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Efficacy and safety of a novel oral isoxazoline, sarolaner (Simparica™), for the treatment of sarcoptic mange in dogs

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ABSTRACT

The efficacy of the novel isoxazoline, sarolaner (Simparica™) was investigated in dogs with clinical signs consistent with sarcoptic mange and harbouring natural infestations of *Sarcoptes scabiei*. One placebo-controlled laboratory study and one multi-centred field study with a commercial comparator containing imidacloprid/moxidectin (Advocate® spot-on) were conducted. Oral or topical treatments were administered on Days 0 and 30. Up to 10 skin scrapings were taken for the assessment of *S. scabiei* infestations from each dog before treatment and on Days 14, 30, 44 and 60 in the laboratory study, and on Days 30 and 60 in the field study. In the laboratory study, efficacy was calculated based on the percent reduction of mean live mite counts compared to the placebo group. In the field study parasitological cure rate (% dogs free of mites) was determined and non-inferiority of sarolaner to the control product was assessed.

In the laboratory study 44 mixed breed dogs were enrolled in four batches. Due to decreasing mite counts in the placebo treated dogs, immunosuppression with dexamethasone (0.4 mg/kg three times per week for two weeks) was initiated in all dogs on study at that time (n = 6) and those subsequently enrolled (n = 14). In the field study, dogs were enrolled in a 2:1 ratio (sarolaner:comparator); 79 dogs were assessed for efficacy and safety, and an additional 45 dogs were assessed for safety only. There were no treatment related adverse events in either study.

In the laboratory study, no mites were found on any sarolaner-treated dogs 14 days after the first treatment except for one dog that had a single mite on Day 44. In the field study, the parasitological cure rate was 88.7% and 100% in the sarolaner group and 84.6% and 96.0% in the imidacloprid/moxidectin group, on Days 30 and 60, respectively. Statistical analysis showed that sarolaner was non-inferior to imidacloprid/moxidectin at both time points. The clinical signs of sarcoptic mange, including hair loss, papules, pruritus, erythema, and scaling/crusting improved throughout the study.

Sarolaner was safe, achieved 100% reduction in the numbers of *S. scabiei* detected and resulted in marked improvement of the clinical signs of sarcoptic mange in dogs following two monthly oral administrations.

1. Introduction

Sarcoptes scabiei var. *canis* is one of the mites most commonly infesting dogs worldwide and causes severe pruritus and may be associated with secondary bacterial pyoderma. Scabies is highly contagious and has zoonotic potential (Miller et al., 2013). Diagnosis is usually based on the presence of clinical signs and the detection of mites in skin scrapings. Infested dogs show severe pruritus, an erythematous rash and yellowish crusts on the skin (Arlian et al., 1995). The licenced treatment options for sarcoptic mange are limited mostly to topical products. Depending on the region, these may include selamectin and moxidectin/imidacloprid containing spot-on products, and in some countries amitraz dip. Shampooing or bathing with medicated or non-medicated products are generally part of the adjunctive therapy for clinical mange to rehydrate the skin and treat seborrhoea, but these procedures may also reduce the efficacy or shorten the residual activity of topical products. Extra-label use of macrocyclic lactones such as moxidectin and ivermectin have been reported to be effective via oral and injectable routes (Wagner and Wendleberger, 2000; Curtis, 2004) but to be

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effective these need to be given at high dose rates (0.2–0.5 mg/kg) and intervals of 1–2 weeks, risking potentially severe side effects. The only oral product approved in some countries for the treatment of sarcoptic mange is milbemycin oxime, however the need for every-other-day administration may not be an affordable or convenient option for most owners. Therefore a proven, convenient and safe, oral treatment option would provide a significant benefit for the care of sarcoptic mange patients.

Sarolaner (Simparica™ chewable tablets, Zoetis), the latest addition to the isoxazoline class of oral ectoparasiticides is a very potent insecticide and acaricide (McTier et al., 2016). With its monthly dosing schedule, sarolaner could provide a very convenient and effective treatment option for dogs suffering from mite infestations. A laboratory study was conducted to evaluate the efficacy of two monthly doses of sarolaner for the treatment of sarcoptic mange in dogs and a multi-centred field study in veterinary patients was conducted to confirm the efficacy and safety of this treatment and dosing regimen.

2. Materials and methods

The laboratory study was a masked, placebo controlled, randomized study conducted in South Africa. The field study was a masked, randomized trial that was conducted at veterinary practices in the UK, Spain, Italy, France, Belgium and Hungary and used a positive control containing imidacloprid and moxidectin (Advocate® Spot on, Bayer) that is approved for the treatment of sarcoptic mange in Europe. In both studies dogs received two monthly treatments. The studies were conducted in compliance with Good Clinical Practice, (VICH guideline GL9, EMEA, 2000). Masking was accomplished by separation of functions of study personnel. The person(s) who made clinical observations and conducted parasite counts was masked to experimental treatments. All treatments were dispensed by a dedicated dispenser, who was not involved in any other study activities. The protocol for the laboratory study was approved by the ClinVet Institutional Animal Care and Use Committee. Ethical approval for the field study was provided by the Zoetis Ethics Review Assessment team.

2.1. Laboratory study

2.1.1. Animals

Forty four mixed breed dogs of both sexes, ranging from seven months to 11 years of age and weighing 5.3–24.6 kg with natural *S. scabiei* infestations were enrolled. The dogs had clinical signs of sarcoptic mange and had live *S. scabiei* (adults, larvae or nymphs) confirmed in deep skin scrapings at enrolment. Dogs were housed in individual runs, so that no physical contact was possible between them. Dogs were fed an appropriate maintenance ration of a commercial dry canine feed for the duration of the study. Water was available *ad libitum*.

2.1.2. Experimental design and methods

Dogs were enrolled in four batches (minimum four dogs/batch) as adequate numbers of animals with clinical signs were confirmed positive for scabies mites in skin scrapings. Within batches, dogs were randomly allocated to treatment with sarolaner or placebo based on pre-treatment mite counts.

The severity of the clinical signs of *S. scabiei* infestation (erythema, scaling/crusting, papules, pustules, alopecia) were evaluated as follows: absent (no signs present); mild (intensity/density of the clinical sign is low and <25% of the animal's body is affected); moderate (clinical sign is of great intensity/density over <25% of the animal's body or is of lesser intensity/density but affects 25–50% of the body); severe (clinical sign is of great intensity/density and covers >50% of the animal's body).

To count mites, deep skin scrapings were taken from at least four separate sites on each dog. If no mites were detected in the first four scrapings, additional scrapings were made until live mites were found or the maximum of ten scrapings was reached. Selected scraping sites were those that had the most severe or most likely evidence of current mite infestation. Scrapings were conducted to an approximately constant depth (to capillary bleeding) over an area of approximately 2.5 cm^2. The collected material was transferred to mineral oil on a microscope slide and live *S. scabiei* mites (larvae, nymphs and adults) and eggs were counted using 20× magnification.

Day 0 for each batch of dogs was the day the first study treatment was given. Prior to treatment each dog was given a detailed physical exam to ensure suitability for inclusion and all dogs were observed for general health at least twice daily throughout the study. On Days 0 and 30, the 22 dogs allocated to treatment with sarolaner received tablets individually shaved and/or sanded to provide the target dose of 2 mg/kg. The 22 placebo-treated dogs received a single placebo tablet. Dogs were offered their normal ration of food approximately1 h prior to tablet administration. Dogs were hand pilled to ensure accurate and complete dosing and observed for general health and any reaction to treatment approximately 1, 3 and 6 h after treatment.

Deep skin scrapings and mite counts were performed on all dogs on Days 14, 30, 44 and 60. During the study it was noted that live mite counts were decreasing in the placebo-treated dogs. As this apparent self-clearing of mite infestations could interfere with the determination of efficacy, immunosuppression was initiated with intramuscular or subcutaneous dexamethasone (0.4 mg/kg three times per week for two weeks, Kortico®, Bayer) of all dogs on study at that time and for dogs subsequently enrolled. At this time, 12 dogs in each treatment group had already completed the study. Three dogs in each treatment group were on study having already received their first parasiticide treatment. Therefore these dogs received their immunosuppressive treatment between study days 0 and 30. Seven dogs in each group were enrolled after the decision was made and received immunosuppression before their first parasiticide treatment. Due to the initiation of immunsuppressive therapy, clinical signs of sarcoptic mange were not evaluated.

2.1.3. Data analysis

The primary variable for analysis was live mite count (adult, nymph and larvae combined). Assessment of efficacy was based on the percent reductions in mean live mite counts relative to placebo and pre-treatment counts calculated for each time point as follows:

$$\%\text{Efficacy} = \frac{(\text{Mean Placebo(Pretreatment)- Mean Treated})}{\text{Mean Placebo(Pretreatment)}} \times 100$$

The numbers and proportions of dogs that were mite free was calculated for each time point.

2.2. Field study

2.2.1. Animals

The patient population was recruited from veterinary practices located in various geographical and climatic locations in the EU. 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 dogs were enrolled as supplementary patients that were only evaluated for safety and palatability. The primary dog had to show clinical signs of sarcoptic mange and harbour live *S. scabiei* mites in deep skin scrapings. Dogs had to be at least 8 weeks of age and weigh at least 1.3 kg. There were no breed or gender restrictions, but dogs intended for breeding or that were pregnant or lactating were not eligible for