

# Efficacy and Safety of the Combination Imidacloprid 10%/moxidectin 1.0% Spot-on (Advocate® Spot-on for Small Cats and Ferrets) in the Treatment of Ear Mite Infection (*Otodectes cynotis*) in Ferrets

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## Abstract

In this study, the efficacy and safety of a treatment with the combination imidacloprid 10%/moxidectin 1.0% spot-on (Advocate® spot-on for small cats and ferrets) was tested in 39 ferrets naturally infested with ear mites (*Otodectes cynotis*). The study was performed as a multicentre, non-randomised, non-controlled (all study animals were treated) and non-blinded clinical field study in two French veterinary practices. Four visits (day (D) 0 = inclusion and first treatment, D14 = second treatment, D28 = possible third treatment, D56 = termination) were planned. The dosage was one pipet per ferret (designed for cats weighing up to 4 kg, corresponding to a dose of moxidectin ranging from 2.2 to 5 mg/kg body weight) two or three times at 14-days intervals (at D0, D14 and possibly D28 depending on the parasitological

examination of the ears at D28). The main efficacy criterion was the absence of the parasite (all stages incl. eggs, larvae, nymphs and adults) from ear scrapings by microscopic examination. At D28 after two treatments (D0 and D14), 76.9% (30/39) of animals were cured. Only 23% (9/39) needed a third treatment. At day 56, 100% were cured. Local symptoms (inflammation and pruritus) were consistently improved (50.6% improvement at D14, 81.0% at D28 and 97.9% at D56) as well as the abnormal cerumen production (14.7% improvement at D14, 77.7% at D28 and 100.0% at D56). No general symptoms were noticed during the study (general health and skin aspect). Advocate® spot-on for small cats and ferrets is an effective and safe treatment for ear mite infection in ferrets. Two or three treatments administered in 14-days intervals to ferrets infested with ear mites provided 100% parasitological cure on D56.

## Introduction

Otoacariosis is caused by the ear mite *Otodectes cynotis* (Hering 1858) and is known for being the most frequent mite in companion animals (Franc 2005). It is a very contagious parasitic disease, which can affect dogs, cats, foxes or ferrets. DNA and morphological studies have established that ear mites of the genus *Otodectes* from the various hosts belong to a single species: *Otodectes cynotis* (Lohse et al. 2002). Contamination occurs further to direct contact with an infected animal: ferret, cat or dog. In ferrets, the parasite has a typical 3-week mite life cycle in the external ear: after hatching, the parasite develops into adults after one larval and two nymphal stages (Franc 2005). In environmental conditions, the mites can survive up to 12 days at temperatures ranging from 12.3 to 14.2 °C (Otranto et al. 2004). *O. cynotis* is a non-burrowing mite that lives on the surface of the ear canal lining. In dogs and cats, ear mites can classically cause intense irritation of the ear canal resulting in otitis externa (Hubert et al. 2005).

In ferrets, however, Otoacariosis is often asymptomatic. Some affected ferrets can exhibit a moderate to severe ear pruritus (Bensignor et al. 2010). Abundant brown earwax is produced. Without treatment, otoacariosis frequently leads to bacterial or fungal complications (Bensignor et al. 2010; Lewington 2007). Diagnosis can be established by otoscope or ear swabbing.

Imidacloprid 10% + moxidectin 1% spot-on (Advocate® spot-on for small cats and ferrets) is a broad-spectrum antiparasiticide for cats and ferrets that is licenced in ferrets against fleas and for the prevention of heartworm disease. In cats, Advocate® is additionally registered against gastrointestinal nematodes and *Otodectes cynotis* infections.

The objective of the present investigation was to study the efficacy and safety of imidacloprid 10% + moxidectin 1% spot-on against naturally acquired *O. cynotis* infestations in ferrets under field conditions. For ethical reasons, there was no untreated control group.

## Materials and methods

### Study design

The study was designed as a multicentre, non-randomised, non-controlled and non-blinded clinical field study, where all experimental animals received the investigated veterinary product. The study protocol was based on 4 visits (D0 = inclusion and first treatment, D14 = second treatment, D28 = possible third treatment, D56 = study termination). Informed consent was obtained from all ferret owners prior to enrolment of the animals.

### Study animals

The ferrets enrolled in the study were recruited among the patients presented to two veterinary clinics located in the Île de France region. Male or female ferrets weighing between 800 g and 2 kg body weight (b.w.) were enrolled. Forty-one ferrets were used (24 male and 17 females, weight range 0.8 kg to 1.8 kg b.w.; mean 1.15 kg b.w., age from 6 months to 5 years and 11 months (mean 2 years and 3 months). None of the ferrets had been treated with an ectoparasiticide during the four-week period preceding day 0 and all were naturally infested with live *Otodectes cynotis* mites as determined by a clinical examination on day 0. The ferrets were kept either in animal parks, partially outside and exposed to external climatic conditions, or in cages inside the house by individual ferret owners.

From the 41 ferrets, which were included, 39 ferrets naturally infested with *O. cynotis* completed the study (Per Protocol Population) over a period from December 2009 to March 2010. These study animals consisted of 23 males and 16 females. The owners were breeders (15 subjects, i.e., 38.5%) or privates (24 subjects, i.e., 61.5%).

### Treatment

The treatment consisted of one pipet (Advocate® spot-on for small cats and ferrets) per ferret containing 0.4 ml. The corresponding administered dose of moxidectin ranged from 2.2 to 5 mg/kg b.w. based on individual b.w..

**Tab. 1** Number of administered treatments during the study

	Visit D0	Visit D14	Visit D28
Number of present study animals	41	41	39*
Number of treatments administered	41	41	9
Percentage of treated animals	100%	100%	23%

\* Two ferrets left the study after D14, further to the protocol deviation. Both were parasite-free at D14

The treatment was administered at D0, D14  $\pm$  2, and if parasites were still observed at D28  $\pm$  2, a third treatment was performed the same day (i.e. at D28  $\pm$  2) (Tab. 1).

The ferret ear canal is narrow and difficult to clean under usual conditions, therefore, the ears of the experimental ferrets were not cleaned during the study.

### Parasitological and clinical examinations

Parasitological and clinical examinations were performed at each visit (i.e. 4 times) on days D0 (inclusion and first treatment), D14 (+/-2), D28 (+/-2) and D56 (+/-2) of the study.

The parasitological examination consisted of a thorough otoscopic scraping and examination of the ear. The clinical parameters recorded during the experimental phase were the health condition (general condition, skin aspect, other clinical observations), the ear examination (left and right: itching and inflammation in the ears (score 0 to 5)) and cerumen level (normal/increased). The parasitological parameters recorded during the otoscopic examinations were the ear mite stage qualification and quantification: number of eggs, larvae and adults/nymphs were defined with three classes: 0, <10 and >10.

Present parasites were collected for further identification and quantification according to the following procedure: The investigator first inspected the ear canal using a magnifying otoscope. If cerumen was present in excessive amounts, it was removed through the use of crocodile forceps or other appropriate instruments. The ear canals of the ferrets were thoroughly scraped with a swab/cotton, while

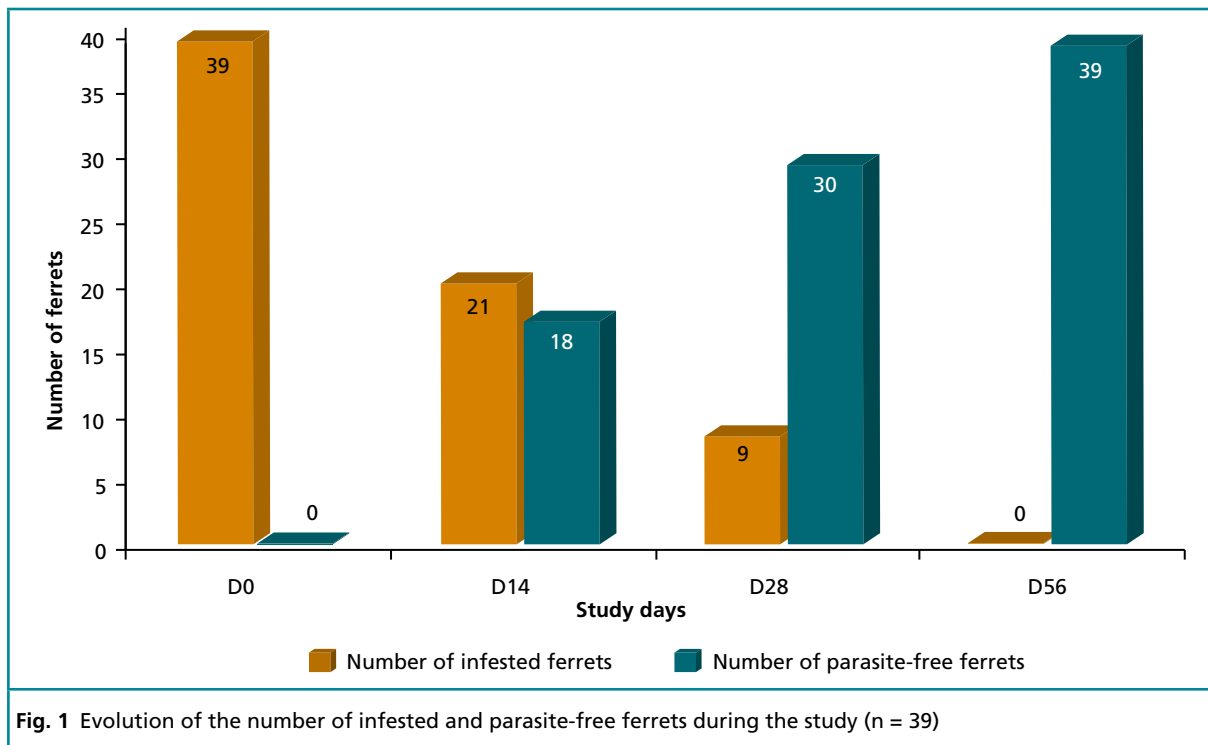
the pinna was straightened up and the swab/cotton was slowly rotated to remove the debris including the different parasite stages (eggs, larvae, nymphs and adults) being in the debris and on the surface of the ear canal skin. All collected debris was put on a glass slide and glycerine, microscopic oil or liquid paraffin was added. The microscopic examination was performed using a magnification of 40x and 100x. Developmental stages were identified by size and typical morphological structures.

### Efficacy evaluation

The main efficacy criterion was the absence of the parasite (all stages incl. eggs, larvae, nymphs and adults) from ear scrapings by microscopic examination. Ear mite presence was analysed at 4 dates (on D0, D14, D28 and D56). Secondary efficacy criteria included clinical parameters (itching score + inflammation score) and decrease of excessive cerumen. In addition, semi-quantitative stage-specific parasite counts have been performed for the whole period (from D0 to D56).

### Statistical analysis

The evolution of infested animals was analysed using the Kaplan-Meier test. Non-normal distributed data (clinical scores, weight) were analysed using the Friedman test. The Pearson chi-square test was performed to compare the parasitism between dates. The signification level was set at  $p \leq 0.05$ . All the statistical calculations were performed using SYSTAT software (Wilkinson, L., SYSTAT: The system for statistics. Evanston, IL: SYSTAT, Inc.), version 12 for Windows.



## Results

Thirty-nine ferrets completed the study. Two ferrets were excluded due to protocol deviations on D14. On D28 after two treatments (on D0 and D14), 30 of 39 (76.9%) of animals were mite-free. Nine ferrets of 39 (23%) received a third treatment on D28. On D56, all animals were mite-free (Fig. 1). The two ferrets which did not complete the study were *O. cynotis*-free at D14.

Local symptoms (inflammation and pruritus score) were consistently improved (50.6% improvement at D14, 81.0% at D28 and 97.9% at D56, Tab. 2). The evolution of clinical score is significant with Friedman rank test ( $p < 0.001$ )

The proportion of ferrets free of the abnormal cerumen level increased over time (14.7% improvement at D14, 77.7% at D28 and 100.0% at D56, Tab. 3). The distribution over time of abnormal cerumen was significantly different at D14, D28 and D56 using the Pearson chi-square test ( $p < 0.001$ )

The prevalence of the different ear mite stages during the study is shown in Tab. 4.

The treatment was well tolerated in all animals and no general symptoms or adverse events were notified during the study.

## Discussion

This study was performed to evaluate the efficacy and safety of the combination imidacloprid 10% + moxidectin 1% spot-on (Advocate® spot-on for small cats and ferrets) for the treatment of otoacariosis of ferrets under field conditions. In cats, Advocate® was proven to be effective and safe against *Otodectes cynotis* (Figs. 2 and 3) (Davis et al. 2007; Farkas et al. 2007; Fourie et al. 2003) with one or two spot-on treatments at 4-week intervals. Furthermore, in ferrets Advocate® is effective for the treatment and the prevention of flea infestation (Wenzel et al. 2008) as well as the prevention of heartworm disease (Schaper et al. 2007).

Clinically in ferrets, contrary to dogs or cats, ear mite infection is known to be possibly asymptomatic. In accordance with this point, we could observe

that 14 ferrets out of 39 (36 %) presented no ear pruritus at D0. Furthermore, the global ear clinical score (pruritus + inflammation, possibly ranking from 0 to 10) was moderate at the beginning of the study (mean 3.6). The cerumen was affected in a larger proportion, since 27 ferrets out of 39 (69 %) presented abnormal cerumen at D0. At D56, all animals had normal cerumen and normal clinical scores.

Since there is no specific medication against ear mites in ferrets, a variety of veterinary products have been evaluated for this indication. Ivermectin

has been administered subcutaneously at a dose of 0.2 to 0.4 mg/kg b.w., repeated every 2 weeks for 3 to 4 treatments, usually with good results. However, some mite infections can be refractory (Bensignor et al. 2010; Orcutt 2003). One selamectin spot-on treatment at 15 mg per ferret was reported to be effective (Fisher et al. 2007), but also repeated selamectin spot-on administrations at 6 mg/kg b.w. 28 days apart were effective (Powers 2009). Selamectin spot-on treatment at 45 mg in the form of a complete 0.75-ml single dose tube administered topically between the shoulder blades, without cleaning the

**Tab. 2** Improvement of clinical score (pruritus and inflammation)

	Initial date	D14	D28	D56
<b>Number of cases (PPP)</b>	39	39	39	39
<b>Median</b>	4	2	0	0
<b>Mean</b>	3.79	1.87	0.72	0.08
<b>% Improvement</b>	NA	50.6	81.0	97.9

Improvement calculated on the initial mean clinical score

**Tab. 3** Time course of distribution of abnormal cerumen (orange, brown, increased secretion)

	Initial date	D14	D28	D56
<b>Number of cases (PPP)</b>	39	39	39	39
<b>Number of affected ferrets</b>	27	23	6	0
<b>Percentage</b>	69.2	59.0	15.4	0.0
<b>% Improvement</b>	NA	14.7	77.7	100.0

Improvement calculated on the initial number of affected ferrets

**Tab. 4** Ear mite infestation and sample observations

	Initial date	D14	D28	D56
<b>Number of infested ferrets</b>	39 (100.0%)	21 (53.8%)	9 (23%)	0 (0.0%)
<b>Number of present ferrets (PPP)</b>	39	39	39	39
<b>Less than 10 in sample</b>	Eggs	22 (56.4%)	8 (20.5%)	0 (0.0%)
	Larvae	29 (74.4%)	8 (20.5%)	0 (0.0%)
	Adults	31 (79.5%)	17 (43.6%)	8 (20.5%)
<b>More than 10 in sample</b>	Eggs	8 (20.5%)	0 (0.0%)	0 (0.0%)
	Larvae	6 (15.4%)	0 (0.0%)	0 (0.0%)
	Adults	8 (20.5%)	0 (0.0%)	1 (2.6%)
<b>% cured</b>	NA	46.1	76.9	100.0

Improvement calculated on the initial number of affected ferrets



**Fig. 2** *O. cynotis* from an ear canal swab (magnification 100x; scale bar 0.1 mm)



**Fig. 3** Eggs of *O. cynotis* from an ear canal swab (magnification 100x; scale bar 0.15 mm)

external ear canal, at one or 4 successive occasions has been tested in a further study (Miller et al. 2006). In this study, single administration was reported to be effective in some ferrets (n=3 ferrets in a group controlled 30 days following treatment, n=10 ferrets in another group controlled 60 days following treatment). However, multiple administrations of selamectin associated with cleaning of the environment were necessary in other cases (n=21 ferrets received 4 treatments and were reported to be parasite-free 109 days following treatment).

The ferret ear canal is narrow and flanked by long hairs, so that direct ear treatments may be difficult to administer or fail to penetrate sufficiently. Although topical treatments labelled for use in cats and/or dogs for the treatment of ear mites are available in some countries, they have not been studied in ferrets. Nevertheless, ivermectin was found to be more effective when applied topically to the ear canals than when administered systemically (Powers 2009; Patterson 1999). Direct ear treatment can consist in massaging ivermectin into each ear at the dose of 0.5 mg/kg b.w. with one half the dose instilled in each ear (Orcutt 2003).

Moxidectin was tested successfully against ear mite infestations in many animal species. Topically applied imidacloprid 10% + moxidectin 1% solution

(Advocate<sup>®</sup> spot-on for cats) was proven to be effective for treatment of otodectic mange in cats after one or two applications: At the minimum recommended dose of 10 mg/kg b.w. of imidacloprid and 1 mg/kg b.w. of moxidectin (equivalent to 0.1 ml/kg b.w. of the spot-on solution for cats), one application provided 92.8% to 100% ear mite efficacy (Davis et al. 2007; Farkas et al. 2007), and two applications 4 weeks apart provided 98.1% to 100% ear mite efficacy (Davis et al. 2007; Fourie et al. 2003). In *O. cynotis*-infested dogs, spot-on treatments with imidacloprid 10% + moxidectin 2.5% solution (Advocate<sup>®</sup> spot-on for dogs) administered twice at 28-days interval (at D0 and D28) provided 85.7% parasitological cure rate on day 56 (Krieger et al. 2005). In rabbits, ear mite infestations are caused by *Psoroptes cuniculi*. In a clinical study, imidacloprid 10% + moxidectin 1% solution (Advocate<sup>®</sup> spot-on for cats) was administered topically to *Psoroptes*-infested rabbits three times in 4-week intervals (at D0, D30 and D60) at a dosage of 40 mg and 4 mg/animal, respectively, and provided 100% cure by D90 (Hansen et al. 2005). In ferrets, topically applied imidacloprid 10% + moxidectin 1% solution was reported to be effective against *O. cynotis* by many authors (Boussarie 2008; Bensignor 2010). The present study confirms that two or three spot-on



applications with imidacloprid 10 % + moxidectin 1 % solution at 14-days intervals provide 100 % ear mite efficacy. The ease of use of a spot-on medication is particularly well adapted for the treatment of exotic pets like ferrets and furthermore facilitates the observance of the treatment by the pet owner. No adverse reactions to the treatment have been observed in any animal at any point in time. Advocate® spot-on for small cats and ferrets is licensed in ferrets, therefore, it provides an alternative to products not licensed in ferrets.

## Conclusion

The combination imidacloprid 10 % + moxidectin 1 % (Advocate® spot-on for small cats and ferrets) applied to ferrets naturally infested with *O. cynotis*

achieved 100 % cure after two or three treatment in two-week intervals. The treatment was well tolerated and no adverse reactions were observed.

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## Compliance statement

The study was performed according to local rules and regulations.

## Disclosure statement

All authors are employees of Bayer. The study was sponsored by Bayer.

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