months old were used, and they were treated with oral spinosad on Day 0 according to label directions (Dryden et al., 2010). 100 cat fleas of the KS1 flea strain were applied to each dog on Days -2, 7, 14, 21, and 28 after treatment, and the fleas were removed with a flea comb six and 24 hours post-infestation. Oral spinosad provided at least 93.9 % efficacy at six hours post-infestation through Day 14, dropping to 54.9 % efficacy on Day 21 and 35 % on Day 28. Efficacy on Day 29 (24 hours post-infestation) was 22 %, and the geometric mean flea counts on treated dogs were not statistically different from untreated controls.

The unpredictably variable efficacy provided by oral spinosad after 16 days post-treatment may be due to different absorption, metabolism and elimination kinetics between dogs. Orally administered spinosad acts by the systemic route after absorption from the gastrointestinal tract (Kirst, 2010). Data from the Comfortis Food and Drug Agency (FDA) Freedom of Information (FOI) summary showed a variable rate of elimination of spinosyns A and D between groups of dogs that had been administered technical grade spinosad in gelatin capsules. In a small group of dogs in which the elimination half-life was 6.8 +/- 3 hours, 48 hours pulicidal efficacy on Day 30 was 89.1 %, compared to 48 hours efficacy of 97.8 % in dogs with slower elimination (10.6 +/- 3.7 hours) of spinosyns A and D. It was also shown that administration of oral spinosad without food markedly reduced peak plasma levels.

Orally administered spinosad can provide rapid speed of kill against existing flea infestations (Blagburn et al., 2010), but if efficacy is not maintained for the monthly application period, or longer if a pet owner is late in re-administering product, surviving fleas can lay eggs and perpetuate an environmental infestation (Franc & Boushira, 2009). In the study reported here the pioneer fipronil/(S)-methoprene topical product provided 100 % flea killing efficacy 24 hours after infestation through six weeks after treatment. Other studies have demonstrated that (S)-methoprene can provide inhibition of flea egg/larvae survival well after the adulticidal efficacy of fipronil begins to decline, providing long-lasting protection against the establishment of new environmental flea infestations (Franc et al., 2007; Young et al., 2004).

This study confirmed that providing relief to a pet and eliminating infestation of a premise by a pet requires regular dosing with formulations providing consistent and sustained activity against both adult and developmental stages of fleas.

Note: FRONLINE® is a registered trademark of Merial. All other marks are the property of their respective owners.
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