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Efficacy of eprinomectin 5 mg/mL topical solution administered pour on at 1 mg per kg body weight against *Przhevalskiana silenus* myiasis in goats

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ABSTRACT

The larvae of the goat warble fly, *Przhevalskiana silenus*, chiefly parasitize domestic goats. Its occurrence in Europe is restricted to the southeastern Mediterranean and the southern Balkans; however, the parasite is prevalent and of considerable economic impact in the Middle East and in parts of Asia. Eprinomectin 5 mg/mL topical solution (EPRINEX® Multi, Boehringer Ingelheim) administered at 1 mg eprinomectin per kg body weight pour on was recently authorized as an anthelmintic for sheep and goats with zero hours milk withdrawal in several European countries. Considering that the product in cattle has claims against a broad range of parasites including infestation with warble fly larvae (*Hypoderma* spp.), this study aimed to test the efficacy of eprinomectin 5 mg/mL topical solution against *P. silenus* myiasis in goats. Forty-five goats sourced from a farm with a history of *P. silenus* infestation were randomly assigned to three groups of 15 animals each. Group 1 was untreated (control) while Groups 2 and 3 were treated once with eprinomectin 5 mg/mL topical solution at 1 mL per 5 kg body weight, either in the absence of clinical evidence of *P. silenus* larvae (Day 0, Group 2) or after warbles had formed (Day 167, Group 3). Goats were examined for warbles on Days 89, 103, 117, 131, 163, 174 and 181, and larvae were collected, examined for viability and speciated. On Day 186, the goats were euthanized, skinned, and examined for remaining larvae. No live larvae were recovered from goats included in treated groups while live larvae were collected from six of the 15 untreated animals (1–3 per animal) ($P < 0.01$ at $\alpha=0.05$) demonstrating complete efficacy of the treatments. All larvae collected were identified as *P. silenus*. The administration of the treatments was well accepted by all animals and no related adverse events were observed. Eprinomectin 5 mg/mL topical solution was demonstrated to be an efficacious and safe treatment against *P. silenus* myiasis both when the larvae of *P. silenus* were expected to be L1/L2 and before skin damage occur, and when warbles with L3 have already developed.

1. Introduction

Goats are hosts to the larvae of a specific warble fly, *Przhevalskiana silenus* (family Oestridae, subfamily Hypodermatinae) causing an obligate myiasis which is referred to as goat warble fly infestation or goat hypodermosis. *Przhevalskiana silenus* is prevalent and of considerable economic impact in the Middle East and in parts of Asia (Tavassoli et al., 2010). In Europe, the occurrence of *P. silenus* is restricted to the southeastern Mediterranean and southern Balkans and documented, referring to the most recent respective publications, from the southern regions of mainland Italy (Puccini et al., 1998; Otranto and Puccini, 2000; Faliero et al., 2001) and the islands Sardinia and Sicily (Scala et al., 1998; Gaglio et al., 2016), Albania (Tagari and Bujari, 1989), North Macedonia (Geru et al., 1998), Bulgaria (Nedelčev et al., 1999), mainland Greece with the Greek islands including Crete, and Cyprus (Le Riche et al., 1973; Papadopoulos, 2004).

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Like the bovine warble fly species of the genus *Hypoderma*, *P. silenus* demonstrates a remarkable host specifity; however, in areas where it is abundant in goats, *P. silenus* can rarely be observed in sheep and cattle and even dogs as was also reported from Cyprus (Austen, 1931; Crowther et al., 1976) and Albania (Tagari and Manehasa, 1973). Interestingly, in contrast to the bovine *Hypoderma* species, *P. silenus* has apparently not been recorded causing accidental infestations of humans (Anderson, 2006).

The parasitic life cycle of *P. silenus* is generally similar to the cattle warble flies *Hypoderma bovis* and *H. lineatum* causing a myiasis which is characterised by the appearance of swellings or lumps ('warbles') in the back of the animals. However, conversely to bovine *Hypoderma* species, the larvae of *P. silenus* appear to remain and develop for up to ten months entirely under the skin of their hosts, as assumed already by Patton (1922). This assumption that *P. silenus* undergo no or at most minor migration exclusively in the hypodermic tissue layer is supported by the fact that the eggs of *P. silenus* have been frequently recorded glued at the hairs on the lower parts of the body of the goats including the limbs (Bhatia, 1934; Soni, 1942; Šergin, 1959, 1968; Sayin et al., 1973; Otranto and Puccini, 2000; Kuchbaev et al., 2004).

Related to the more limited geographic distribution of the parasite and the substantially lower value of the host animals, caprine *P. silenus* myiasis has an overall much lower global economic impact than cattle hypodermosis, associated with this, received much less attention, at least in Europe. Nevertheless, goat hypodermosis is considered as an underestimated constraint contributing to lower income from goat farming (Papadopoulos, 2004; Sotiraki and Hall, 2012; Fthenakis and Papadopoulos, 2018), depending on the specific socioeconomic situation and the relative importance of the products the goats are primarily kept for milk, meat, skin (leather) and/or fibre.

As in bovine hypodermosis, economic losses are primarily and obviously related to tissue damage in the course of the development of the warbles which substantially degrades the value of the skin along the midline of the back from which the high-quality leather is sourced. The skin damage includes holes left by the emerging larvae and scars that remain for several months after the emergence. In addition, losses of meat can also occur due to larval damage to the underlying flesh requiring carcass trimming (Tagari and Manehasa, 1973; Liakos, 1979; Tagari and Bujari, 1989; Papadopoulos et al., 1997; Yadav et al., 2012). It has, for instance, been reported from Greece that tanneries refuse the use of local goat skins because of the high frequency of warble fly parasitism related damage and use instead skins imported from warble fly-free countries (Papadopoulos, pers. comm., 2021). In addition, the larval damage to the underlying flesh requires carcass trimming as illustrated with skinned carcasses of warbled slaughter goats from Sicily (Gaglio et al., 2016). Adverse effects of goat warble fly infestation on performance traits like milk production and growth are more difficult to quantify. This is likely because there is high inter-individual variation in response which may depend on the nutritional level of the animals and their assessment requires to avoid the impact of confounding factors, e. g. helminth endoparasitism. However, there are historical studies which documented significantly higher weight gains in insecticide-treated goats than in untreated controls (Tašmatova and Vinokurov, 1971; Liakos, 1986a).

There are no drugs authorized in the European Union for the treatment of *P. silenus* myiasis in goats. However, based on the exceptional potency of the macrocyclic lactones against larval bovine *Hypoderma* species in general and ivermectin in particular (Drummond, 1984; Scholl, 2006; Colwell et al., 2009), products licensed for cattle were used in goats and reported to provide excellent efficacy against the parasitic larval stages of *P. silenus*. Most of this work was done with ivermectin-based injectable and pour on products (Zeybek, 1985; Tassi et al., 1987; Bujari and Hoxha, 1988; Yousif et al., 1988; Khan et al., 1991, 1994, 1997; Rahbari and Ghasemi, 1997; Ayaz, 1998; Nedelčev et al., 1999; Giangaspero et al., 2003; Yadav et al., 2014; Hasan et al., 2016), although there is also some information on other macrocyclic lactones (Niutta et al., 1997; Nedelčev et al., 1999) including one paper reporting on the activity of a topical generic eprinomectin preparation under field conditions in a *P. silenus* endemic area in India (Yadav et al., 2014).

The 5 mg/mL topical solution of the macrocyclic lactone eprinomectin (EPRINEX® Multi, Boehringer Ingelheim), which has a broad spectrum of endo and ecto parasiticidal activity and low milk partitioning in cattle (Shoop and Soll, 2002), was recently authorized for pour on administration at 1 mL per 5 kg body weight (equivalent to 1 mg eprinomectin per kg body weight) as an anthelmintic for sheep and goats with zero hours milk withdrawal in several countries in Europe (HMA, 2020).

The first case of the infestation of a domestic goat with warble fly larvae, previously described on three adult flies as *Hypoderma silenus* by Friedrich Brauer (1858), was reported in 1902 in Sicily (Provenza, 1902), and the endemicity of *P. silenus* in Sicily has been confirmed repeatedly until recently by an abattoir survey which found a farm prevalence of nearly 90 % and an intra-herd prevalence of almost 50 % (Romboli, 1950; Pugliese et al., 1994; Niutta et al., 1997; Gaglio et al., 2016).

This paper describes one negative control clinical study which was conducted to generate regulatory compliant data on the therapeutic efficacy of EPRINEX® Multi against caprine *P. silenus* myiasis. The objective of the study reported here was to evaluate the efficacy of the product in the treatment of goats harboring naturally acquired infestations of the three parasitic larval stages of *P. silenus*.

2. Material and methods

The design of the study was in accordance with and consistent to the World Association for the Advancement of Veterinary Parasitology (WAAVP) guideline for evaluating the efficacy of ectoparasiticides against myiasis causing parasites (Holdsworth et al., 2006). The study complied with VICH GL9, entitled *Good Clinical Practice*, and was performed as a blinded study, *i.e.*, personnel making health observations and collecting efficacy data were masked as to the treatment assignment of the animals.

The study was conducted in one extensive mixed sheep and goat farm located in the Messina province of Sicily with a history of warble fly infestation in the goats (Gaglio et al., 2016), the farm reared about 200 and 300 crossbreed goats and sheep, respectively, and housed in separated pens.

2.1. Selection of study animals, allocation to study groups, administration of treatments, animal husbandry

In order to select 45 animals for the study, 70 goats of the farm were screened for previous exposure to *P. silenus* by ELISA prior to enrolment in the study (October 2019, nine days prior to the start of the study on Day 0). For analysis, a commercial cattle hypodermosis ELISA kit (ID Screen® Hypodermosis Indirect; Innovative Diagnostics SAS, Grables, France) was used following Otranto et al. (1999). All serum samples were analyzed in duplicate and optical density was read at 450 nm using a Sirio microwell plate reader (SEAC, Florence, Italy) following the manufacturer's instructions. For each sample, the cut-off absorbance was set at 0.351 and the sample-to-positive ratio (S/P%) was calculated.

Of the 70 goats, 19 tested antibody positive (S/P% $\geq$55), two doubtful (S/P% >45 % to <55 %) and 49 negative (S/P% $\leq$45 %) at the prior-to-enrolment testing. Considering the ELISA results and the endemicity of *P. silenus* in the area, two categories of goats were formed for enrolment of the animals into the study and their allocation to the study groups: 21 animals which tested ELISA positive or doubtful and 24 animals that tested ELISA negative (randomly chosen from the 49 negative tested goats). Two unique randomization lists generated using PLAN procedure in SAS Version 9.4 were used to assign equal numbers of animals of each category completely at random to three study groups

such that each group had 15 animals including seven and eight goats which tested ELISA positive/doubtful or negative, respectively. A physical examination of the animals by a veterinarian confirmed their suitability for inclusion into the study. The goats at the farm had not been previously treated with macrocyclic lactone parasiticides or other systemic insecticides. Animal descriptions and details are presented in Table 1.

Goats allocated to Group 1 (control) were left untreated; goats allocated to Groups 2 and 3 received eprinomectin 5 mg/mL topical solution (EPRINEX® Multi, Boehringer Ingelheim) administered pour on at 1 mL per 5 kg body weight along the backline, directly onto the skin. In particular, Group 2 animals received the treatment on Day 0 (24 Oct 2019) when the animals did not show clinical evidence of warble fly infestation (i.e., corresponding to the expected presence of first and/or second larval instars [L1/L2]), while Group 3 animals received the treatment on Day 167 (08 Apr 2020) when warbles containing mature larvae (third larval instars [L3]) had been diagnosed in at least six goats each in Groups 1 and 3.

All animals were weighed with a verified scale prior to or at the respective treatment days and at the last day of the study, prior to slaughter (Days −1, 167 and 186) for dose calculation purposes and to monitor the body weight over the course of the study. At these occasions, blood samples were collected from the animals for the generation of serum which was tested using the ELISA kit as described before.

General health observations were made daily. In addition, animals of Groups 2 and 3 were observed at approximately two and four hours after administration of treatment for reactions to the treatment.

Throughout the study, the animals were managed as per local practice. The study animals were comingled with the remaining (non-study) goats, grazed permanent extensive pasture during day and were offered hay/straw and water from the site well provided via tanks during night housing. Group 2 and Group 3 animals were separated from the other goats for one week after administration of the treatment at Day 0 and Day 167, respectively. During these periods, the animals were kept in a covered shelter at the farm with hay and water supplied.

2.2. Examination of animals for warbles, warble fly larvae collection, count and identification

As the season for warble formation and larval emergence approached, the goats were examined for warbles starting on Day 89 (21 Jan 2020) and continuing on Days 103, 117, 131, 163, 174 and 181. Due to restrictions on movement related to COVID pandemic regulations, examination of the animals was suspended after Day 131 and re-initiated by Day 163. During the examinations at Days 174 and 181, sufficiently mature larvae were expressed from the warbles by gentle manual pressure, collected, and their viability was determined (motile larvae were considered alive). On Day 186 (end of the study), the animals were slaughtered, skinned, and skin and carcass of each animal were inspected for potentially remaining goat warble fly larvae.

Unless identification was prevented by disintegration, the larvae were identified to larval instar and species based on morphological characters (Zumpt, 1965) accepting that the three species previously reported to infest goats are in fact a single species, *P. silenus* (Otranto and Traversa, 2004). All warble fly larvae were stored in 70 % ethanol before and after identification.

2.3. Data analysis

The variable for the assessment of the treatment efficacy was the sum of live *P. silenus* larvae collected. The *P. silenus* live larval counts were transformed to the natural logarithm of (count +1) for statistical analysis. Efficacy was determined for total live *P. silenus* larvae by calculating the percent efficacy as 100x[(C-T)/C], where C is the geometric mean obtained by the back transformation of the least squares means from the statistical model in the untreated (control) group and T is the geometric mean obtained by the back transformation of the least squares means from the statistical model in the eprinomectin 5 mg/L topical solution-treated groups.

The log-counts of each treated group were compared to the log-counts of the untreated controls using an F-test. The MIXED procedure in SAS version 9.4 was used for the analysis with the treatment groups listed as a fixed effect. All testing was two-sided at the significance level $\alpha = 0.05$.

3. Results

The dosing of the animals pour on at 1 mL of eprinomectin 5 mg/mL topical solution per 5 kg body weight provided actual eprinomectin dose rates of 1.03 ± 0.02 mg per kg body weight for the goats (n = 30). The administration of the product was well accepted by the goats and no abnormal reactions related to the treatment were observed in any animal.

At the first examination on Day 89 (21 January 2020), two, three and five warbles were detected in three goats of Groups 1 and Group 3 (Fig. 1). While no warbles were detected over the course of the study in any of the goats of Group 2 which were administered eprinomectin 5 mg/L topical solution in late October when there was no clinical evidence of infestation. The number of warble-positive animals in the two other groups of goats (Group 1 and 3) increased over time (Day 103, 5 animals; Day 117, six animals; Day 131, nine animals). After detection of warbles on Day 163 in seven animals of Group 1 (range, 2–6 warbles) and in eight animals of Group 3 (range, 1–7 warbles), eprinomectin 5 mg/L topical solution was administered to the Group 3 animals on Day 167 (08 April 2020).

By examination of the goats on Days 174, 181 and 186, total 14 live *P. silenus* L3 larvae were collected from six of the 15 untreated (control) animals (range, 1–3 larvae) and no live *P. silenus* larvae were recovered from any of the eprinomectin 5 mg/L topical solution-treated goats (Fig. 2). However, three dead *P. silenus* L3 larvae were removed from one goat of the untreated Group 1 and total 15 dead *P. silenus* L3 larvae from six of the 15 goats of Group 3 (range, 1–5 larvae) which had been

Table 1
Description of study animals according to groups, ELISA results and body weight.

Group[a]	Animals		ELISA[b]	Body Weight (kg), mean ± SD[c]		
	Sex	Age	Day −9	Day -1	Day 167	Day 186
1 - Untreated (control), n = 15	2 M; 13 F	1–5 years old	6 P; 1D; 8 N	33.9 ± 6.0	34.6 ± 5.6	34.2 ± 5.5
2 - Eprinomectin 5 mg/mL topical solution L1/L2, n = 15	1 M; 14 F	1 < 1 year and 14 1–5 years old	7 P; 8 N	32.2 ± 7.3	37.1 ± 8.6	36.5 ± 8.8
3 - Eprinomectin 5 mg/mL topical solution L3, n = 15	4 M; 11 F	1 < 1 year and 14 1–5 years old	6 P; 1D; 8 N	35.0 ± 6.5	37.2 ± 7.5	37.5 ± 7.3

[a] 1, Untreated; 2, Eprinomectin 5 mg/mL topical solution L1/L2, administered at 1 mL per 5 kg body weight once on Day 0 during the first/second larval stages (L1/L2) of development; 3, Eprinomectin 5 mg/mL topical solution L3, administered at 1 mL per 5 kg body weight once on Day 167 during the third larval stage (L3) of development.
[b] P, positive; D, doubtful; N, negative.
[c] SD = standard deviation.

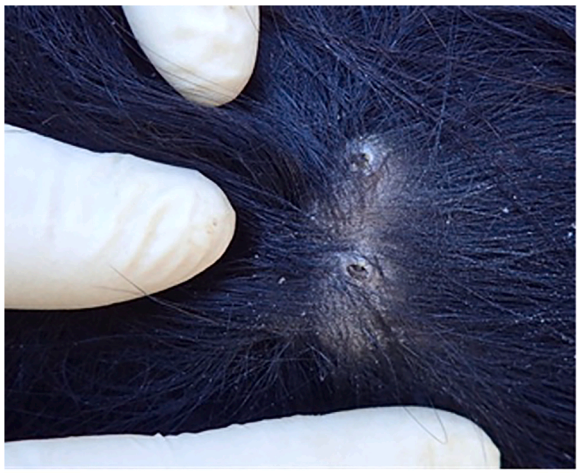

Fig. 1. *Przhevalskiana silenus* warbles showing the respiratory holes on the back of a goat (Group 1, SD 89, January 21st 2020).

Fig. 2. Collection of a live *Przhevalskiana silenus* larva from a warble using gentle manual pressure (Group 1, SD 181, April 22nd 2020).

administered eprinomectin 5 mg/L topical solution on Day 167. In addition, one dead larva was collected from one more Group 3 animal; however, decomposition did not allow for the speciation of this specimen.

Goats of the eprinomectin 5 mg/L topical solution-treated Groups 2 and 3 were negative for live larval *P. silenus* resulting in a geometric mean number of larvae significantly fewer than the untreated (control) group ($P < 0.01$ at α=0.05) and 100 % efficacy of the treatments (Table 2).

The results of the testing of the goats' serum with the bovine hypodermosis ELISA are summarized in Table 3. Considering the goats of Group 2 which were administered eprinomectin 5 mg/L topical solution in the absence of clinical evidence of infestation, goats testing ELISA positive before study start (Days −9 and −1) became ELISA negative or doubtful after treatment and goats testing ELISA negative or doubtful before treatment were ELISA negative thereafter. Most of the goats of untreated Group 1 testing ELISA positive or doubtful before study start (Days −9 and −1) tested ELISA negative or doubtful at the end of the study while half of the goats of Group 1 testing ELISA negative before study start were ELISA positive at the study end. In the Group 3 goats which received treatment on Day 167 after warbles detection, about half of the animals testing ELISA positive or doubtful before study start tested ELISA negative at the end of the study while the goats testing ELISA negative on Day −9 tested all ELISA negative at the study end although some of them tested positive and/or doubtful on Day −1 and/or Day 167.

Table 2
Number of live *Przhevalskiana silenus* larvae collected and efficacy of EPRINEX® Multi against infestation with first and second stage (L1/L2), and third stage (L3) larvae of *P. silenus*.

Group[a]	Count of live *P. silenus* L3 collected		Efficacy (%)	P-value
	NI/NG[b]	Geometric Mean, range		
1 - Untreated (control)	6/15	0.6 (0−3)	—	—
2 - Eprinomectin 5 mg/mL topical solution L1/L2	0/14[c]	0	100	0.0011
3 - Eprinomectin 5 mg/mL topical solution L3	0/15	0	100	0.0009

[a] 1, Untreated; 2, Eprinomectin 5 mg/mL topical solution L1/L2, administered at 1 mL per 5 kg body weight once on Day 0 during the first/second larval stages (L1/L2) of development; 3, Eprinomectin 5 mg/mL topical solution L3, administered at 1 mL per 5 kg body weight once on Day 167 during the third larval stage (L3) of development.
[b] Number of infested goats (NI); Number of goats in group (NG)
[c] One animal was found dead at Day 18.

Table 3
Summary of ELISA Antibody Testing.

Group	Categories for Allocation to Groups[a]	Number of Animals with ELISA Testing P, D or N			
		Day −9 15 Oct 2019	Day −1 23 Oct 2019	Day 167 08 Apr 2020	Day 186 27 Apr 2020
1 - Untreated (control), n = 15	ELISA P + D at Day −9	6 P, 1D	6 P, 1 N	1 P, 1D, 5 N	2 P, 5 N
	ELISA N at Day −9	8 N	1 P, 7 N	4 P, 4 N	4 P, 1D, 3 N
2 - Eprinomectin 5 mg/mL topical solution L1/L2, n = 15[b]	ELISA P + D at Day −9	7 P	7 P	1D, 5 N	1D, 5 N
	ELISA N at Day −9	8 N	1D, 7 N	8 N	8 N
3 - Eprinomectin 5 mg/mL topical solution L3, n = 15	ELISA P + D at Day −9	6 P, 1D	6 P, 1 N	4 P, 3 N	3 P, 4 N
	ELISA N at Day −9	8 N	2 P, 1D, 5 N	1D, 7 N	8 N

[a] For the allocation to study groups, animals were formed in two categories based on Day −9 ELISA testing (21 animals testing positive or doubtful [P + D] and 24 animals testing negative [N]) and then assigned completely at random to the three groups within category.
[b] One ELISA P-tested animal was found dead at Day 18.

No health problems were observed during the study but one five-year-old female goat of Group 2, not reported to be clinically apparent before, was found dead 18 days after treatment. Necropsy of the animal at the Department of Veterinary Sciences, University of Messina, revealed catarrhal bronchopneumonia followed by failure of the pulmonary and cardiovascular system. In addition, skinning of the carcass demonstrated focal lesions along the back which, as shown by microscopic examination, contained remnants of degrading larval structures (cuticule body segment spinulation, cephaloskeleton fragments). The death of this animal was considered not to be related to the treatment. No concurrent medication was administered to any animal in the study.

4. Discussion

Results of this study demonstrated an excellent level of efficacy of eprinomectin 5 mg/mL topical solution (EPRINEX® Multi) administered

as a pour on at 1 mL per 5 kg body weight in goats naturally infested with the parasitic stages of the goat warble fly, *P. silenus* and thus extend the indications of this product beyond the broad spectrum of nematode endoparasites and oestrosis (Hamel et al., 2015, 2021; Gao et al., 2022; Rehbein et al., 2024) and the promising activity reported against lice, chorioptic mites and *Rhipicephalus* ticks (Prelezov et al., 2022; Rehbein et al., 2023).

Live third stage larvae of *P. silenus* were recovered from six control animals thus an adequate infestation for the evaluation of parasiticides against myiasis causing parasites in ruminants according to the WAAVP guidelines (Holdsworth et al., 2006) was demonstrated in the study. Efficacy was demonstrated both when there was (yet) no clinical (external) evidence of larvae presence and thus before causing a decrease in the value of the skin and carcass, and as a therapeutic treatment while the larvae were in their warbles associated with damage to skin and carcass. This basic management principle for warble fly control with two options to interfere with the development of the parasitic larvae in the host has been previously shown to be highly effective in cattle administered eprinomectin 5 mg/mL topical solution for the treatment of warble fly infestation (Holste et al., 1997). In the single study reported previously testing the activity of a topical eprinomectin product against *P. silenus* in India only the effect of the treatment of the clinically inapparent larval stages was tested (Yadav et al., 2014). Interestingly, all studies done in goats in the past (Zeybek, 1985; Tassi et al., 1987; Bujari and Hoxha, 1988; Yousif et al., 1988; Khan et al., 1991, 1994, 1997; Niutta et al., 1997; Rahbari and Ghasemi, 1997; Ayaz, 1998; Nedelčev et al., 1999; Giangaspero et al., 2003; Yadav et al., 2014; Hasan et al., 2016) assessed the effect of the treatments with macrocyclic lactone products based on the observation and count of warbles, i.e. either the formation of warbles in animals treated when there was no clinical evidence for infestation or the resolution of warbles in animals treated after warbles had been formed. The present study, however, evaluated the efficacy of the treatment based on the recovery and count of the larvae that developed in the warbles in accordance with the WAAVP guidelines for the evaluation of ectoparasiticides in ruminants which require the assessment of treatments based on live parasite counts rather than counts of lesions resultant from the parasite infestation (Holdsworth et al., 2006, 2022) and established the efficacy of eprinomectin 5 mg/mL topical solution against all parasitic larval stages of the goat warble fly *P. silenus*.

As in warble fly control studies in cattle (Hendrickx et al., 1993; Holste et al., 1997; Rehbein et al., 2013; Otranto et al., 2016; Lia et al., 2019), sero-diagnosis was applied in an attempt to identify the animals for the present study as it is the only way to detect animals with exposure to warble fly larvae before warbles appear in the backs of the animals. In the absence of commercial antibody tests for goat warble fly infestation, a cattle hypodermosis ELISA kit containing hypodermin antigen extracted from *H. lineatum* L1 larvae was used as its suitability has been reported by several authors (Otranto et al., 1999; Faliero et al., 2001; Jan et al., 2014; Liaqat et al., 2023). Only 21 out of 70 goats screened tested ELISA positive (19 goats) or doubtful (2 goats) at inclusion although this farm was historically known to be endemic of *P. silenus*. Because of this it was decided to allocate seven of these 21 goats at random to each the three study groups and to add to each group eight animals which tested antibody negative. Development of warbles in this study was ultimately recorded in 50 % of the 30 combined controls and animals treated after warbles had developed (Groups 1 and 3). Overall, the warble detection rate of 50 % in the study animals is in line with more recently reported warble fly surveys from Sicily (Pugliese et al., 1994; Gaglio et al., 2016).

The infestation pattern, in terms of the development of warbles in the backs of goats, overlapped with the seasonality of *P. silenus* infestation observed previously in Italy and countries in southeastern Europe (Tagari and Manehasa, 1973; Liakos, 1979; Bujari, 1983; Geru et al., 1998; Otranto and Puccini, 2000; Gaglio et al., 2016) which indicates, as discussed for bovine *Hypoderma* species (Hendrickx et al., 1993; Reina et al., 1998; Lia et al., 2019), year to year variation of four to eight weeks related to seasonal and geographic differences in local environmental conditions. The level of infestation, in terms of the number of warbles counted per goat, appeared to be lower compared to counts established in the recently reported abattoir survey from Sicily (Gaglio et al., 2016) and earlier reported clinical studies from the south of mainland Italy (Tassi et al., 1989).

The 15 warbled goats among the 30 animals of Groups 1 and 3 in the present study included 10 of 14 animals (71.4 %) which tested antibody positive/doubtful at inclusion in the study and five of 16 animals (31.3 %) animals which tested antibody negative at inclusion in the study. The frequency of warbled animals in the two categories of animals is not quite statistically significant ($P = 0.0656$; Fisher's exact test).

The observed warble detection rate of 71.4 % among the goats testing antibody positive/doubtful is within the range of this parameter estimated from anti-*Hypoderma* antibody positive cattle enrolled in seven warble fly control studies reported earlier – 68.4–95 % (Holste et al., 1997; Rehbein et al., 2013; Otranto et al., 2016; Lia et al., 2019). Thirteen of the 14 ELISA positive/doubtful-tested animals which were left untreated or received treatment after warbles had developed were approximately two years and older. These goats were likely infested with larvae when tested via ELISA in October which is approximately three to four months after the end of the activity of the adult *P. silenus* flies (Tagari and Manehasa, 1973; Liakos, 1979; Bujari, 1983; Otranto and Puccini, 2000). However, a larger portion of the larvae were apparently unable to complete their development and died before warbles formed suggesting that the animals acquired resistance from previous infestation as was shown in *Hypoderma* infested cattle (Boulard, 2006). Similar mechanisms were assumed to be relevant for the infestation of goats with *P. silenus* (Otranto and Puccini, 2000) which is supported by observations that on carcasses of older slaughter goats in Greece frequently only remnants of dead *P. silenus* L1 and L2 larvae were found (Liakos, 1979).

It is worth to note that in the present study the development of warbles was detected in almost one third – five of 16 – of the goats from the combined controls and animals treated after warbles had developed groups which tested antibody negative at inclusion in the study. When the goats were tested again eight days after the study inclusion testing (end of October), three of these five goats (all five were two years and older) were ELISA positive (2) or doubtful (1) and two tested negatives. Tested again parallel to the treatment of the goats after warbles developed in early April, two of the three goats testing positive/doubtful by end of October gave negative results and the other animal tested seropositive; the two goats that tested negative in both tests in October were ELISA positive in the early April testing. Whether these findings may be related to timing of the testing for the inclusion of the goats into the study in the mid of October while highest antibody levels in goats have been observed in November and December (Otranto et al., 1999; Faliero et al., 2001) or potentially reflect limitations of the test to detect low antibody levels in goats, is not completely clear. However, it is interesting to note that in cattle naturally infested with *H. lineatum* and/or *H. bovis* it was found that a proportion of animals presenting low level infestations (1–4 warbles) produced false negative ELISA results. Most of these animals were infested with *H. bovis* exclusively, were ELISA negative through October to January and became ELISA positive only in February (Colwell and Baron, 1990). In addition, in a *H. bovis* control study, conducted in an endemic area in France, which included 154 untreated cattle from those 113 tested ELISA positive at inclusion, the development of warbles was detected in 134 animals indicating that the number of infested cattle was underestimated by the ELISA test (Hendrickx et al., 1993). Taking the findings in *H. bovis*-infested cattle and the observations in the goats in the present study together, it cannot be excluded that *H. lineatum* antigen-based ELISA tests may have a reduced sensitivity in low level *H. bovis* and *P. silenus* infestations and/or antibodies had not risen to detection level at the time of testing because

of variation in the period of activity of the adult warble flies and/or the development of the larvae after infestation of the host.

5. Conclusion

A number of reports documenting the high efficacy of macrocyclic lactone-based products against goat warble fly infestation in goats has been published following the first publications on the exceptional activity of ivermectin against bovine *Hypoderma* species in the early 1980s but there is no product indicated for the treatment and control of caprine warbly fly myiasis in Europe.

The present work demonstrated that one single appropriately timed treatment of eprinomectin 5 mg/mL topical solution administered as a pour on at 1 mL per 5 kg body weight is an efficacious treatment against existing infestations of *P. silenus* in goats. The treatment of goats when there is not yet clinical evidence of infestation will prevent losses typically associated with the subcutaneous parasitism of the larvae of the goat warble fly.

The results of the present study provide evidence that EPRINEX® Multi is an efficacious treatment for caprine *P. silenus* myiasis and thus extend the indications of this product beyond the broad spectrum of nematode endoparasites and oestrosis.

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Ethical Statement

All study procedures complied with the appropriate local animal welfare regulations and were authorized by the applicable legal body (Ministero della Salute, Rome, Italy; 0026168–14/10/2019-DGSAF-MDS-P) and approved by the company's animal welfare committee.

CRediT authorship contribution statement

Rehbein Steffen: Writing – original draft, Validation, Supervision, Conceptualization. **Kley Katrin:** Writing – review & editing, Validation, Methodology, Investigation. **Napoli Ettore:** Writing – original draft, Investigation, Formal analysis, Data curation. **De Benedetto Giovanni:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Remesar Susana:** Writing – original draft, Investigation, Formal analysis. **Gaglio Gabriella:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Arfuso Francesca:** Writing – review & editing, Methodology, Formal analysis. **Pansera Lidia:** Writing – review & editing, Investigation. **Brianti Emanuele:** Writing – review & editing, Validation, Supervision, Methodology, Investigation. **Fankhauser Becky:** Writing – review & editing, Validation, Methodology, Investigation.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ettore Napoli, Susana Remesar, Giovanni de Benedetto, Francesca Arfuso, Gabriella Gaglio, Emanuele Brianti, Lidia Pansera reports equipment, drugs, or supplies and statistical analysis were provided by Boehringer Ingelheim Animal Health. Becky Fankhauserc, Katrin Kley, Steffen Rehbein reports a relationship with Boehringer Ingelheim Animal Health that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability statement

Raw data and derived data supporting the findings of this study are available from the corresponding author Giovanni De Benedetto on request.

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