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ORIGINAL RESEARCH

Efficacy and safety of enflicoxib for treatment of canine osteoarthritis: A 6-week randomised, controlled, blind, multicentre clinical trial

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Abstract

Background: Enflicoxib is a new COX-2 selective NSAID intended for the treatment of pain and inflammation associated with canine osteoarthritis.

Methods: A prospective, multisite, blinded, randomised, controlled, parallel-group field study was performed to determine the efficacy and safety of enflicoxib in canine osteoarthritis. A total of 242 dogs were randomised to receive enflicoxib at 4 or 2 mg/kg, mavacoxib at 2 mg/kg or placebo, orally. Enflicoxib and placebo were administered once weekly from day 0 to day 35. Mavacoxib was administered on D0 and day 14. Veterinarians assessed efficacy with a numerical rating scale and owners used the Canine Brief Pain Inventory.

Results: After 6 weeks, enflicoxib at 4 mg/kg showed the highest percentage of responders as assessed by the veterinarians (68%) and the owners (84%), followed by mavacoxib (62and 83%, respectively), and enflicoxib at 2 mg/kg (57 and 80%, respectively). All treatments reached statistical significance versus placebo, which obtained success rates of 37% and 53%, respectively. No differences in the incidence of adverse reactions were detected among the different groups.

Conclusions: Enflicoxib administered weekly for 6 weeks, at 4 mg/kg PO with an initial loading dose of 8 mg/kg, is efficacious and safe for the treatment of canine osteoarthritis.

KEYWORDS
dogs, enflicoxib, non-steroidal anti-inflammatory drugs (NSAIDs), osteoarthritis, pain

INTRODUCTION

Osteoarthritis (OA) is a progressive degenerative disease of synovial joints and is characterised by structural and functional changes to the cartilage secondary to inflammatory, biomechanical and metabolic components.[1,2] It is highly prevalent in dogs[3],[4] with 20 per cent of the canine population over the age of 1 year old affected by the disease[5,6]. This musculoskeletal disease results in lameness, loss of joint function and mobility, chronic pain, and reduced quality of life.[7] The management of OA in dogs is a lifetime commitment, involving a multimodal approach. Other than surgical management for a number of select groups of arthritic patients, there are no disease-modifying therapies with strong evidence of efficacy in canine OA. Therefore, its management is based on relieving the symptoms of the disease by treating pain and inflammation, improving mobility and hence quality of life, whilst protecting joints from OA.[8–11] Nutritional supplementation, physiotherapy and weight management are essential to alleviate the symptoms of the disease, however, non-steroidal anti-inflammatory drugs (NSAIDs) are still considered the medical cornerstone for the management of canine OA.[12,13]

The pain associated with osteoarthritis is chronic[14] and long-term continuous NSAID treatment has been shown to be more efficacious than short-term treatment periods, with no evidence of any increase in NSAID-related side effects.[15] However, although the incidence is low in comparison to NSAID frequency

of use,[16] gastrointestinal, hepatic and renal side effects may occur and should be monitored.[17–20]

Most NSAIDs require daily oral administration to ensure their efficacy. However, compliance with long-term daily administration of medicines in routine veterinary clinical practice is known to be relatively poor and a major barrier to adequate treatment,[21] with daily doses being missed even during a relatively short 10-day treatment course.[22,23] Therefore, long-acting NSAID preparations with less frequent dosing, likely to achieve an increased overall compliance,[24] may be more reliable to treat chronic pain in dogs with clinical symptoms of OA.

Enflicoxib is a new NSAID of the Coxib group with long-lasting activity in dogs. Pharmacokinetic/pharmacodynamic analysis based on data obtained in previous pharmacokinetic, toxicity and efficacy studies using an arthritis-induced model in dogs, suggested that a dosage of 4 mg/kg of enflicoxib, once a week, with an initial loading dose of 8 mg/kg, could be safe and efficacious for the treatment of canine OA.[25]

The objective of the present study was to confirm the efficacy and safety of enflicoxib for the treatment of naturally occurring canine OA. With the aim to choose the lowest effective dose, two doses of enflicoxib were compared to a negative control group, which received the same tablets but without any active ingredient (placebo). An approved and effective NSAID for the treatment of canine OA (mavacoxib, Trocoxil®, Zoetis) was included as a positive control and to serve as a reference for the comparison of the time response profile of NSAIDs.

MATERIALS AND METHODS

A prospective, multisite, blinded, randomized, controlled, parallel-group field study was conducted in compliance with the Veterinary International Conference on Harmonization guideline for Good Clinical Practice[26] at 28 veterinary practices located throughout Spain and France. Approval was obtained from the appropriate regulatory authorities and satisfied national regulatory and animal welfare standards and requirements. Informed consent was obtained from all dog owners prior to enrolment.

Animal selection

All dogs were client-owned and presented as veterinary patients at the practices. Any breed of dogs was included and both sexes. The dogs were required to have clinical signs of pain and lameness for at least 3 weeks along with radiographic evidence of OA in at least one joint (presence of articular lesions compatible with OA, such as subchondral bone sclerosis, bone remodelling, osteophytes, irregular or diminished joint space). All dogs were evaluated and scored for possible inclusion in the study. The inclusion period lasted for 6 months.

Prior to inclusion in the study, dogs should not have received any treatment with short-acting NSAIDs, corticosteroids or opioids for at least 14 days, pentosan polysulphate sodium, PSGAG (polysulphated glycosaminoglycan), long-acting systemic corticosteroids or mavacoxib for at least 30 days or intra-articular injections of corticosteroids for 90 days. Additionally, dogs should not have received chondroitin sulphate or glucosamine or a specific OA prescription diet containing chondroprotective agents, except if these products had been administered at a constant dosage for at least one month before the start of the present study and administration would not be altered during the study. Dogs known to have severe or uncontrolled concomitant disorders (e.g. kidney, liver, heart, gastrointestinal tract, or haemorrhagic disorders including hypovolemic, dehydrated, hypotensive or unexplained bleeding episodes) that are contraindications for the use of NSAIDs, or that could interfere with the evaluation of treatment effect, were excluded from participation. Dogs in which surgery had been performed on any joint in the previous 60 days or with axial skeleton disease, or in which the presenting lameness was associated with active infectious arthritis, neoplasia, a primary neurological disorder or known immunological disorder, were also excluded. Dogs were not eligible for enrolment if gross instability of the hip or the stifle joint was present. Females that were pregnant or lactating, or animals intended for breeding were not included.

Concomitant treatment with analgesic drugs, NSAIDs or systemic corticosteroids was not permitted during the study. Administration of other concomitant medications was permitted but had to be recorded. Dogs with mild and controlled conditions could participate, and their medication could be continued, if it was not expected to alter the study results. Other limitations included in the summary of product characteristics of mavacoxib such as a minimum weight of 5 kg and being older than 12 months at inclusion, or treatments specifically contra-indicated for the concomitant use with mavacoxib were also implemented.

The severity of clinical signs of OA was evaluated by both the veterinarian and the owner on the day of inclusion, before first treatment administration.

The veterinarians assessed pain and lameness using numerical rating scales (NRS) as described by several authors.[27–29] This NRS included the assessment of four parameters in the following order: posture while the dog was standing, lameness at walk, lameness at trot and pain at palpation/manipulation of the affected joint as described in Table 1. A factor of two was applied to place more weight on lameness at walk and at trot as part of the clinical picture of OA.[29–31] The clinical sum score (CSS) was the sum of scores for these four parameters and ranged from 0 to 18.

The owner evaluation was performed using the Canine Brief Pain Inventory (CBPI).[32,33] The CBPI is a two-part instrument: the pain severity score (PSS) is the arithmetic mean of four items scored on an

TABLE 1 Veterinarian clinical sum score (CSS)

1. Posture (dog standing)	
Score	**Description**
0	Normal stance
1	Slightly abnormal stance: partial weight bearing of limb, but paw remains firmly in contact with floor
2	Markedly abnormal stance: partial weight bearing of limb with minimal contact between paw and the floor
3	Severely abnormal stance: no weight bearing
2. Lameness at Walk	
Score	**Description**
0	No lameness: normal weight bearing on all limbs
2	Mild lameness with partial weight bearing
4	Obvious lameness with partial weight bearing
6	Marked lameness with no weight bearing
3. Lameness at Trot	
Score	**Description**
0	No lameness: normal weight bearing on all limbs
2	Mild lameness with partial weight bearing
4	Obvious lameness with partial weight bearing
6	Marked lameness with no weight bearing
4. Pain on Palpation/Manipulation	
Score	**Description**
0	No pain on palpation/manipulation of effected joint
1	Mild pain (e.g. turns head in recognition)
2	Moderate pain (e.g. pulls limb away)
3	Severe pain (e.g. vocalizes or becomes aggressive or will not allow veterinarians to palpate/manipulate the joint due to pain)

11-point (0−10) numerical scale, and the pain interference score (PIS) is the mean of 6 items scored similarly (0 = no pain or interference and 10 = severe pain or interference).

Dogs selected for inclusion in the study had to have clinical signs of OA as evidenced by a CSS≥6 and basal PSS and PIS scores ≥ 2 on Day 0, prior to treatment. All dogs included in the study were in good general health based on a complete general physical examination, and routine blood (haematology and biochemistry) examination results were within normal limits. Some dogs had mild and well-controlled health conditions unrelated to OA. The owners were instructed not to change, as far as possible, the daily exercise routine or home management of their dogs during the study in order not to have an impact on the evaluation of the efficacy of the test products.

Any dog could be withdrawn from the study in case of occurrence of an adverse event that required stopping the treatment or which could interfere with the evaluation of the study treatment; an unsatisfactory therapeutic response; forbidden concomitant treatment; a major protocol deviation, or withdrawal of the owner's consent. For cases with unsatisfactory therapeutic response, additional veterinary care including rescue analgesia was permitted after withdrawal of the dog from the study.

Treatments

Dogs that met the inclusion criteria were enrolled by the veterinarian and randomly allocated to one of four oral treatment groups (enflicoxib at 4 or 2 mg/kg, placebo or mavacoxib 2 mg/kg) by use of a randomised block schedule generated by the statistician. The block size was four, with all treatments in each block. Day 0 was defined as the day of inclusion and the first day of treatment. Dogs allocated to enflicoxib groups received an initial loading dose of 8 or 4 mg/kg, with subsequent treatments at once weekly maintenance doses of 4 mg/kg or 2 mg/kg, respectively, for 5 additional weeks on days 7, 14, 21, 28 and 35 (±2 days) . Dogs allocated in the placebo group received placebo tablets at the same dose regimen. Dogs in the mavacoxib group received 2 mg/kg on Day 0 and Day 14 as per label recommendation and the administration of a placebo tablet on days 7, 21, 28 and 35 to ensure blinding.

Enflicoxib and placebo tablets were similar, but mavacoxib had a different appearance. Therefore, to preserve blinding of the veterinarians and the owners, a dispenser was identified at each site for the allocation, administration and dispensing of study treatments. The random allocation was implemented using sequentially numbered containers. Treatment

on days 0, 7, 14 and 28 was administered at the veterinary practice by the dispenser, while treatment on days 21 and 35 was administered by the owner at home. Dose calculations for study treatments were performed using the body weight determined on Day 0. As food increases its absorption, and following their label indications, enflicoxib, mavacoxib or placebo tablets were administered with food or immediately before feeding.[34,35] At the end of the study, the owner assessed the general level of acceptance of the products by the animal for the treatments given at home as poor, satisfactory, good or excellent.

Assessments

General physical examinations and clinical assessments of pain and lameness were performed by the veterinarian on Day 0, prior to treatment and thereafter at each study visit on days 7, 14, 28 and 42 (±2 days) using the CSS. The most severely affected joint was selected on Day 0, prior to the start of treatment administration, and evaluated throughout the study regardless of whether another joint was also affected. In addition, during each visit the veterinarian interviewed the owner to record their assessments using the CBPI. The owner was not aware of the required threshold level for PSS and PIS scores for inclusion in the study and did not have access to the scores of previous assessments when completing each CBPI.

Efficacy outcome measures

For the veterinary assessment, a predefined criterion of treatment response was used. A dog was classified as a responder if the CSS score was < 6 in any of the follow-up visits. The primary efficacy endpoint was the percentage of CSS responders at the end of the study (Day 42).

For the owner assessment, CBPI was used and a dog was classified as a responder if it had a decrease ≥1 in PSS, and ≥2 in PIS in any visit compared to basal scores. The secondary efficacy endpoint was the percentage of CBPI responders at the end of the study (Day 42).

The percentage of CSS and CBPI responders were additionally evaluated at each time point.

Any dog not classified as a responder using these criteria or withdrawn from the study because of lack of efficacy prior to Day 42 was classified as a treatment failure. The treatment failure classification and clinical scores at the time of withdrawal from the study were carried forward to all subsequent time points subjected to the Last Observation Carried Forward (LOCF).

Safety outcome measures

Safety was evaluated by recording adverse events (AEs) that occurred throughout the study. Owners were informed about the most common AEs related to NSAID administration and were instructed to daily observe the animals and to immediately report any suspected AE to the veterinarian. An AE being defined as any observation in animals that is unfavourable and unintended and occurs after the use of enflicoxib, mavacoxib or placebo, whether or not considered to be product related.[36] Each AE was described by clinical signs using the Veterinary Dictionary for Drug Regulatory Activities (VeDDRA) terms.[37] The severity of the clinical signs (mild, moderate, severe), the outcome of the AE, and whether it was serious or not was also indicated. A Serious Adverse Event (SAE) was considered an AE that results in death, is life-threatening, results in significant disability or incapacity, is a congenital anomaly/birth defect, or results in permanent or prolonged signs. By default, any AE not falling into the definition of SAE is considered "Non-Serious". At the end of the study, all AE were assessed using the ABON system of causality assessment,[38] where A = probable, B = possible, O = unclassifiable/unassessable, O1 = inconclusive and N = unlikely to be treatment related. This assessment considered that NSAIDs have the potential to cause or exacerbate gastrointestinal, renal and hepatic disorders.

For the calculation of the incidence, when several AEs were observed in a single animal at an overlapped time frame, according to current guidelines[39] they were considered as different clinical signs of the same AE.

Data management

The study data were recorded contemporaneously by the veterinarians and dispensers in electronic CRFs (Case Record Forms). The validated study-specific EDC (Electronic Data Capture) database was designed and validated by Ondax Scientific using the Ennov® system as described in the Data Management Plan. Data was subjected to 100% quality control (QC) checks. Following data query resolution and database quality audit (QA), the database was locked, and data exported in .sas and .dat data files for statistical analysis.

Sample size

The sample size was calculated for the comparison of each treated group to the placebo group with respect to the primary efficacy endpoint. From preliminary studies, the proportion of responders in the placebo group was assumed to be approximately 30% whereas in each treated group it was assumed to be approximately 60%. Thus, a sample size of 42 animals per group would provide a statistical power of 80% when testing for differences by means of a chi-square test. Considering a 20% of possible drop-outs, the number of dogs to be recruited was set to 60 animals per group.

TABLE 2 Basal homogeneity analysis of the main variables of the study

	Enflicoxib4 mg/kg n = 61	Enflicoxib2 mg/kg n = 60	Placebo n = 63	Mavacoxib n = 58	*P*-value[†]
Sex, n (%)					
intact male	22 (36.1%)	25 (41.7%)	25 (39.7%)	22 (37.9%)	0.7279
castrated males	8 (13.1%)	5 (8.3%)	12 (19.0%)	8 (13.8%)	
intact female	9 (14.7%)	10 (16.7%)	11 (17.5%)	10 (17.2%)	
spayed females	22 (36.1%)	20 (33.3%)	15 (23.8%)	18 (31.1%)	
Age, years					
mean (SD)	9.27 (3.01)	9.58 (3.27)	9.16 (3.06)	9.40 (3.19)	0.7407
range	1.5 - 15	1.17 - 14	1 - 15	1 - 14	
Bodyweight, kg					
mean (SD)	27.39 (12.62)	30.15 (10.60)	29.30 (10.45)	27.00 (10.74)	0.6019
range	5 – 48	5 - 65	7 - 56	5 - 44	
Breed, n (%)					
mongrel	19 (31.1%)	11 (18.3%)	16 (25.4%)	16 (27.6%)	0.3889
purebred	42 (68.8%)	49 (81.6%)	47 (74.6%)	42 (72.41%)	
CSS					
mean (SD)	9.02 (2.66)	9.78 (2.48)	9.10 (2.73)	9.33 (2.47)	0.1887
range	6-17	6-15	6-18	6-18	
PSS					
mean (SD)	4.49 (1.88)	4.8 (1.77)	4.47 (1.67)	5.05 (1.71)	0.2631
range	0-9.0	0-8.0	0-7.75	0.75-8.5	
PIS					
mean (SD)	5.79 (1.81)	6.03 (1.84)	5.51 (1.84)	6.09 (1.99)	0.3362
range	2.16-6.0	1.25-9.16	0-9.5	1.3-8.5	

[†]P value relates to differences among treatments. Significance level $p < 0.05$.

Statistical analysis

The statistical analysis was performed in two different populations. The Intention To Treat (ITT) population included all animals that were randomized and received at least one dose of study treatments. The Per Protocol (PP) population included dogs that were fully compliant with the protocol except for cases with minor deviations that would not affect the results. Further statistical analyses were carried out on a subset of the PP population including dogs with initial CSS ≥8 to assess the effect of treatment in dogs with more severe clinical signs of OA.

Demographic and baseline data evaluation was carried out on the ITT population. Baseline differences between groups for quantitative variables were analysed by means of the appropriate test (ANOVA, Kruskal-Wallis). The compliance of application criteria was assessed by means of Kolmogorov-Smirnov normality test and Levene's test for homogeneity of variances. For categorical variables, differences between groups were evaluated by means of the appropriate test (Chi-Square test, Fischer's exact test or LR Chi-Square test). The compliance of application criteria was assessed by means of the Cochran's rule. Baseline analyses were considered from a qualitative point of view to evaluate if groups were properly balanced.

The evaluation of the efficacy endpoints was conducted on the PP population, while the evaluation of the level of acceptance and safety was performed on the ITT population. Differences between groups were analysed using the afore-mentioned procedures for categorical variables. Moreover, the effect of explanatory variables (age, gender, weight, breed, affected limb, as well as baseline CSS, PSS and PIS) on each efficacy criterium was also analysed for each treatment by means of logistic regression. No multiplicity correction was applied for secondary endpoints. The statistical analysis was performed using SAS System® v9.4 (SAS Institute Inc., Cary, NC, USA). For all statistical tests, a nominal significance level of 5% ($P < 0.05$) was applied.

RESULTS

Animals

A total of 242 dogs (126 females and 116 males) were enrolled and included in the ITT population. Mean initial bodyweight at enrolment was 28.5 kg, ranging from 5 to 65 kg and age ranged from 1 to 15 years with a mean age of 9.35 years. Affected joints were the hip in 49% of cases, elbow in 24% and stifle in 17%. Distribution of dogs in the treatment groups was balanced

TABLE 3 Reasons for withdrawal from the efficacy analysis (PP population) in each treatment group (n)

Dogs Enrolled/Allocated to treatment Safety (ITT) population (242)	Enflicoxib 4 mg/kg 61	Enflicoxib 2 mg/kg 60	Placebo 63	Mavacoxib 58
Excluded before first visit (≤ D7)				
Abnormal pre-inclusion laboratory value	1			1
Inclusion/exclusion criteria not met	2	3	5	3
Treatment allocation error	1	1		
Overdose	1			
Adverse event	1	1		1
Withdrawn during follow up				
Owner decision		1	1	1
Adverse event	4	1	3	1
Overdose	1			2
Underdose		2		
Forbidden concomitant treatment			1	
Efficacy data missing		2		1
Total	11	11	10	10

for all baseline characteristics. See Table 2 for the basal homogeneity analysis of the main variables.

Out of the ITT population, 42 dogs were excluded from the efficacy analysis for different reasons, mainly due to unacceptable non-compliances with the protocol, as described in Table 3. Therefore, the final PP population included 200 dogs distributed similarly across the treatment groups (n = 50, 49, 53 and 48 in the enflicoxib at 4 or 2 mg/kg, placebo and mavacoxib groups, respectively). The subset of dogs with more severe clinical signs of OA was limited to 138 dogs complying with having a baseline CSS≥8 on day 0 (n = 33, 37, 32 and 36 in each group, respectively).

Eighty dogs received medications that were administered concurrently with either enflicoxib, mavacoxib or placebo during the study. The types of medications included vaccinations, anthelmintic treatments, antimicrobials, topical skin, aural and otitis treatment preparations, flea and tick treatments and products to treat the gastrointestinal disorders (nausea, emesis, diarrhoea) observed in the adverse events reported during the study.

Efficacy evaluation

Veterinary assessment: At the end of the study (day 42) enflicoxib at the 4 mg/kg dose showed the highest percentage of responders with high statistical significance ($P < 0.01$) when compared to placebo. The multivariate analysis of possible interfering factors showed no other influence in the success rate of the group treated with enflicoxib at 4 mg/kg. However, for the group treated with enflicoxib at 2 mg/kg the success rate was negatively influenced by the severity of the disease (baseline CSS) (p < 0,01). The success rate of the mavacoxib group was also negatively influenced by baseline PIS ($P < 0.05$), and the success rate in the placebo group was affected by age ($P < 0.05$), weight ($P < 0.05$) and baseline CSS on day 0 ($P < 0.01$).

Figure 1a shows the percentage of CSS responders at different time points during the study. At the first assessment on day 7, only the highest enflicoxib dose (4 mg/kg) showed statistically significant differences versus placebo on the percentage of dogs responding to treatment. Thereafter, the percentage of responders was significantly higher for all treated groups versus placebo at all timepoints.

The analysis of the subset of dogs with more severe clinical signs of OA (n = 138 with initial CSS≥8) revealed that the percentage of CSS responders is greatly reduced in the first weeks of treatment compared to the efficacy observed in the PP population (see Figure 1b). However, at the end of the study (Day 42) the percentage of responders was similar for the groups treated with enflicoxib at 4 mg/kg and mavacoxib. These groups showed a significantly higher percentage of responders compared to placebo from day 14 onwards. However, the efficacy of the group treated with enflicoxib at 2 mg/kg did not show statistically significant differences versus the placebo group at any time point.

Owner assessment: The percentage of responders for the CBPI on day 42 showed statistically significant differences for all treated groups versus placebo ($P < 0.01$). See Figure 2a. The multivariate analysis of possible interfering factors on day 42 showed no influence of any factor in the success rate of the group enflicoxib at 4 mg/kg or mavacoxib. However, for the group treated with enflicoxib at 2 mg/kg, the success rate was negatively influenced by the baseline score of CSS and PSS ($P < 0.05$). No factors seemed to affect the score of the placebo-treated dogs.

The percentage of CBPI responders on day 42 was also significantly higher for all treatments versus placebo when the subset of dogs with more severe clinical signs of OA was evaluated (Figure 2b).

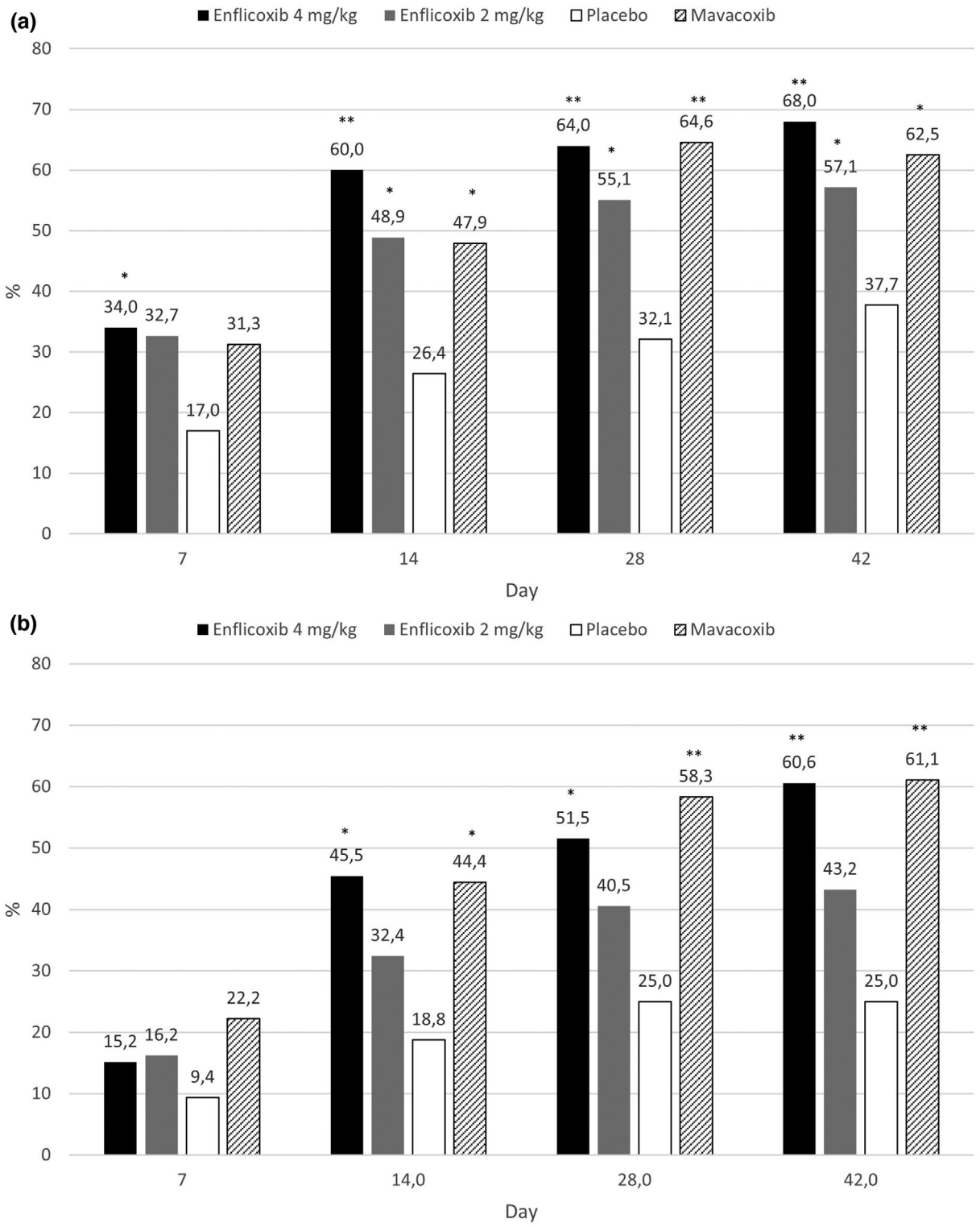

FIGURE 1 (a) Percentage of CSS responders (CSS < 6) in each treatment group and time point during the study in the dog population with initial CSS≥6. (b) Percentage of CSS responders in the dog population with initial CSS≥8. *$P < 0.05$; **$P < 0.01$. No multiplicity correction was applied for secondary endpoints

No statistically significant differences were observed among the groups that received enflicoxib or mavacoxib for the primary or the secondary variables.

Safety assessment

The safety was evaluated on the ITT population including 242 dogs that had received at least one dose of treatment. A total of 112 AEs in 67 dogs were reported during the study, with a global incidence of 27.7%. Following the ABON system of causality assessment, a total of 58 reported AEs were classified as "N", and therefore excluded from further analysis. All other AEs (54) fell into categories "A", "B" or "O", as a causal relation to product administration could not be ruled out, with a global incidence of 13.6%. The incidence of AEs per treatment group was 19.7%, 10%, 14.3%

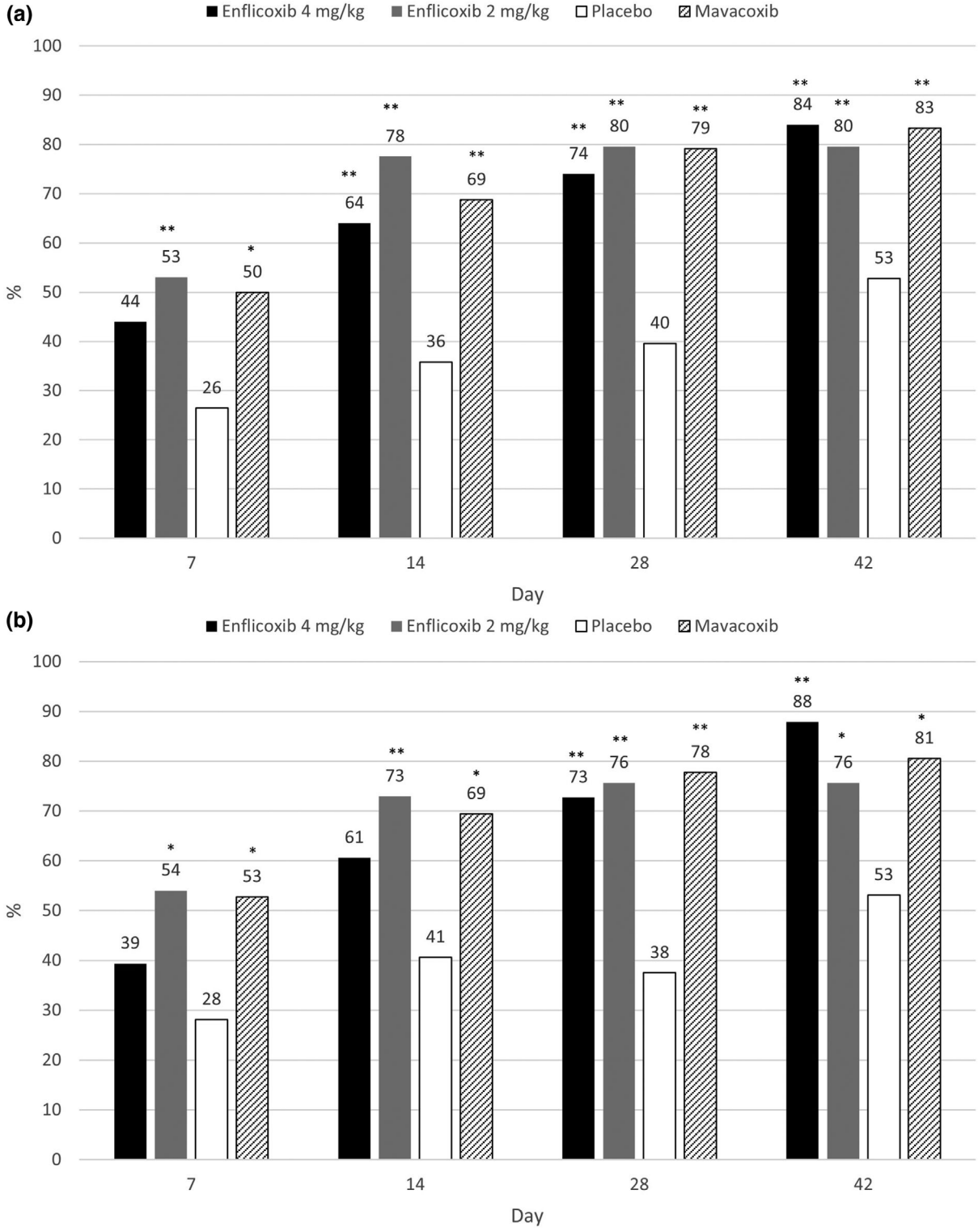

FIGURE 2 (a) Percentage of CBPI responders (reduction in PSS≥1 and PIS≥2) in each treatment group and time point during the study in the dog population with initial CSS≥6. (b) Percentage of CBPI responders in the dog population with initial CSS≥8. *$P < 0.05$; **$P < 0.01$. No multiplicity correction was applied for secondary endpoints

and 10.3% in the enflicoxib at 4 mg/kg, enflicoxib at 2 mg/kg, placebo and mavacoxib groups, respectively. The frequency of AEs and the distribution among treatments, including placebo, did not show any statistically significant difference ($P = 0.374$). Table 4 summarizes the adverse events observed in the study and which were potentially related to treatment, including those dogs withdrawn due to an AE.

The majority of AE were related to the gastrointestinal system and the AE with the highest number of reports in all treatment groups was emesis. See Table 5 for details on the severity and duration of all AE related to the GI system. Most cases showing emesis were mild and sporadic, and the frequency did not seem to increase on subsequent product administrations. Diarrhoea or soft faeces were also frequent

TABLE 4 Summary of AEs reported classified as "A", "B" or "O" according to the type of event

Number of animals presenting AEs (%)	Enflicoxib 4 mg/kgn = 61	Enflicoxib 2 mg/kgn = 60	Placebo n = 63	Mavacoxib n = 58	Total n = 242
Emesis or nausea	7 (11.5)	3 (5.0)	8 (12.7)	4 (6.9)	22 (9.1)
Diarrhoea or pasty stools	5 (8.2)	4 (6.7)	4 (6.3)	3 (5.2)	16 (6.6)
Apathy	2 (3.3)	1 (1.7)	0	0	3 (1.2)
Polydipsia	1 (1.6)	0	1 (1.6)	0	2 (0.8)
Weight loss	0	1 (1.7)	1 (1.6)	0	2 (0.8)
Abdominal pain	0	0	1 (1.6)	0	1 (0.4)
Constipation	0	0	0	1 (1.7)	1 (0.4)
Acute renal failure	0	0	0	1 (1.7)	1 (0.4)
Increased salivation	1 (1.6)	0	0	0	1 (0.4)
Total[a]	12 (19.7)	6 (10%)	9 (14.3)	6 (10.3)	33 (13.6)

[a]Some of the AEs reported included more than one clinical sign in the same dog.

TABLE 5 Description of the reported AEs related to the GI system

	Enflicoxib 4 mg/kgn = 61	Enflicoxib 2 mg/kgn = 60	Placebo n = 63	Mavacoxib n = 58
Emesis and nausea				
Number of events	9	3	8	6
Mean duration (days)	1.4	3	1.6	4.2
Duration range (days)	1-3	1-6[a]	1-5[a]	1-14[a]
Treatment needed[b]	2	0	2	2
Diarrhoea / pasty stools				
Number of events	7	3	6	3
Mean duration (days)	3	5.6	6.6	2
Duration range (days)	1-4	2-8	2-18[a]	1-4
Treatment needed[b]	3	1	3	0

[a]One animal.
[b]Treatments included probiotics, antiemetics, antacids, gastric protectants, nutritional supplements and antibiotics.

and mild, and no clear relation with product administration could be established for any given treatment. Due to the fact that the products have a long treatment interval, for most cases showing AE, although some needed symptomatic treatment, they were completely recovered when the next dose was due, and therefore did not need to be withdrawn from the study.

Only three SAEs were reported, one in the mavacoxib group and two in the enflicoxib at 2 mg/kg group. The one in the mavacoxib group presented with acute renal failure and emesis after the second product administration and was withdrawn from the study. The animal recovered after 2 weeks of treatment but, altered renal parameters remained until the end of the study. One of the dogs in the enflicoxib at 2 mg/kg group was reported with haemorrhagic diarrhoea and weight loss for one week after the first product administration. The dog was withdrawn from the study before the second administration and recovered completely within one week with no treatment. The second dog had dark faeces, nausea and apathy for 1 week after the second product administration. The dog was withdrawn from the study and recovered completely.

Product level of acceptance

According to the owner's assessment, approximately 75% of dogs readily accepted (good or excellent acceptance) the enflicoxib tablets. No statistically significant differences were detected versus placebo tablets. The level of acceptance was not evaluated for the mavacoxib tablets since mavacoxib was not administered by the owners at home.

DISCUSSION

This randomized, placebo-controlled, multicentre double-blinded study in dogs with OA showed that oral enflicoxib treatment at a weekly maintenance dose of 4 mg/kg resulted in a significant number of dogs with decreased CSS (to < 6) as evaluated by the veterinarians (68%), and a decrease in PSS and PIS as

evaluated by the owners (84%). In addition, enflicoxib treatment for 6 consecutive weeks showed a good safety profile, with mostly mild and transient adverse events, mainly related to the GI system.

The primary efficacy tool used in this study, the CSS, could be considered as a subjective assessment method compared to gait analysis, force plate, GPS, or accelerometers for mobility tracking and this probably accounts for the relatively high placebo response observed. These more objective methods were not used because the study was designed as a multicentre field study to be conducted in general practices where this type of equipment is not normally available. However, the CSS is based on the parameters described in a number of publications to construct an NRS for the veterinary assessment of the efficacy of NSAIDs in the treatment of canine osteoarthritis in multicentre studies[27–31] and the possible bias due to the subjectivity of this method has been minimised by maintaining the veterinarian blinding to treatment at all times.

In this study, an individual predetermined definition of treatment response was used to classify each dog as either a treatment success or a failure. This approach avoids masking any lack of efficacy in some individuals as happens when using mean population data that reflects only an overall response.[40]

Treatment success according to the veterinary evaluation was defined as the achievement of a CSS lower than that needed for inclusion. At inclusion, a CSS ≥ 6 was considered as a sufficient degree of disease on which a therapeutic administration of an NSAID would be clinically justified. Indeed, 10% of the dogs were included with a baseline score of 6, thus indicating that this breakpoint defines a sufficient degree of severity of the disease. OA had to be confirmed by radiography of the selected limb of every dog included in the study thus strengthening confidence in the diagnosis of OA. Results were additionally analysed in the subpopulation with a more restrictive CSS ≥ 8 at inclusion (58% of the included cases), which assures both the severity of the disease in this subgroup and a more stringent requirement for, at least, a three points reduction in CSS in order to be considered a treatment success.

The results indicate that, from Day 14 onwards, with enflicoxib at 4 mg/kg, nearly 10% more responders were consistently achieved compared to the 2 mg/kg dose. After Day 28, the percentage of responders at the high dose was similar to that of the positive control mavacoxib, although in the first weeks the percentage of responders showed a tendency to be higher for the enflicoxib group. In fact, enflicoxib at 4 mg/kg is the only treatment that showed statistically significant differences versus placebo on the first week, which suggests that the use of an initial higher loading dose effectively accelerated the onset of action. Also, on the Day 14 evaluation, enflicoxib resulted in a higher percentage of responders compared to mavacoxib (60% vs 48%, respectively) probably because enflicoxib had received a second dose on Day 7. The study design allowed the detection of these different rates of improvement in the first weeks of treatment. However, no differences in longer-term treatments can be inferred from the results of this relatively short-term study design.

As the severity of the disease (basal CSS) was a clear factor affecting treatment efficacy, the analysis of the subpopulation of more severe cases (basal CSS$\geq$8) resulted in even higher differences in efficacy (close to 20%) between the two enflicoxib doses tested. These results confirm that 4 mg enflicoxib/kg are needed for optimum and faster efficacy, particularly in severe cases, where the low dose efficacy was not statistically different from placebo at any time.

There is an element of inherent subjectivity in the owner evaluation which has been limited by using a validated tool (CBPI)[32,33] with a previously established inclusion criteria and treatment success definition,[41] as well as keeping the owners blinded to treatment to avoid any bias. Moreover, owner evaluation followed the criteria used in the assessment of efficacy for other NSAIDs[32,40] and all treatments seem to yield adequate efficacy compared to placebo. In this case, although the severity of the disease was also a factor affecting this parameter, no difference in efficacy between treatments was observed when only the severe cases were evaluated.

The efficacy of enflicoxib was more evident and dose dependent when the veterinary clinical assessment was considered through the CSS score. The owner evaluation also showed a very significant response in CBPI, but no dose dependency was observed. The reason for this discrepancy is not obvious as, unlike the CSS used in this study, the CBPI is a validated scoring system that should be able to detect these differences. In this study, the veterinary clinical assessment was selected as a primary efficacy parameter, over the owner's assessment, as owners are focused on the dog as a whole and its ability to perform its daily activities in its home environment, as opposed to increased or decreased use of a single limb at a walk or trot.[42] This latter approach is better captured in the CSS and it seems to be a more clinically precise procedure to measure pain. Although, in a chronic pain disease such as OA, the quality of life is an important parameter to be scored, which is more reflected by the CBPI. The CSS score measures pain in different situations, but does not include a direct measure of inflammation, as it would be very difficult to assess accurately in the clinical setting. However, inflammation is an essential component of OA and a decrease in inflammation would also be expected to occur based on the mechanism of action of enflicoxib and the activity seen in specific animal models.[43]

The global incidence of AEs attributed to product administration including Placebo (categorised as "A", "B" or "O") was 13,6%. This relatively high incidence must be taken in the context of field clinical trials with dogs suffering from canine osteoarthritis, since osteoarthritis is a disease typical for older dogs (average age of dogs at enrolment was over 9 years), and both owners and veterinarians are asked to report all abnormal observations whatever their causality or severity. Moreover, sixty-one dogs presented with

some previous or concomitant medical conditions, and, in some cases, these animals were receiving concomitant treatments, which is even more challenging from the safety point of view. Higher incidence of AE related to the administration of NSAIDs has previously been described in other similar clinical studies including Payne-Johnson et al.,[28] where 29 and 30 AEs were reported respectively, in 62 dogs treated with mavacoxib and 62 with carprofen and Walton et al.,[20] where 13 and 11 AEs were reported respectively, in 53 dogs treated with meloxicam and 58 with mavacoxib.

In all treatment groups, most of the reactions were considered mild and mainly related to emesis and other gastrointestinal disturbances with no clear pattern among the different treatments, including placebo. This suggests that other factors independent of the active ingredient could have played a role in these AEs (See Table 5). In fact, although the incidence of emesis was higher in the group treated with enflicoxib at 4 mg/kg, these events were mostly isolated and often occurred in situations described, for example, as while in the car on the ride home from the veterinary practice.

More severe disturbances such as haemorrhagic diarrhoea occurred in two dogs treated with the low dose of enflicoxib, and an acute renal failure developed in one dog treated with mavacoxib. However, no serious reactions were described in the dogs treated with the high enflicoxib dose and, consequently, no dose relationship can be established in the enflicoxib treated dogs. The incidence of gastrointestinal reactions is in line with a recently published systematic review of NSAID-induced AEs, where the most observed clinical signs were related to the digestive tract[19] and are compatible with the pharmacology of NSAIDs.

This is the first study demonstrating the efficacy and safety of a once a week oral treatment of enflicoxib in dogs with naturally occurring OA. Although the duration of the study is short in relation to the chronicity of the disease treated, the AEs were as expected for treatment with this class of compounds and tend to occur in the initial stages of therapy. This was confirmed by Lascelles (2005),[44] who showed that most cases of NSAID-associated GI toxicity occur within 48 to 72 hours after treatment is initiated and that most NSAID-associated hepatopathies including idiosyncratic[45] or adverse events of any kind[46] occur within the first 3 weeks of treatment. Moreover, long-term treatment with NSAIDs is not associated with an increase in the incidence of AEs.[15] In addition, Homedes et al. [47] published a 7 months study that demonstrated a broad safety margin, with no adverse effects with administration of up to fivefold the recommended therapeutic dose of enflicoxib. However, this study was conducted in young healthy Beagle dogs with no comorbidities, and receiving no potentially interfering medications. Therefore, care should be taken in translating such an apparently large safety margin as applicable to a clinical population of older dogs with comorbidities.

Overall, the results of this study demonstrate that enflicoxib is efficacious and safe for the treatment of canine OA. Considering that the efficacy of enflicoxib at 2 mg/kg was less evident, and the AE profile was similar in all groups, it is concluded that the highest maintenance dose of 4 mg/kg weekly with an initial loading dose of 8 mg/kg is the most efficacious for the treatment of canine OA.

Finally, treatment compliance is one of the most important problems in the therapy of canine OA and, in consequence, many dogs experience unmanaged pain due to the difficulties of daily dosing. This may be due to the reluctance of the dogs to be medicated or simply the owners fail to recall the timing of administration, as pain is not always obvious for the owner in this kind of processes.[24,48] An efficacious product to be administered at weekly intervals, is an opportunity to improve these potential treatment compliance issues. It might be easier for an owner to remember to treat the dog only on the same day of the week and the reduced dosage frequency may be more suitable for some dogs. The fact that enflicoxib tablets were well accepted by most dogs facilitates this objective. Alongside these study results, it has also been shown that the pharmacokinetic profile of enflicoxib, as described in Homedes et al.,[34] assures constant concentrations of its active metabolite in blood during the complete treatment period. This pharmacokinetic profile assures better pain control as compared with a daily administered product that shows great fluctuations in blood concentrations.[49] Improved owner compliance combined with efficacious constant concentrations may therefore have important consequences in animal welfare in these patients.

CONCLUSIONS

Enflicoxib administered orally at an initial loading dose of 8 mg/kg and weekly maintenance doses of 4 mg/kg for a total period of 6 weeks showed consistent efficacy and an adequate level of safety when compared to placebo-treated dogs with naturally occurring osteoarthritis.

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CONFLICT OF INTEREST

MS and JH are employees of Ecuphar Veterinaria SLU (Animalcare group). LB and PS have declared no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

ETHICAL STATEMENT

Approval was obtained from the Spanish (AEMPS) and French (ANSES) regulatory authorities and satisfied national regulatory and animal welfare standards and requirements. The study was conducted in compliance with the Veterinary International Conference on Harmonization guideline for Good Clinical Practice (VICH 2000). Written informed consent was obtained from all dog owners prior to enrolment of their dogs in the study. Dogs remained under the care of their owners at home during and after the study.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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