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# Efficacy and safety of a novel oral isoxazoline, sarolaner (Simparica™) in the treatment of naturally occurring flea and tick infestations in dogs presented as veterinary patients in Europe

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ABSTRACT

Two randomised, blinded, multi-centered field studies were conducted in Europe to demonstrate the efficacy and safety of three monthly oral doses of sarolaner (Simparica™, Zoetis) administered at a minimum dosage of 2.0 mg/kg (range 2–4 mg/kg) against natural flea or tick infestation of dogs presented as veterinary patients. In the flea study, the improvement in clinical signs associated with flea allergy dermatitis (FAD) was also investigated. The palatability of the sarolaner chewable tablet formulation was evaluated in both studies. Spinosad (Comfortis® Chewable Tablets, Elanco) and fipronil (Frontline® Spot on, Merial) were used as positive controls in the flea and tick study, respectively. Treatments were administered on Days 0, 30 and 60. Efficacy was calculated based on the mean percent reduction of live parasite counts on post-treatment days 14, 30, 60 and 90 versus the pre-treatment count on Day 0. Non-inferiority of sarolaner to the control products was assessed at each time-point using a margin of 15% at the one-sided 0.025 significance level.

Dogs were enrolled in a 2:1 ratio (sarolaner:comparator); 285 flea- and 181 tick-infested dogs were assessed for efficacy and safety, and 137 and 48 dogs were assessed for safety only, in the flea and tick study, respectively. There were no treatment-related adverse events.

Efficacy against fleas was 98.8%, 99.4%, >99.9% and >99.9% in the sarolaner-treated group and 98.9%, 93.7%, 96.8% and 95.1% in the spinosad-treated group on Days 14, 30, 60 and 90, respectively. Sarolaner was non-inferior to spinosad at all time-points and was superior on Day 30. For the 42 dogs identified as having FAD at enrolment, the clinical signs of FAD improved in all dogs and the incidence was markedly reduced by the end of the study.

Efficacy against ticks was 97.4%, 97.6%, 99.8% and 100% in the sarolaner-treated group and 94.1%, 88.5%, 89.9% and 98.1% in the fipronil-treated group on Days 14, 30, 60 and 90, respectively. Sarolaner was non-inferior to fipronil at all time-points, and was superior on Days 30 and 60. Sarolaner tablets were voluntarily and fully consumed within one minute in 93% of the 1280 occasions offered.

Sarolaner administered orally at monthly intervals at a minimum dosage of 2 mg/kg was safe and highly effective against natural infestations of fleas and ticks on dogs. In addition, clinical signs FAD improved in dogs treated with sarolaner, and the flavored, chewable tablets were highly palatable.



## 1. Introduction

Treatment and prevention of ectoparasite infestations on companion animals is an integral part of general veterinary practice around the world. It has been reported that flea infestations account for over 50% of the dermatological cases presented to veterinarians and dealing with flea infestations comprises 35% of their total case load (Bevier-Tournay, 1989; Kwochka, 1987). In recent studies, the prevalence of flea infestations in canine veterinary patients was found to be up to 27.1% in Hungary, 40.3% in Greece, 17.9% in Italy and 30.3% in Mexico (Koutinas et al., 1995; Cruz-Vazquez et al., 2001; Rinaldi et al., 2007; Farkas et al., 2009). The economic impact

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**Table 1**
Demographic characteristics of dogs presented as veterinary patients and dosed with sarolaner or spinosad tablets administered orally, or treated with fipronil topically once a month for three months.

| | Tick study | | Flea study | |
|---|---|---|---|---|
| | Sarolaner | Fipronil | Sarolaner | Spinosad |
| Number of dogs enrolled | 150 | 79 | 287 | 141 |
| Purebred | 68.0% | 62.0% | 65.9% | 64.5% |
| Non-purebred | 32.0% | 38.0% | 34.1% | 35.5% |
| Live indoors and outdoors | 47.3% | 49.4% | 33.4% | 38.3% |
| Live mostly indoors | 4.7% | 3.8% | 12.5% | 5.7% |
| Live mostly outdoors | 48.0% | 46.8% | 54.0% | 56.0% |
| Male | 46.7% | 50.6% | 46.7% | 52.5% |
| Female | 53.3% | 49.4% | 53.3% | 47.5% |
| Long hair | 20.7% | 27.8% | 15.3% | 14.2% |
| Medium length hair | 41.3% | 38.0% | 41.5% | 48.2% |
| Short hair | 38.0% | 34.2% | 43.2% | 37.6% |
| Receiving concurrent medication* | 5.3% | 7.6% | 5.2% | 6.4% |
| Not receiving concurrent medication | 94.7% | 92.4% | 94.8% | 93.6% |

*In the sarolaner-treated group dogs were receiving the following concurrent medication at enrolment: doxycycline, meloxicam, vaccines, firocoxib, dexamethasone, benzylpenicillin, dihydrostreptomycin sulfate, moxidectin, ivermectin, carprofen, benazepril, amoxicillin in combination with clavulanic acid, medetomidine, cephalexine, pyrantel + ivermectin, spiramycine + metronidazole, phenobarbital, pentosan polysulphate.

of flea treatments is also high; it has been estimated globally that pet owners spend more than 2 billion USD annually on flea products alone (Conniff, 1995; Krämer and Mencke, 2001; Rust 2005).

Tick infestations are similarly a common problem in dogs. The median frequency of dogs carrying ticks in Great Britain was found to be 14.9% (Smith et al., 2011). Ticks are one of the most important vectors of diseases caused by pathogenic protozoa (e.g. *Babesia* spp.), viruses (e.g. tick-borne encephalitis virus), rickettsia, and bacteria (e.g. *Borrelia burgdorferi* s.l., *Ehrlichia* spp., *Francisella tularensis*, *Anaplasma* spp.) in dogs, many of which are zoonotic.

Due to the prevalence of flea and tick infestations and the potential severity of tick-borne diseases there is high need for safe and efficacious products to treat flea and tick infestations on dogs. Sarolaner (Simparica™) is the latest addition to the isoxazoline class of oral ectoparasiticides. Two clinical field studies were conducted in Europe to evaluate its efficacy and safety against natural flea and tick infestations in canine veterinary patients.

## 2. Materials and methods

Two randomised, blinded, positive-controlled clinical field studies were conducted at veterinary clinics in Belgium, Hungary, Italy, France and the United Kingdom enrolling dogs presenting with flea and/or tick infestations. All personnel (e.g., the Examining Veterinarian) involved with the collection of efficacy and safety data were blinded to treatment All treatments were dispensed to the Owners by separate study personnel (Dispenser), who were not involved in any other study activities. The studies were conducted in compliance with Good Clinical Practice, (VICH guideline GL9, EMEA, 2000) and the study protocols were reviewed and approved by the Zoetis Ethics Review Assessment team.

### 2.1. Animals

Enrolment was limited to households with three or fewer dogs. One dog in each household was allowed to be enrolled as the primary patient and only that dog received efficacy evaluations. Other dogs living in the same household as the primary dog were enrolled as supplementary patients and received the same treatment but were only evaluated for safety and palatability, not for efficacy. The primary patient had to harbor ≥5 live fleas or ≥3 live attached ticks at enrolment. Within each clinic the primary dogs were randomly allocated to the two treatment groups (separately in each study) in a ratio of 2:1, so that for every two patients that received sarolaner, one patient received the positive control product (spinosad in the flea study and fipronil in the tick study). Supplementary dogs in the flea study had to be enrolled and treated, while in the tick study, the enrolment and treatment of the supplementary dogs was optional for the Owners. Dogs that were pregnant, lactating or intended for breeding were excluded from the studies. All dogs received a physical examination by a veterinarian at study inclusion. The minimum age for enrolment was eight weeks in the tick study and 14 weeks (due to the age restrictions of the comparator product) in the flea study. Each dog was enrolled with the written informed consent of its owner.

### 2.2. Treatment administration

Dogs received three consecutive monthly treatments on study days 0, 30 and 60. For the follow up treatments and evaluations on Days 30 and 60 these could be conducted ± 3 days of the target date, but these are reported as Days 30 and 60. All treatments were dispensed according to a randomization plan that was provided for each clinic before study start. Treatment dispensing was based upon the body weights recorded on Day 0, 30 and 60, and treatments were administered by the Owner in the home environment after the clinic visits. The dogs' owners were not blinded to treatment allocation. Animals were dosed with the appropriate strength sarolaner tablet (Simparica™, Zoetis) to provide the

**Table 2**
Efficacy against fleas: Number of dogs, arithmetic mean live flea counts (all species), ranges and percent efficacies relative to pre-treatment counts for dogs presented as veterinary patients and dosed with sarolaner or spinosad tablets administered orally once a month for three months.

| Study Day | Treatment group | Number of dogs | Flea counts | | Efficacy[a] (%) | |
|---|---|---|---|---|---|---|
| | | | Arithmetic mean | Range | Arithmetic mean | 95% Confidence interval |
| −1 to 0 | Sarolaner | 189 | 23.1 | 5 to 1029 | – | – |
| | Spinosad | 95 | 18.7 | 5 to 173 | N/A | – |
| 14 ± 3 | Sarolaner | 184 | 0.2 | 0 to 10 | 98.8 | 97.8 – 99.8 |
| | Spinosad | 88 | 0.2 | 0 to 4 | 98.9 | 98.1 – 99.8 |
| 30 ± 3 | Sarolaner | 186 | 0.1 | 0 to 8 | 99.4 | 98.8 – 99.9 |
| | Spinosad | 89 | 1.3 | 0 to 38 | 93.7 | 89.0 – 98.6 |
| 60 ± 3 | Sarolaner | 186 | <0.1 | 0 to 1 | >99.9 | 99.7 – 100.1 |
| | Spinosad | 87 | 0.3 | 0 to 17 | 96.8 | 91.3 – 102.7 |
| 90 ± 3 | Sarolaner | 182 | <0.1 | 0 to 1 | >99.9 | 99.7 – 100.1 |
| | Spinosad | 92 | 0.4 | 0 to 19 | 95.1 | 87.0 – 103.3 |

[a] Efficacy is the arithmetic mean of the percent reduction relative to pre-treatment calculated for each dog individually.