A European Field Assessment of the efficacy of fluralaner (Bravecto®) chewable and spot-on formulations for treatment of dogs with generalized demodicosis

Ivo Petersen

MSD Animal Health Innovation GmbH

Rafael Chiummo

MSD Animal Health Innovation GmbH

Eva Zschiesche

MSD Animal Health Innovation GmbH

Joanna Karas-Tecza

Dermawet, Warsaw

Dhimiter Rapti

Faculty of veterinary medicine, Tirana

Rainer Roepke

MSD Animal Health Innovation GmbH

emmanuel thomas (✉ emmanuel.thomas@msd.de)

Research

Keywords: Bravecto®, Demodex, dog, field study, fluralaner, generalized demodicosis

Posted Date: April 13th, 2020

DOI: <https://doi.org/10.21203/rs.2.19478/v2>

License: This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Version of Record: A version of this preprint was published at Parasites & Vectors on June 11th, 2020. See the published version at <https://doi.org/10.1186/s13071-020-04159-2>.

Abstract

Background: Recent reports indicate that the isoxazoline compounds have the potential to provide safe and effective treatment of canine generalized demodicosis, a condition that has been traditionally difficult to cure. Controlled field studies are needed to confirm this potential. A study was therefore initiated to investigate the efficacy of a single oral or spot-on treatment with fluralaner, an isoxazoline, compared with multiple topical treatments with imidacloprid-moxidectin, in dogs naturally affected by generalized demodicosis.

Methods: Veterinary clinics in 5 European countries enrolled 134 dogs diagnosed with generalized demodicosis. Dogs were randomized to treatment with either fluralaner chewables, fluralaner spot-on, or topical imidacloprid-moxidectin in a 2:2:1 ratio. Both fluralaner formulations were administered once, at the approved dose rate, on day 0. Imidacloprid-moxidectin was administered per label on day 0, and every 4 weeks, more frequently if necessary. At each visit (days 0, 28, 56, 84), dogs were monitored for demodectic mites, using deep skin scrapings, and observed for health and for severity of skin lesions. Treatment was considered efficacious if more than 90% of the dogs were free of live mites at both days 56 and 84.

Results: Of 124 dogs completing the study, 57 were diagnosed with juvenile-onset demodicosis and 67 with the adult-onset form. A single treatment with oral or spot-on fluralaner was efficacious, each eliminating mites from at least 98.0% of treated dogs on days 56 and 84. Against juvenile-onset demodicosis, efficacy of the oral and spot-on formulations was 96.0% and 100%, respectively, and against adult-onset demodicosis 100% and 96.7%. Multiple administrations of imidacloprid-moxidectin were not efficacious, eliminating mites from 87.5% of dogs (92.0% with juvenile-onset demodicosis cured; 81.8% with adult-onset demodicosis). All groups showed a marked reduction in skin lesions by day 28, with continuing clinical improvement at each subsequent visit through day 84. There were no treatment-related adverse events.

Conclusion: A single administration of fluralaner chewables or fluralaner spot-on is highly effective against juvenile-onset and adult-onset forms of generalized canine demodicosis. Topically applied imidacloprid-moxidectin at weekly to monthly intervals over the 84-day study did not achieve the proportion of mite-free dogs required to demonstrate efficacy.

Background

The mite *Demodex canis*, regarded as a normal inhabitant of the canine integument, is passed from the bitch to her nursing puppies by direct contact [1, 2]. The mites spend their entire life cycle in the lumen of the hair follicles, although in heavy infestations, may also invade sebaceous glands [3]. Female mites lay eggs that develop into eight-legged, slender cigar-shaped adults within approximately 3-4 weeks [3]. In some dogs there is an abnormal proliferation of mites which can manifest as a localized alopecia that resolves either spontaneously or following acaricidal treatment. In a smaller proportion of dogs, possibly with a hereditary predisposition, underlying disease (e.g. hyperadrenocorticism, hypothyroidism, diabetes mellitus, neoplasia) or treatment related immunosuppression (e.g. corticosteroids, chemotherapeutic agents), the infestation persists, and potentially becomes generalized and life-threatening [2]. Generalized demodicosis can occur in dogs aged from 2 to 18 months (juvenile demodicosis), or as an adult-onset form in mature dogs [2]. Dogs with generalized demodicosis may develop severe pustular lesions because of secondary infections, leading to deep pyoderma, furunculosis

and cellulitis. At this point the treatment, often lasting 6 to 8 weeks, can only be successful if the mites are eradicated [2, 3].

Products that are approved for the treatment of generalized demodicosis require topical or oral administration, daily, at weekly or two-weekly intervals, or at monthly intervals for up to six or more months, with the frequency and duration of treatments governed by the clinical response and progress to parasitological cure [4 - 9]. Recent reports indicate that orally administered isoxazoline compounds can provide safe and effective treatment of generalized canine demodicosis, even with very severe presenting signs, and three of these compounds, sarolaner, afoxolaner and fluralaner, are now approved in Europe for this indication [10 -17].

The extended activity of fluralaner with an efficacy duration of up to 12 weeks, against fleas and ticks, offers potential for successful cure of generalized demodicosis following a single treatment [18, 19]. Two laboratory studies showed that a single administration of either an oral or spot-on formulation of fluralaner to dogs affected by generalized demodicosis resulted in elimination of *Demodex* spp. mites, based on deep skin scrapings, and resolution of clinical signs. A non-blinded, uncontrolled, open-label study with orally administered fluralaner provided evidence that those laboratory results could translate into field efficacy [10, 16, 17].

An investigator-masked, positive controlled, multicenter study was initiated to provide field-based confirmation of the efficacy of single treatment with fluralaner chewables or fluralaner spot-on against canine generalized demodicosis. The study was conducted in Europe to support a label indication for fluralaner for the treatment of dogs presenting with the disease.

Materials And Methods

This study was conducted following Good Clinical Practices, VICH Guideline 9 [20], Guideline on Statistical Principles for Veterinary Clinical Trials [21], and Guideline for the Demonstration of Efficacy of Ectoparasiticides [22]. Seven veterinary practices across Albania, Poland, Spain, Germany and Portugal enrolled client-owned dogs presented with generalized demodicosis. All dog owners provided informed consent following written and oral explanation of the study objectives and treatments.

Enrollment of dogs

Generalized demodicosis was diagnosed by the presence of more than 4 affected skin areas with lesion diameter >2.5 cm, or pododemodicosis in at least one paw; with positive skin scrapings (≥ 3 *Demodex* spp mites) [2, 11, 14]. Dogs were at least 8 weeks old and weighed at least 2.0 kg. Any dog needing intensive care, or that had been treated with injectable corticosteroids in the past 30 days was excluded. Ongoing treatment with oral or topical corticosteroids had to be discontinued before inclusion in the study. Dogs were excluded if treated with: fluralaner in the previous 3 months; other isoxazoline products within 35 days; macrocyclic lactone parasiticides, except at approved heartworm prevention doses, within 30 days; amitraz, fipronil, pyriproxyfen, metaflumizone, pyrethrins, deltamethrin or permethrin, within 30 days; or shorter-acting products with miticidal activity within 14 days. Treatment of enrolled dogs with corticosteroids, immunosuppressants (cyclosporine, oclacitinib) or with any product having miticidal activity was not permitted during the study, and owners were instructed to avoid using in-house or on-property acaricides, and to avoid shampooing the study dog during the 3 days following each treatment. Each owner was also instructed to observe their dog for any unfavourable or unexpected events, and

to report any such observations to the study clinic. Enrolled dogs were maintained in their home environment throughout the study, and owners returned their dog to the clinic on days 28, 56 and 84.

Treatments

Qualifying dogs enrolled in each clinic were randomly allocated to either a fluralaner group (oral or spot-on) or to a topical imidacloprid-moxidectin group. The study enrollment target was 50 dogs in each fluralaner group and 25 dogs in the imidacloprid - moxidectin group.

Dogs in one fluralaner group received a single oral fluralaner chewable (Bravecto® chewable tablets, MSD Animal Health) administered at the label dose rate of 25-56 mg/kg. These dogs were fed within one hour of treatment and observed for 10 minutes after treatment to verify that the tablets were retained. In the other fluralaner group, dogs received a single spot-on 28% w/v fluralaner application (Bravecto® Spot-On Solution, MSD Animal Health), at the label dose rate of 25-56 mg/kg. Dogs in the imidacloprid-moxidectin group received multiple sequential applications of at least 10mg/kg imidacloprid and 2.5 mg/kg moxidectin (Advocate® for Dogs, Bayer). In this group, dogs with mild to moderate demodicosis were treated every 4 weeks, while at the discretion of the dispensing veterinarian the treatment frequency of severely affected dogs could be increased to up to once per week. All products were administered according to the product prescribing information directions. Fluralaner treatment and the initial imidacloprid-moxidectin treatment were administered on day 0.

When clinical signs of *Demodex*-associated pyoderma were observed, study dogs could receive antibiotics or topical antiseptics at the discretion of the attending veterinarian.

Assessments of demodicosis

At each scheduled visit, deep skin scrapings for *Demodex* mites were made at five different skin areas, each scraping approximately 1 cm². Where necessary (e.g. long or medium-haired dogs), hair was removed at the area to be scraped, and the skin was firmly squeezed prior to and during scraping to eject mites from hair follicles [2, 14, 15]. Scrapings were made in the direction of hair growth with a blade or spatula, covered with mineral oil, until capillary oozing was observed. Hairs were plucked from affected areas where obtaining a scraping was difficult (e.g. periorcular and interdigital areas). Efforts were made to scrape the same affected areas at all assessments, unless those areas appeared normal and other active lesions were present. The collected material was transferred to a slide, mixed with mineral oil, placed under a cover slip and examined under a microscope (4x or 10x objective) to count live mites (larvae, nymphs and adult stages) (eggs were not counted). Clinical signs and extent of demodectic lesions on each dog were assessed on the days on which scrapings were made. Dermatological signs of alopecia, erythema, crusts, scales and papules were assessed and graded absent, mild, moderate or severe. Estimates were made of the overall extent of skin lesions using a scale of 0 (no lesions), 1 – 9% of the body affected, 10 – 29%, 30 – 49%, and ≥50%.

Statistical Analysis

Primary efficacy was determined for each study group using the percentage of dogs free of live mites at both of the last two evaluation time points (days 56 and 84). Treatment was considered efficacious if the percentage of animals that were free of live mites at both evaluation time points exceeded 90%. The percentage of dogs free of live mites was also calculated separately for each visit. A descriptive analysis was performed for mite counts and

skin lesions: the distribution of mite counts and the number of dogs free of skin lesions were determined at each visit, as well as the distribution of types and extent of skin lesions.

Results

Across Albania (60), Germany (3), Spain (7), Portugal (14), and Poland (50), 134 dogs were enrolled, ranging in age in the oral fluralaner group from 10 weeks to 13 years (mean 3.1; standard deviation $\pm$ 2.9 years), in the spot-on fluralaner group from 4 months to 12 years (3.5 ± 3.2 years), and in the topical imidacloprid-moxidectin group from 11 weeks to 9 years (2.9 ± 2.9 years). In each group there was representation of both juvenile onset and adult onset demodicosis cases. A broad range of breed categories was represented, with approximately 50% of dogs mixed breed, 22% were companion-toy dogs, and approximately 9% were terriers.

During the study 10 dogs became ineligible for inclusion in study efficacy assessments. Four dogs in the fluralaner spot-on group, two in the fluralaner chewable group and one dog in the imidacloprid-moxidectin group were excluded because of an owner failure to adhere to follow-up visit schedules. Two dogs were excluded because of treatment with study-prohibited drugs: one dog in the fluralaner chewable group received oclacitinib and dexamethasone, and a dog in the fluralaner spot-on group received dexamethasone. The death prior to day 56 of a fluralaner spot-on group dog that had shown weakness, anorexia, dyspnea and dehydration, was diagnosed as cardiac failure, unrelated to treatment. Thus, data from 124 dogs were available for determination of product efficacy, 50 in each of the fluralaner groups and 24 in the imidacloprid-moxidectin group. In the latter group most dogs received 4 treatments (once every 4 weeks), 5 dogs required 3 treatments; 2 dogs received 13 treatments (one per week); one received 10; and one received 7 treatments.

On days 56 and 84, in both fluralaner groups 98.0% of dogs had shown a parasitological cure (free of mites at two consecutive assessments) (Table 1). In the imidacloprid-moxidectin group, the percentage of mite-free dogs at both days 56 and 84 was 87.5%, below the pre-determined efficacy threshold of 90%. On day 84, 100% of fluralaner chewable and 98% of fluralaner spot-on treated dogs were free of live mites, as were 91.7% of dogs in the topical imidacloprid-moxidectin group.

Table 1. Number (per cent) of dogs treated once on day 0 with oral or topical fluralaner or on multiple occasions with topical imidacloprid-moxidectin that were negative for live mites on days 28, 56 and 84

	Oral Fluralaner	Topical Fluralaner	Topical Imidacloprid-moxidectin
n	50	50	24
Mite free at day 28	46 (92.0)	46 (92.0)	19 (79.2)
Mite free at day 56	49 (98.0)	49 (98.0)	21 (87.5)
Mite free at day 84	50 (100)	49 (98.0)	22 (91.7)
Mite free at days 56 and 84	49 (98.0*)	49 (98.0)	21 (87.5)

*One dog treated with fluralaner chewable had 500 mites on day 0, 52 on day 28, 1 mite on day 56 and 0 on day 84 and had improved condition. However, this dog was considered a treatment failure because it was not free of mites on both day 56 and day 84.

Mean mite counts on day 0 in the fluralaner spot-on and chewable groups were 53.2 and 30.4, respectively, and 37.8 in the topical imidacloprid-moxidectin group (Table 2). A severely affected dog in the fluralaner chewable group had a day 0 mite count of 500. Oral and spot-on fluralaner treatments were both effective against juvenile-onset (efficacy of 96% and 100%, respectively) and adult-onset demodicosis (100% and 96.7%, respectively) (Fig 1). Topical imidacloprid-moxidectin was effective against juvenile onset demodicosis (92.0%) but was not effective (81.8%) against adult demodicosis.

Table 2. Mite counts (mean ± standard deviation) in dogs with generalized demodicosis, treated once on day 0 with fluralaner chewables or fluralaner spot-on, or on multiple occasions with topical imidacloprid-moxidectin.

Day	Fluralaner		Imidacloprid-moxidectin
	Oral	Topical	Oral
	(n = 50)	(n = 50)	(n = 50)
0	53.2 ± 80.3	30.4 ± 21.9	37.8 ± 28.8
28	1.1 ± 7.4	0.4 ± 2.2	1.2 ± 4.1
56	0.0 ± 0.1	0.0 ± 0.1	0.3 ± 0.7
84	0.0 ± 0.0	0.0 ± 0.1	0.1 ± 0.3

At the first visit (day 0), all enrolled dogs had clinical signs of generalized demodicosis, most commonly alopecia which was present in all study dogs. By day 84, there was no observable alopecia in 94.0% of oral fluralaner-treated dogs, 84.0% of spot-on fluralaner-treated dogs, and 75.0% of topical imidacloprid-moxidectin treated dogs. Other initial clinical signs included crusts (61.3% of dogs), erythema (58.9%), scales (34.7%), papules (26.6%), pustules (13.7%), ulcerations (9.7%) and comedones (4.0%). All signs of erythema, comedones, papules, pustules and ulcerations resolved in dogs in all groups by day 84. Overall there was a marked reduction in skin lesions in all groups at day 28, with substantial hair regrowth by Day 56 (Fig 2). Continuing improvement was observed at each subsequent visit through the final visit on day 84.

No treatment-related adverse events were observed in any dogs in any of the three study groups.

Discussion

These results show that under field conditions a single oral or spot-on administration of fluralaner is effective in the treatment of generalized demodicosis, whether for treatment of generalized juvenile or adult-onset manifestations of the disease. Evidence of the potent fluralaner effect, in both oral and spot-on formulations, was present as early as 28 days following treatment, when 92.0% of dogs were found to be free of live mites. In comparison, topical imidacloprid-moxidectin did not reach the pre-defined efficacy threshold for generalized

demodicosis. At the day 28 assessment, 79.2% of imidacloprid-moxidectin treated dogs were live-mite free, indicating that the miticidal onset was not reaching the 90% threshold at this time.

This is the first controlled field study with fluralaner, and just the second controlled field study with any isoxazoline, to demonstrate field efficacy in the treatment of generalized demodicosis. In the only other controlled isoxazoline field study, in Europe, dogs with generalized demodicosis were treated orally at monthly intervals with sarolaner at a dose rate of 2 – 4 mg/kg, or with imidacloprid-moxidectin as used in the current study [14]. At day 30, 15.1 and 17.9% of dogs treated with sarolaner or imidacloprid-moxidectin were mite-free, respectively. The study concluded 180 days after the first treatment, with up to 6 administrations of sarolaner producing a parasitological cure in all dogs that remained in the study, and up to 24 weekly doses of imidacloprid-moxidectin producing a parasitological cure in 91.7% of the remaining dogs in that group.

In an uncontrolled study in Europe, two formulations of afoxolaner for oral administration, one as a single entity product, the other in combination with milbemycin oxime, were administered on days 0, 28, and 56 to dogs presenting with generalized demodicosis [15]. Although mite counts were reduced from pre-treatment levels by 87.6% on day 28 and by 98.1% on day 84, just 29 of 48 (60.4%) dogs were mite free on day 56, so the maximum possible cure rate (two consecutive assessments in which dogs were mite free) following those three treatments would be 39.6%.

In another uncontrolled field study, in Thailand, a parasitological cure was observed in 100% of dogs (n = 67) within 3 months following treatment with orally administered fluralaner [16]. An extended duration of follow up found that 4 of 46 successfully treated adult-onset dogs had relapsed at 2, 7, 10, or 12 months following cure. The possibility of relapse, as long as 12 months after successful treatment, emphasizes the need for extended post-cure vigilance, particularly of older dogs, in which a cure has been realized.

Six laboratory studies, all from a single facility in South Africa, have shown the potential of each of the isoxazolines in the treatment of canine generalized demodicosis [10 - 13, 17, 23]. Three consecutive treatments at 4-weekly or monthly intervals were used in separate studies of sarolaner [11] and afoxolaner [12], and in an uncontrolled study with lotilaner [13]. Two studies, one uncontrolled, investigated single-treatment fluralaner efficacy using the chewable formulation [10, 23], and one controlled study involved the spot-on formulation [17]. The multiple treatments with afoxolaner, sarolaner, and lotilaner, and the single treatment controlled study with either fluralaner formulation, all reduced mean demodectic mite counts by >99% within the month following the day 0 treatment, and by 100% at days 81 or 84. Across those studies, the reported efficacies of imidacloprid-moxidectin within the month after the first treatment ranged from 9.8 to 89.8%, and on day 84, following multiple treatments, from 0 to 100%. In the uncontrolled oral fluralaner study, PCR analysis of hair collected from treated dogs found that *Demodex* DNA levels progressively declined throughout the study, and on day 112 were reduced 1000-fold from pre-treatment levels [23]. Thus, the accumulating data in which the isoxazolines have shown potent efficacy and superiority over imidacloprid-moxidectin indicate that they would be the treatment of choice for generalized demodicosis, although further controlled studies would be helpful to confirm that the miticidal efficacy of afoxolaner and lotilaner is maintained under field conditions.

Regardless of the efficacy of these products, generalized demodicosis, particularly in older dogs, becomes clinically apparent in those affected by another disease process, or by immunosuppressive therapy, factors which can also predispose successfully treated dogs to a relapse [2, 5, 16]. A corollary of that risk of relapse is the requirement for continued vigilance of cured dogs, and the associated potential need for repeated miticidal

treatments over an extended period. In this regard, the long efficacy duration of fluralaner has been linked to better owner adherence compared with use of monthly treatments [24]. The sustained action and convenience of fluralaner formulations could also help to improve the long-term cure rate of dogs with generalized demodicosis.

Conclusion

Fluralaner (Bravecto®) chewable and spot-on formulations were highly efficacious in providing a parasitological and clinical cure in dogs affected with generalized canine demodicosis over a period of 12 weeks following a single administration at a dose rate of 25-56 mg/kg.

Abbreviations

VICH: Veterinary International Cooperation on Harmonisation.

Declarations

Acknowledgements

The authors would like to thank all the field veterinarians who participated in this study, Monika Borchert-Stuhlraeger for monitoring the study, and Sabrina Fuhrmann for conducting the data management.

Authors' contributions

IP, RC and ET coordinated the study. RR was involved in the study design and the interpretation of the results. EZ performed the statistical analysis. JKT and DR were the major investigators. All authors revised and approved the final manuscript.

Funding

The study was funded by MSD Animal Health.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due to confidentiality agreements. All original study documentation is archived by the sponsor at MSD facilities (Germany).

Ethics approval and consent to participate

The study protocol was in alignment with local, national and global guidelines and owners of all dogs were fully advised of all study procedures prior to signing informed consent.

Consent for publication

Not applicable.

Competing interests

IP, RC, EZ, RR and EZ are employees of MSD Animal Health.

Authors details

¹ MSD Animal Health Innovation GmbH, Zur Propstei, 55270 Schwabenheim, Germany.

² Dermatology Clinic for dogs and cats, Dermawet, Warsaw, Poland.

³ Faculty of Veterinary Medicine, Agriculture University of Tirana, Tirana, Albania

References

1. Ravera I, Altet L, Francino O, Sanchez A, Roldan W, Villanueva S, et al. Small Demodex populations colonize most parts of the skin of healthy dogs. *Vet Dermatol*. 2013;24:168–73.
2. Miller V, Griffin C, Campbell K. Canine Demodicosis. In: Muller & Kirk's small animal dermatology. 7th ed. St. Louis: Elsevier; 2013.
3. European Scientific Counsel Companion Animal Parasites. Control of ectoparasites in dogs and cats. 2018. Available at: https://www.esccap.org/uploads/docs/v5sc2etz_0720_ESCCAP_Guideline_GL3_update_v8_1p.pdf. Accessed October 25, 2019.
4. Paradis M. New approaches to the treatment of canine demodicosis. *Vet Clin N Am-Small*. 1999;29:1425-36.
5. Arsenović M, Pezo L, Vasić N, Ćirić R, Stefanović M. The main factors influencing canine demodicosis treatment outcome and determination of optimal therapy. *Parasitol Res*. 2015;114:2415-26.
6. Mueller RS, Meyer D, Bensignor E, Sauter-Louis C. Treatment of canine generalized demodicosis with a spot-on formulation containing 10% moxidectin and 2.5% imidacloprid (Advocate, Bayer Healthcare). *Vet Dermatol*. 2009;20:441-6.
7. Perego R, Spada E, Foppa C, Proverbio D. Critically appraised topic for the most effective and safe treatment for canine generalised demodicosis. *BMC Vet Res*. 2019;15:17.
8. Summary of Product Characteristics. European Medicines Agency. Available at: https://www.ema.europa.eu/en/documents/product-information/advocate-epar-product-information_en.pdf. Accessed October 25, 2019.
9. Paterson TE, Halliwell RE, Fields PJ, Louw ML, Ball G, Louw J, et al. Canine generalized demodicosis treated with varying doses of a 2.5% moxidectin+10% imidacloprid spot-on and oral ivermectin: parasitocidal effects and long-term treatment outcomes. *Vet Parasitol*. 2014;205:687-96.
10. Fourie JJ, Liebenberg JE, Horak IG, Taenzler J, Heckerroth AR, Frénais R. Efficacy of orally administered fluralaner (Bravecto™) or topically applied imidacloprid/moxidectin (Advocate®) against generalized demodicosis in dogs. *Parasit Vectors*. 2015;8:187.
11. Six RH, Becskei C, Mazaleski MM, Fourie JJ, Mahabir SP, Myers MR, et al. Efficacy of sarolaner, a novel oral isoxazoline, against two common mite infestations in dogs: *Demodex* spp. and *Otodectes cynotis*. *Vet Parasitol*. 2016; 222:62-6.
12. Beugnet F, Halos L, Larsen D, de Vos C. Efficacy of oral afoxolaner for the treatment of canine generalised demodicosis. *Parasite*. 2016;23:14.
13. Snyder DE, Wiseman S, Liebenberg JE. Efficacy of lotilaner (Credelio™), a novel oral isoxazoline against naturally occurring mange mite infestations in dogs caused by *Demodex* *Parasit Vectors*. 2017;10:532.

14. Becskei C, Cuppens O, Mahabir SP. Efficacy and safety of sarolaner against generalized demodicosis in dogs in European countries: a non-inferiority study. *Vet Dermatol*. 2018;29:203-e72.
15. Lebon W, Beccati M, Bourdeau P, Brement T, Bruet V, Cekiera A, et al. Efficacy of two formulations of afoxolaner (NexGard® and NexGard Spectra®) for the treatment of generalised demodicosis in dogs, in veterinary dermatology referral centers in Europe. *Parasit Vectors*. 2018;11:506.
16. Duangkaew L, Larsuprom L, Anukkul P, Lekcharoensuk C, Chen C. A field trial in Thailand of the efficacy of oral fluralaner for the treatment of dogs with generalized demodicosis. *Vet Dermatol*. 2018;29:208-e74.
17. Fourie JJ, Meyer L, Thomas E. Efficacy of topically administered fluralaner or imidacloprid/moxidectin on dogs with generalised demodicosis. *Parasit Vectors*. 2019;12:59.
18. Dryden MW, Smith V, Bennett T, Math L, Kallman J, Heaney K, et al. Efficacy of fluralaner flavored chews (Bravecto) administered to dogs against the adult cat flea, *Ctenocephalides felis felis* and egg production. *Parasit Vectors*. 2015;8:364.
19. Taenzler J, Liebenberg J, Roepke RK, Heckerroth AR. Prevention of transmission of *Babesia canis* by *Dermacentor reticulatus* ticks to dogs treated orally with fluralaner chewable tablets (Bravecto™). *Parasit Vectors*. 2015;8:305.
20. VICH Topic GL9 (GCP). Guideline on Good Clinical Practices. The European Agency for the Evaluation of Medicinal Products (EMA/CVMP/VICH/595/98-Final). 2000.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004343.pdf. Accessed 14 November 2019.
21. European Medicines Agency. Guideline on statistical principles for veterinary clinical trials (EMA/CVMP/EWP/81976/2010). 2010. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-statistical-principles-veterinary-clinical-trials_en.pdf. Accessed 14 November 2019.
22. European Medicines Agency. Demonstration of efficacy of ectoparasiticides (7AE17a). 1984.
https://www.ema.europa.eu/en/documents/scientific-guideline/demonstration-efficacy-ectoparasiticides_en.pdf. Accessed on 14 November 2019.
23. Djuric M, Milcic Matic N, Davitkov D, Glavinic U, Davitkov D, Vejnovic B, et al. Efficacy of oral fluralaner for the treatment of canine generalized demodicosis: a molecular-level confirmation. *Parasit Vectors*. 2019;12:270.
24. Lavan R, Armstrong R, Tunceli K, Normile D. Dog owner flea/tick medication purchases in the USA. *Parasit Vectors*. 2018;11:581.

Figures

Figure 1

centage of dogs presenting with juvenile- or adult-onset demodicosis that were free of mites on days 56 and 84, after a single treatment on day 0 with fluralaner chewables or fluralaner spot-on, or multiple treatments with topical imidacloprid-moxidectin

Figure 2

Photographs on day 0 of dogs with demodicosis-related dermatological lesions, and day 56 showing hair regrowth following a single fluralaner treatment on day 0; left fluralaner spot-on; right fluralaner chewable.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Slide1.png](#)