A European Field Assessment of the efficacy of fluralaner (Bravecto®) chewable and spot-on formulations for treatment of client-owned 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: December 23rd, 2019

DOI: https://doi.org/10.21203/rs.2.19478/v1

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: Generalized canine demodicosis is unlikely to resolve without therapy and has been traditionally difficult to cure, however there are recent reports of isoxazoline compounds providing safe and effective treatment. This field study compared the efficacy of either oral or topically administered of fluralaner, an isoxazoline, with multiple topical treatments (as often as weekly) with imidacloprid-moxidectin for the treatment of naturally infested dogs with generalized demodicosis.

Methods: This study in 5 European countries included 134 dogs randomized for treatment with either fluralaner chewable tablets, fluralaner spot-on, or topical imidacloprid-moxidectin. Both fluralaner formulations were administered once at the approved dose on day 0, while imidacloprid-moxidectin was administered at the approved dose once every 4 weeks or more frequently if necessary. Dogs were monitored for mites, using deep skin scrapings, and clinical signs prior to treatment on day 0, and then on approximately 28, 56 and 84 days after initial treatment. Treatment was considered efficacious if more than 90% of the dogs were free of live mites at days 56 and 84.

Results: Treatment with topical or oral fluralaner was 98.0% effective while imidacloprid-moxidectin treatment was 87.5% effective. All groups showed a marked reduction in skin lesions by day 28, with continuing improvement at each subsequent visit through the final assessment on day 84. There were no treatment-related adverse events.

Conclusion: Fluralaner chewable tablets and fluralaner spot-on are highly effective for treating dogs affected with generalized canine demodicosis following a single administration. Topical imidacloprid-moxidectin at weekly to monthly intervals did not achieve the mite-free levels required for adequate efficacy over the 12 weeks study period.

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].

Previous recommended treatments for demodicosis have included amitraz rinses or acaricidal spot-on formulations applied at weekly or two-weekly intervals, oral ivermectin administered daily at 300 μg/kg, milbemycin at 2 mg/kg and moxidectin at 400 μg/kg [4–7]. A topical formulation of imidacloprid-moxidectin is

approved in Europe for this indication, to be administered every 4 weeks for 2 to 4 months, with severe cases requiring increased frequency and prolonged duration of treatments [8]. In one study, treatments were continued for 54 weeks to achieve full cure [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 [10–15].

Fluralaner is the only isoxazoline that provides efficacy against fleas and ticks for up to 12 weeks with a single treatment. Two previous, separate laboratory studies showed that a single administration of either an oral or topical formulation of fluralaner to naturally infested dogs resulted in elimination of Demodex spp. mites, based on deep skin scrapings, and resolution of clinical signs [10, 15].

The objective of the study was to evaluate the efficacy of fluralaner given orally or topically once at a dose registered against tick and flea infestations compared to topical imidacloprid-moxidectin at dose registered for treatment of generalized demodicosis. The study was conducted under field conditions in Europe for the treatment of client-owned dogs suffering from generalized demodicosis.

Materials And Methods

This study was conducted following Good Clinical Practices, VICH Guideline 9 [16], Guideline on Statistical Principles for Veterinary Clinical Trials [17], and Guideline for the Demonstration of Efficacy of Ectoparasiticides [18]. All dog owners provided informed consent following written and oral explanation of the study objectives and treatments. Seven veterinary practices across Albania, Poland, Spain, Germany and Portugal enrolled client-owned dogs presented with generalized demodicosis.

Enrollment of dogs

Generalized demodicosis was diagnosed by the presence of more than four affected skin areas with lesion diameter >2.5 cm or pododemodicosis in at least one paw; with positive skin scrapings (≥3 *Demodex spp* mites). Dogs were at least 8 weeks old and weighed at least 2.0 kg. Dogs needing intensive care, or that were treated with injectable corticosteroids in the past 30 days were excluded. Any 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 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 topical) or to a topical imidacloprid-moxidectin group. The study enrolment target was 50 dogs in each fluralaner group and 25

dogs in the imidacloprid - moxidectin group. Dogs in this group with mild to moderate demodicosis were treated every 4 weeks, while severely affected dogs had an increased treatment frequency to once per week, at the discretion of the dispensing veterinarian. All products were administered according to the product prescribing information directions.

ogs in one fluralaner group received a single oral fluralaner chewable tablet (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 topical 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 administrations of at least 10mg/kg imidacloprid and 2.5 mg moxidectin (Advocate® for Dogs, Bayer). Dogs in this group with mild to moderate demodicosis were treated every 4 weeks while severely affected dogs had an increased treatment frequency to once per week at the discretion of the dispensing veterinarian. Fluralaner treatment and the initial imidacloprid-moxidectin treatment were administered on day 0.

When clinical signs of *Demodex*-associated pyoderma were observed, study dogs received 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 skin scarping approximately 1 cm^2. Where necessary (e.g. long or medium-haired dog), 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]. 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. periocular 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 and estimates 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 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

There were 134 dogs enrolled across Albania (60), Germany (3), Spain (7), Portugal (14), and Poland (50), ranging in age in the oral fluralaner group from 10 weeks to 13 years (mean 3.1; standard deviation ± 2.9 years), in the topical fluralaner group from 4 months to 12 years (3.5 ± 3.2) and in the topical imidacloprid-moxidectin group from 11 weeks to 9 years (2.9 ± 2.9). 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.

Ten dogs were removed from the study because of failure to adhere to retreatment schedules or because of use of other treatments resulting in data from 124 dogs being available for determination of product efficacy. Most imidacloprid-moxidectin group dogs received 4 treatments (once every 4 weeks), while 5 dogs required 3 treatments; 2 dogs received 13 treatments (one treatment per week); one received 10 treatments; and one received 7 treatments.

In both fluralaner treated groups the percentage of mite-free dogs was 98.0%, while in the imidacloprid-moxidectin group the percentage of mite-free dogs was 87.5%, which was below the pre-determined threshold of 90% within 12 weeks (Table 1). The proportion of mite-free dogs in the imidacloprid-moxidectin group exceeded 90% only on day 84 (91.7%), while more than 90% of dogs were free of mites at all visits for both fluralaner groups. On day 84, 100% of oral fluralaner and 98% of fluralaner spot-on treated dogs were free of live mites (Fig. 1).

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

	Oral Fluralaner	Topical Fluralaner	Topical Imidacloprid-moxidectin
n	50	50	24
Mite free at days 56 and 84	49 (98.0%)	49 (98.0%)	21 (87.5%)
Mite free at day 84	50 (100%)	49 (98.0%)	22 (91.7%)
*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.			

At day 84, mean mite counts were 0.0 in both oral and topical fluralaner groups and 0.1 in the topical imidacloprid-moxidectin group and (Table 2). Both oral and topical fluralaner treatments were effective against juvenile onset (96% and 100%) and adult onset demodicosis (100% and 96.7%) (Table 3). Topical imidacloprid was effective against juvenile onset demodicosis (92.0%) but was not effective (81.8%) against the adult demodicosis because this treatment did not achieve the 90% threshold on day 56 and 84.

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

Day	Oral Fluralaner	Topical Fluralaner	Topical Imidacloprid-moxidectin
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

Table 3
Percentage of dogs presenting with juvenile or adult onset of demodicosis that were free of mites on days 56 and 84 after a single oral or topical treatment with fluralaner or multiple treatments with topical imidacloprid-moxidectin

Age group*	Oral Fluralaner	Topical Fluralaner	Topical Imidacloprid-moxidectin
< 18 months (juvenile)	96.0% (24 of 25)	100.0% (20 of 20)	91.7% (11 of 12)
≥ 18 months (adult)	100.0% (25 of 25)	96.7% (29 of 30)	83.3% (10 of 12)

At the first visit on 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 topical 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 continuing improvement observed at each subsequent visit through the final visit on day 84 (Fig. 2).

There were no treatment-related adverse events recorded in any dogs in any of the three study groups.

Discussion

These results show that a single oral or topical administration of fluralaner is effective for treatment of generalized juvenile onset or adult onset demodicosis in naturally infested dogs managed under normal home conditions. Topical imidacloprid-moxidectin did not reach the pre-defined efficacy threshold for adult-onset demodicosis under these conditions, however this treatment was effective for juvenile demodicosis. Therefore, the efficacy target of at least 90% of dogs being mite-free on two consecutive assessments was met. Furthermore, the efficacy target of > 90% of dogs assessed as mite free on skin scrapings was also met for fluralaner treated dogs at day 28. Therefore it could be considered that the fluralaner miticidal effect has an onset

within 28 days. 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.

Results from this controlled field study confirm results from a recent uncontrolled field study in which parasitological cures were observed over three months after fluralaner treatment in all dogs presented with juvenile-onset demodicosis [19]. Fluralaner treatment was also effective in dogs with adult onset demodicosis one month following a second treatment, administered 12 weeks after the first. In that study, four of 46 dogs that received a single treatment relapsed at two, seven, 10 or 12 months following parasitological cure. Underlying diseases (Cushing's disease, neurological disease with steroid treatment) were thought to have contributed both to the initial appearance of clinical disease and to the recurrent infestation. Those results suggest that regular clinical monitoring of dogs with generalized demodicosis should be maintained even after parasitological cure, particularly in dogs with an underlying disease that could precipitate resurgence of mite infestation. In addition, follow up treatment is recommended in these dogs for effective flea and tick control and to reduce the risk of recurrence of demodicosis.

A corollary of the risk of a relapse of demodicosis-cured dogs and the need for vigilance is the 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 [20]. 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.

Declarations

Acknowledgements

The authors would like to thank all the field veterinarians who participated in this study, Monika Borchert-Stuhltraeger 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 data generated or analyzed during this study are included partially in this published article. They are the property of the sponsor and will not be further provided.

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

Abbreviations

VICH: Veterinary International Cooperation on Harmonisation.

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: Published by Elsevier; 2013. p. 304–13.
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(6):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(7):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(5-6):441-6.

7. Perego R, Spada E, Foppa C, Proverbio D. BMC Vet Res. 2019;15(1):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: parasiticidal effects and long-term treatment outcomes. Vet Parasitol. 2014;205(3-4):687-96.
10. Fourie JJ, Liebenberg JE, Horak IG, Taenzler J, Heckeroth 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 spp. Parasit Vectors. 2017;10(1):532.
14. 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(1):506.
15. Fourie JJ, Meyer L, Thomas E. Efficacy of topically administered fluralaner or imidacloprid/moxidectin on dogs with generalised demodicosis. Parasit Vectors. 2019;12(1):59.
16. VICH Topic GL9 (GCP). Guideline on Good Clinical Practices. The European Agency for the Evaluation of Medicinal Products (EMEA/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 t 2019.
17. 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.
18. 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.
19. 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(3):208-e74.
20. Lavan R, Armstrong R, Tunceli K, Normile D. Dog owner flea/tick medication purchases in the USA. Parasit Vectors. 2018 Nov 6;11(1):581.a

Figures

Figure 1

Figure 2

Figure 3