Efficacy and Safety of Firocoxib in the Management of Canine Osteoarthritis under Field Conditions*

Peter D. Hanson, DVM, PhD, DACVS[a]
Kenneth C. Brooks, DVM[b]
Jerry Case, DVM[c]
Michael Conzemius, DVM, PhD, DACVS[d]
Wanda Gordon, DVM, MS[d]
James Schuessler, DVM, DABVP[e]
Bert Shelley, DVM, MS, DACVS[f]
Roger Sifferman, DVM[f]
Marlene Drag, DVM, MS, DACLAM[a]
Roberto Alva, DVM, MS, PhD[a]
Laura Bell, BS[a]
Davida Romano, MPH[a]
Candis Fleishman, MStat[a]

[a]*Merial Limited*
3239 Satellite Boulevard
Duluth, GA 30096

[b]*Lodi Veterinary Hospital*
705 N. Main Street
Lodi, WI 53555

[c]*Case Veterinary Hospital*
111 Eisenhower Drive
Savannah, GA 31406

[d]*Department of Veterinary Clinical Sciences*
College of Veterinary Medicine
Iowa State University
1600 SE 16th Street
Ames, IA 50011-1250

[e]*Kirkwood Animal Hospital*
11114 Manchester Road
Kirkwood, MO 63122

[f]*Bradford Park Veterinary Hospital*
1255 E. Independence Street
Springfield, MO 65804

CLINICAL RELEVANCE

A total of 249 client-owned dogs with osteoarthritis were treated with firocoxib (5 mg/kg/day) or a positive control, etodolac (10–15 mg/kg/day), for 30 days. Veterinary examinations were performed on approximately days 0 (visit 1), 14 (visit 2), and 29 (visit 3). Based on defined noninferiority criteria, firocoxib and etodolac were comparable. Based on the magnitude of the change from baseline, improvement with firocoxib was significantly greater than with etodolac for lameness at a trot (visits 2 and 3) and for lameness at a walk, pain on manipulation, and range of motion (visit 3) ($P < .05$). In weekly owner evaluations, firocoxib provided significantly greater improvement than etodolac ($P < .05$) at each scoring.

INTRODUCTION

The benefits of NSAIDs used to control pain and inflammation associated with osteoarthritis in dogs are well established. These benefits have been linked to the NSAID property of preventing inflammatory prostaglandin synthesis through inhibition of the precursor steps that involve the enzyme cyclooxygenase

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(COX)-2.[1] Risks of gastrointestinal and other side effects are known to accompany NSAID treatment, and animals may be more susceptible than humans to NSAID-induced gastrointestinal damage.[2,3] These adverse effects have been linked to the lack of selectivity of traditional NSAIDs, such as aspirin and naproxen, which also inhibit COX-1.[3]

Recognition of the different physiologic effects of COX-1 and COX-2 led to the search for drugs that could provide the same or improved antiinflammatory benefits as traditional NSAIDs while potentially decreasing the risk of the most common side effects.[4] That search yielded a new NSAID subclass known as coxibs that selectively inhibit COX-2 and spare the activity of COX-1 across their therapeutic range. Clinical studies with compounds from this new subclass suggest there is greater opportunity for selecting the dose that produces the maximum therapeutic effect while maintaining the desired safety profile.[5–7] Coxibs, therefore, offer potential for more consistent efficacy and a reduction in the number of side effects.

Firocoxib (ML-1,785,713) was developed specifically for veterinary use and has high selectivity (greater than 380-fold) for COX-2 in canine whole blood assays, leading to substantially greater sparing of COX-1 than previously available.[5,6,8–10] In support of the hypothesis that inhibition of COX-2 is important for efficacy of NSAIDs, a preclinical study in a urate crystal model of induced lameness demonstrated that firocoxib provided greater efficacy than carprofen in a dose-dependent manner.[6] Carprofen is preferential for COX-2 (6.5- to 16.8-fold in canine whole blood), and both compounds inhibit COX-2 to a high degree.[5,8,9]

This article describes a multicenter, positive-controlled, clinical trial of firocoxib in client-owned dogs to confirm its efficacy and safety under field conditions. Additionally, a second objective of the study was to demonstrate that firocoxib is at least as effective and safe as an existing NSAID approved for the same indication in dogs. At the time the study was performed, approved NSAIDs for dogs in the United States consisted of aspirin, carprofen, etodolac, meclofenamic acid, and phenylbutazone. Of these, only etodolac had both the same dosing interval (i.e., once daily) and duration of use (i.e., at least 30 days) as was proposed for this study with firocoxib. Etodolac is a traditional NSAID that is COX-1 selective to nonselective in canine whole blood.[9] As such, its mechanism of action inhibits both COX-1 and COX-2 at therapeutic levels. Efficacy with etodolac has been previously demonstrated in the urate crystal model of lameness and in an 8-day field trial.[11,12]

Firocoxib was developed specifically for veterinary use and has high selectivity for COX-2, leading to substantially greater sparing of COX-1 than previously available.

MATERIALS AND METHODS

Six studies were conducted in dogs across five locations in the United States in a positive-control, double-blinded, multicenter clinical trial to assess the efficacy, safety, and acceptability of firocoxib oral chewable tablets for the control of pain and inflammation associated with osteoarthritis. Etodolac was used as the positive control (a separate group of studies,[7] reported elsewhere, was undertaken to compare firocoxib with carprofen). The experimental protocol was in compliance with

and approved by the Merial Institutional Animal Care and Use Committee (IACUC), any applicable local regulations, and requirements of any local IACUC.

Dog Selection and Randomization

Selection criteria for dogs entering the study were presentation with osteoarthritis and either (1) a lameness score of at least 2 at a walk or trot or (2) a combined score for lameness at a walk or trot and pain on manipulation of at least 3 (see Evaluations, below, for scoring criteria); degenerative change or other radiographic evidence of osteoarthritis on radiographs taken within 28 days before enrollment was also required. Exclusion criteria included treatment with an antiinflammatory or other antiarthritic drugs (e.g., glycosaminoglycans, NSAIDs) within the previous 7 days or with corticosteroids within the previous 30 days, the presence of any systemic disease or infectious arthritis, pregnancy, and fractiousness or other unsuitability for inclusion as judged by the enrolling veterinarian. Two unique, randomized allocation sequences were used: one for dogs with frontlimb lameness and one for those with hindlimb lameness. At each location, replicates of two dogs were formed in order of presentation of either front- or hindleg lameness. A total of 249 client-owned dogs of various breeds were enrolled and evaluated by veterinary clinicians. The selection process resulted in a close balance between groups in demographic and key variables.

TABLE 1. Dose Table Followed to Administer Firocoxib at a Minimum Rate of 5 mg/kg/day

Body Weight		*No. of Tablets by Size*	
lb	*kg*	*57 mg*	*227 mg*
7.0–12.5	3.2–5.6	0.5	—
12.6–25	5.7–11.3	1	—
25.1–37.5	11.4–17	1.5	—
37.6–50	17.1–22.6	—	0.5
50.1–100	22.7–45.4	—	1
100.1–150	45.5–68.2	—	1.5

Treatments

Within replicates, each dog was randomly allocated to treatment with either firocoxib (Previcox, Merial) at a minimum rate of 5 mg/kg/day (n = 128; Table 1) or with etodolac (Etogesic, Wyeth) at the recommended dose rate of 10 to 15 mg/kg/day (n = 121). Dosage was calculated based on the weight of the dog at the initial physical examination (day 0). All treatments were administered orally at approximately 24-hour intervals from day 0 to day 29 (±3 days). The allocated drug was dispensed to each owner by a person not involved in observing the dogs, allowing the investigators to remain blinded to treatment; owners and investigators remained blinded throughout the study. The dogs remained with their owners during and after completion of the study.

The firocoxib group showed significantly greater improvement at the study end for lameness at a trot, lameness at a walk, pain on manipulation, and range of motion

Evaluations

The investigators conducted a physical examination and lameness evaluation at the initial visit (baseline; visit 1, between day –6 and

day 0) and at the second (visit 2) and third (visit 3) visits on days 14 (±2 days) and 29 (±3 days), respectively.

The lameness evaluation included overall lameness at a walk and a trot, and lameness was scored as follows:

- 0 = No lameness
- 1 = Mild lameness (dog touches toe to the floor on all strides)
- 2 = Moderate lameness (dog touches toe to the floor on all strides)
- 3 = Severe lameness (dog touches toe to the floor on at least 50% of strides)
- 4 = Non–weight-bearing lameness (dog touches toe to the floor on <50% of strides)

Range of motion of the most severely affected limb was scored as follows:

- 0 = Normal range of motion
- 1 = Slightly reduced (<25% reduction in range)
- 2 = Moderately reduced (25% to 50% reduction in range)
- 3 = Severely reduced (>50% reduction in range)

At three study sites, peak vertical force of the affected limb while trotting was recorded at visits 1 and 3 using force plate gait analysis. The peak vertical force of each dog was measured by use of a force platform. A data acquisition program sampled data from the force plate channels and in turn computed the ground reaction forces. At each time point for each dog, an attempt was made to record six valid observations for the designated limb. All force plate values were recorded as N/kg body weight. A valid observation was defined as passage by a dog over the force plate in which the forepaw contacted the surface of the plate and was followed by contact of the ipsilateral hind paw. The trot was the standard gait of the dogs during the analyses, and a velocity range of approximately 1.5 to 3.0 m/sec was targeted.

Owners judged firocoxib to be easier to administer and more palatable to dogs compared with etodolac.

Pain on manipulation of the most severely affected limb was scored as follows:

- 0 = No pain or not applicable
- 1 = Slightly painful (scarcely withdraws limb)
- 2 = Moderately painful (definitely withdraws limb)
- 3 = Severely painful (prominently withdraws limb)

Joint swelling of the most severely affected limb was scored as follows:

- 0 = No swelling or not applicable
- 1 = Mild swelling (fibrosis or mild, palpable fluid distension)
- 2 = Moderate swelling (obvious, palpable fluctuant fluid distension)
- 3 = Severe swelling (pronounced, palpable firm fluid distension)

Owners subjectively scored improvement from visit 1 on days 7, 14, 21, and 29 (±3 days for each) based on the following scale:

- 0 = Greatly improved from initial visit
- 1 = Moderately improved from initial visit
- 2 = Mildly improved from initial visit
- 3 = No improvement from initial visit

At the end of each study, owners assessed ("yes" or "no") if the treatment was convenient to administer and whether they felt that their dog found the treatment to be palatable. Owners also recorded potential abnormal events daily. Investigators subsequently reviewed these and assessed the relationship to treatment.

At three locations, blood samples were collected on the day before or the day of initiation of treatment and again on approximately day 29 (±3 days). Samples were analyzed for plasma chemistry and hematology profiles at a common laboratory (LabCorp, Research Triangle Park, NC).

Statistical Analysis

Efficacy

Individual endpoints included investigator evaluation scores for lameness (at a trot and walk), pain on manipulation, range of motion, swelling of the affected limb(s) and/or joint, and owner observation of improvement. Overall incidence of improvement at visits 2 and 3—defined as a reduction in lameness score of one or more at a walk or trot and/or a reduction of two or more among the combined scores for pain on manipulation, range of motion, and joint swelling—was assessed using a noninferiority comparison with a one-sided lower 95% confidence limit for the difference in incidence of improvement between the two groups. If the confidence limit was less than 0.15 (15%), firocoxib was declared not inferior (i.e., comparable) to etodolac. Additional analysis of these endpoints was performed using a Cochran-Mantel-Haenszel row mean scores test, controlling for study. The dependent variables for analysis was the difference between the final (visit 3) and baseline (visit 1) and between the intermediate visit (visit 2) and baseline (visit 1) investigator evaluation scores.

In the analysis of peak vertical force, treatments were compared using two types of analysis: mixed-model analysis of variance and a noninferiority comparison. Animals with non–weight-bearing limbs were excluded from analyses of peak vertical force. Treatment comparisons evaluated by analysis of variance were based on the change from baseline in peak vertical force. Factors included in the model were treatment as a fixed effect and study and interaction as random effects. The noninferiority comparison, using the normal approximation to the binomial, compared the proportion of dogs improved between treatments. A dog was classified as "improved" if its peak vertical force increased from its baseline by at least two times the pooled within-dog standard deviation. (This standard deviation refers to the variation among repeated force plate trials within dogs and was estimated by the square root of the mean squared error from a one-way analysis of variance on baseline peak vertical force data with dog identification number as the independent variable and as a classification variable.) A one-sided 95% confidence limit for the difference in incidence of improvement in the two groups was computed, and if the confidence limit was less than 0.15 (15%), firocoxib was declared comparable to etodolac.

Fewer abnormal health events were recorded by owners of dogs treated with firocoxib than with etodolac.

TABLE 2. Demographic Variables by Treatment Group for Dogs Treated with Etodolac or Firocoxib

Variable	*Firocoxib* (n = *128)*	*Etodolac* (n = *121)*
Mean body weight in kg (range)	33.3 (5.9–79.0)	32.7 (2.8–77.2)
Mean age in years (range)	7.5 (0.9–15.5)	7.1 (1.5–20.0)
Sex (no. of dogs)		
Intact females/spayed females	12/65	13/55
Intact males/castrated males	11/40	20/33
Most severely affected limb (no. of dogs)		
Left fore	14	14
Right fore	11	8
Left hind	56	45
Right hind	47	54
Osteoarthritis subtype (no. of dogs)		
Degenerative joint disease	94	88
Degenerative joint disease, hip dysplasia	2	0
Elbow dysplasia	1	4
Hip dysplasia	28	27
Other	28	2

Dropouts

Dogs that dropped out of the studies were summarized by treatment group according to three criteria: overall, due to an adverse effect, and due to lack of effect. For each criterion, the dropout incidence was analyzed by analysis of variance. For efficacy evaluations, dropouts due to an adverse reaction to study medication or due to deterioration of the diagnosed condition were classified as treatment failures and assigned the worst possible efficacy scores. For dropouts due to other or unknown reasons, the last posttreatment scores, if available, were carried forward (imputed). If no posttreatment scores were available, then the values after dropout were kept as missing. Protocol violators were handled in the same way as the "other/unknown" dropouts, from the occurrence of the violation onward. Acceptability data (i.e., palatability and convenience) were summarized by treatment. All statistical testing was two-sided and performed at the 0.05 significance level (i.e., $P < .05$).

Adverse Events

Owners recorded potential abnormal events daily. The investigators subsequently reviewed these and assessed the relationship to treatment. Potential abnormalities were coded using VEDDRA (Veterinary Medical Dictionary for Drug Regulatory Authorities, listed in EMEA/CVMP/413/99-Consultation, European Medicines Agency, London) terms by an individual blinded to treatment group assignment. Analysis of adverse events was performed on all events recorded and secondarily stratified by the investigators' assignment of relation to treatment. For each treatment, incidence of each specific VEDDRA term (i.e., number of dogs with that event reported at

TABLE 3. Baseline (Visit 1) Clinical Scores and Comparison between the Groups

	Baseline Scores[a]					
Variable	*0*	*1*	*2*	*3*	*4*	**P *Value*[b]**
Lameness at a trot						
Firocoxib (*n* = 128)	0	20	67	9	4	.9103
Etodolac (*n* = 121)	0	17	71	8	4	
Lameness at a walk						
Firocoxib (*n* = 128)	0	27	62	9	2	.4825
Etodolac (*n* = 121)	1	21	69	6	3	
Pain on manipulation						
Firocoxib (*n* = 128)	0	14	75	11	N/A	.0980
Etodolac (*n* = 121)	2	17	74	7	N/A	
Joint swelling						
Firocoxib (*n* = 128)	3	45	45	7	N/A	.1637
Etodolac (*n* = 121)	4	52	40	4	N/A	
Range of motion						
Firocoxib (*n* = 128)	32	44	21	3	N/A	.7775
Etodolac (*n* = 121)	30	48	22	0	N/A	

[a]Expressed as percentage of dogs at each score.
[b]*P* values based on a Cochran-Mantel-Haenszel row mean scores test comparing the treatments.
N/A = not applicable.

least once) and overall incidence of abnormalities (i.e., number of dogs with at least one abnormality reported) were analyzed using the Pearson chi-square exact test.

RESULTS

There were 128 dogs treated with firocoxib and 121 dogs treated with etodolac in the study. A total of 19 dogs dropped out over the course of the study. The mean ages, body weights, sex distribution, limb involved, and type of arthritis were similar between groups (Table 2), as was the distribution of baseline clinical scores (Table 3).

For investigator evaluations of change for each variable between visit 1 and visit 3, relative to etodolac-treated dogs, the firocoxib group showed significantly greater improvement at the study end for lameness at a trot, lameness at a walk, pain on manipulation, and range of motion (P = .0042–.0302; Table 4). For the change between visit 1 and visit 2, dogs treated with firocoxib versus those treated with etodolac had significantly greater improvement at the interim visit for lameness at a trot (P = .0280), and there was also greater, though not statistically significant, improvement in pain on manipulation and range of motion (P = .0532–.0641; Table 5). Compared with baseline values in both groups for all variables except range of motion in the etodolac group, more dogs had improved at visit 3 than visit 2, suggesting that improvement continued during the second 2-week period of treatment.

For the overall incidence of dogs meeting the criteria for improved by at least one lameness

TABLE 4. Percentage of Dogs Improved from Baseline by Indicated Score for Lameness, Pain, Joint Swelling, and Range of Motion at Visit 3, the Final Evaluation

	Improvement in Score from Baseline[a]								
Variable	*–3*	*–2*	*–1*	*0*	*1*	*2*	*3*	*4*	**P *Value*[b]**
Lameness at a trot									
Firocoxib (*n* = 126)	0.0	2.4	5.6	21.4	**49.2**	**16.7**	**4.0**	**0.8**	.0295
Etodolac (*n* = 121)	0.0	5.8	3.3	25.6	**53.7**	**11.6**	**0.0**	**0.0**	
Lameness at a walk									
Firocoxib (*n* = 126)	0.8	1.6	3.2	15.1	**46.8**	**25.4**	**7.1**	**0.0**	.0158
Etodolac (*n* = 121)	0.8	5.0	1.7	14.9	**61.2**	**15.7**	**0.8**	**0.0**	
Pain on manipulation									
Firocoxib (*n* = 125)	0.0	0.0	3.2	12.8	**52.0**	**28.8**	**3.2**	N/A	.0042
Etodolac (*n* = 121)	0.0	1.7	6.6	21.5	**50.4**	**16.5**	**3.3**	N/A	
Joint swelling									
Firocoxib (*n* = 125)	1.6	0.8	2.4	66.4	**26.4**	**2.4**	**0.0**	N/A	.2190
Etodolac (*n* = 121)	1.7	2.5	4.1	71.1	**17.4**	**3.3**	**0.0**	N/A	
Range of motion									
Firocoxib (*n* = 125)	0.0	0.8	4.0	42.4	**47.2**	**5.6**	**0.0**	N/A	.0302
Etodolac (*n* = 121)	0.0	4.1	5.8	49.6	**35.5**	**5.0**	**0.0**	N/A	

[a]Expressed as percentage of dogs improved by score; values in **bold** are the percentage of dogs improved by 1–4 grade levels.
[b]*P* values based on a Cochran-Mantel-Haenszel row mean scores test comparing the treatments.
N/A = not applicable.

grade or by a combined reduction of at least two among the scores for pain on manipulation, range of motion, and joint swelling, firocoxib and etodolac had similar percentages, with 80.8% and 87.3% of firocoxib-treated dogs improved and 79.3% and 83.5% of etodolac-treated dogs improved at visit 2 and visit 3, respectively. Based on the number of dogs that improved by two or more grades for lameness at a walk and trot, more dogs improved to this level in the firocoxib group and both groups had more dogs with improvement at visit 3 than at visit 2 (Tables 4 and 5).

A total of 171 dogs (89 on firocoxib and 82 on etodolac) were included in the analysis of peak vertical force. The mean peak vertical force at baseline was 6.60 N/kg for the firocoxib-treated group and 6.72 N/kg for the etodolac-treated group, and mean values increased to 6.74 N/kg and 6.92 N/kg at visit 3, respectively. For both groups, 62% of dogs had an increase in peak vertical force (i.e., more weight bearing) at visit 3. Based on the noninferiority comparison, firocoxib and etodolac were comparable for peak vertical force in dogs with osteoarthritis.

Owner evaluations showed that throughout the study, the level of improvement from baseline for firocoxib-treated dogs was significantly greater than that for etodolac-treated dogs (*P* = .0009–.0055; Table 6). As with the investigator evaluations, both groups had greater levels

TABLE 5. Percentage of Dogs Improved from Baseline by Indicated Score for Lameness, Pain, Joint Swelling, and Range of Motion at Visit 2, the Interim Evaluation

	Improvement in Score from Baseline[a]								
Variable	*–3*	*–2*	*–1*	*0*	*1*	*2*	*3*	*4*	**P *Value*[b]**
Lameness at a trot									
Firocoxib (*n* = 125)	0.0	2.4	3.2	27.2	**46.4**	**16.8**	**4.0**	**0.0**	0.0280
Etodolac (*n* = 121)	0.0	5.0	1.7	32.2	**51.2**	**9.9**	**0.0**	**0.0**	
Lameness at a walk									
Firocoxib (*n* = 125)	0.0	2.4	4.0	20.8	**50.4**	**18.4**	**4.0**	**0.0**	0.1453
Etodolac (*n* = 121)	0.8	5.0	0.0	19.0	**64.5**	**10.7**	**0.0**	**0.0**	
Pain on manipulation									
Firocoxib (*n* = 124)	0.0	0.0	3.2	20.2	**55.7**	**18.6**	**2.4**	N/A	0.0532
Etodolac (*n* = 121)	0.0	0.8	7.4	24.0	**52.1**	**14.1**	**1.7**	N/A	
Joint swelling									
Firocoxib (*n* = 124)	1.6	0	4.8	69.4	**21.8**	**2.4**	**0.0**	N/A	0.1917
Etodolac (*n* = 121)	1.7	2.5	4.1	76.0	**13.2**	**2.5**	**0.0**	N/A	
Range of motion									
Firocoxib (*n* = 124)	0.0	0.8	4.8	45.2	**42.7**	**6.5**	**0.0**	N/A	0.0641
Etodolac (*n* = 121)	0.0	4.1	6.6	47.9	**37.2**	**4.1**	**0.0**	N/A	

[a]Expressed as percentage of dogs improved by score; values in **bold** are the percentage of dogs improved by 1–4 grade levels.
[b]*P* values based on a Cochran-Mantel-Haenszel row mean scores test comparing the treatments.
N/A = not applicable.

of improvement with continued treatment. Treatment was judged convenient to administer in 96.5% of the firocoxib-treated dogs and 86.5% of the etodolac-treated dogs. Treatment was judged palatable to dogs by the owners in 66.4% of the firocoxib-treated dogs and 52.3% of the etodolac-treated dogs.

Seventy-one dogs (39 treated with firocoxib and 32 treated with etodolac) received a variety of concomitant medications during the studies, including drugs with cardiovascular (angiotensin-converting enzyme inhibitors), endocrine (thyroxine, estrogen), ophthalmic, antibacterial, and antiparasitic (e.g., heartworm and flea) activity. There were no apparent interactions between these medications and either firocoxib or etodolac.

Physical examination, hematology, and clinical chemistry results were largely consistent with the general animal population included in the studies, and no clinically significant treatment-related adverse findings were noted (Tables 7 and 8). Dogs that dropped out of the study for any reason included 10 (7.8%) treated with firocoxib and nine (7.4%) treated with etodolac. Eight of 19 dogs that dropped out during the study did so because of adverse experiences. Of these, six were considered treatment related: one dog treated with firocoxib (0.8% incidence; posttreatment vomiting) and five dogs treated with etodolac (4.1% incidence; vomiting with or without inappetence and lethargy in two dogs; diarrhea with

TABLE 6. Percentage of Dogs Assessed by Owners as Improved from Baseline at Days 7, 14, 21, and 29

	Improvement from Baseline[a]				
Visit	*None*	*Mild*	*Moderate*	*Great*	**P *Value*[b]**
Day 7					
Firocoxib (*n* = 124)	20.2	38.7	21.0	20.2	.0047
Etodolac (*n* = 117)	24.8	50.4	18.0	6.8	
Day 14					
Firocoxib (*n* = 125)	14.4	31.2	32.8	21.6	.0055
Etodolac (*n* = 119)	21.0	38.7	31.9	8.4	
Day 21					
Firocoxib (*n* = 125)	12.8	25.6	32.0	29.6	.0009
Etodolac (*n* = 119)	18.5	36.1	35.3	10.1	
Day 29					
Firocoxib (*n* = 124)	12.9	23.4	29.8	33.9	.0024
Etodolac (*n* = 119)	21.0	30.2	31.9	16.8	

[a]Expressed as percentage of dogs improved by score.
[b]*P* values based on a Cochran-Mantel-Haenszel row mean scores test comparing the treatments.

or without abdominal pain in three dogs). Three firocoxib-treated dogs and three etodolac-treated dogs dropped out because their condition worsened. Five dogs dropped out or were excluded for other or unknown reasons.

Fewer abnormal health events were recorded by owners of dogs treated with firocoxib than with etodolac. At least one abnormal event regardless of relationship to treatment was recorded for 21 (17.4%) etodolac-treated dogs and 12 (9.4%) firocoxib-treated dogs (Table 9). Diarrhea was reported in significantly more dogs receiving etodolac (10 dogs) than those receiving firocoxib (one dog; $P = .0044$). One dog treated with firocoxib had one abnormal event (vomiting) considered related to treatment by the investigator. In contrast, five dogs treated with etodolac had six abnormal events (vomiting, anorexia, diarrhea, lethargy, melena, and pain) considered related to treatment by the investigator, and two of these dogs had more than one event.

DISCUSSION

Multicenter field trials of this type offer many challenges compared with smaller, controlled laboratory studies. Although training with all investigators together was provided, it is not possible to ensure absolute uniformity in clinical assessment across all sites. Similarly, although owner assessment is valuable, it is also prone to considerable variation among owners. These potential deficiencies are offset at least somewhat by the relatively large sample sizes afforded in such a multicenter trial. Sampling for hematology and clinical chemistries in this study did not require fasted samples, which introduced variability in those parameters for which diet (e.g., amount of fat and protein ingested) may affect results. Use of a force plate was included at three of the study sites. Variability in force results may have been reduced if the velocity range were tightened.[13] However, in a large population of dogs with varying degrees

TABLE 7. Mean Hematology Values at Baseline and Study End[a]

	Firocoxib		*Etodolac*	
Variable	*Day 0*	*Day 29*	*Day 0*	*Day 29*
Erythrocyte count (10^6/µl)	7.13	6.90	7.21	7.05
Leukocyte count (10^3/µl)	8.73	9.13	8.91	10.3
Bands (absolute count [10^3/µl])	0.01	0.00	0.00	0.03
Bands (%)	0.07	0.03	0.01	0.19
Basophils (absolute count [10^3/µl])	0.03	0.00	0.02	0.00
Basophils (%)	0.21	0.01	0.15	0.01
Eosinophils (absolute count [10^3/µl])	0.44	0.44	0.44	0.49
Eosinophils (%)	4.63	4.79	4.91	4.76
Lymphocyte (absolute count [10^3/µl])	1.85	1.98	1.87	2.00
Lymphocyte (%)	21.5	22.1	21.6	20.3
Monocytes (absolute count [10^3/µl])	0.34	0.44	0.39	0.43
Monocytes (%)	4.02	4.52	4.25	4.12
Neutrophils (absolute count [10^3/µl])	6.09	6.28	6.19	7.31
Neutrophils (%)	69.8	68.5	69.1	70.6
Platelet count (10^5/µl)	2.88	2.94	2.71	3.05
Mean platelet volume (fl)	10.3	10.3	10.3	10.2
Hemoglobin (g/dl)	17.0	16.6	17.2	16.9
Hematocrit (%)	49.9	47.3	49.7	48.1
Mean corpuscular volume (fl)	69.1	68.7	69.1	68.4
Mean corpuscular hemoglobin (pg)	23.9	24.1	23.9	23.9
Mean corpuscular hemoglobin concentration (%)	34.6	35.1	34.6	35.0

[a]Dogs were not required to be fasted before blood was collected, which may have affected variables on which diet (e.g., fat, protein) has an effect.

and causes of lameness, further reduction of the velocity range was not practical. Interestingly, it was noted that velocity was relatively consistent throughout the trial for any given dog.

At each investigator observation following the start of treatment, significantly more firocoxib-treated dogs than etodolac-treated dogs showed improvement in lameness measured at a trot; at visit 3, the differences favoring firocoxib were also significant for lameness at a walk, pain on manipulation, and range of motion. These results were driven by more dogs treated with firocoxib having greater levels of improvement relative to baseline. Both firocoxib and etodolac provided substantial improvement in the clinical signs of canine osteoarthritis as assessed by veterinarians and dog owners. The efficacy benefit of treatment with each product appeared to increase as the trial progressed, with additional dogs showing greater levels of improvement during the later 2-week period of the study. This increase in improvement over time may be a direct benefit of treatment. Alternatively, it may be a combination effect of the dog having less pain and being willing to exercise more, leading to improved muscling and improved body condition to overcome the lameness.

For selective COX-2 inhibitors, a potential benefit of sparing the COX-1 enzyme is that

TABLE 8. Mean Clinical Chemistry Values at Baseline and Study End[a]

	Firocoxib		*Etodolac*	
Variable	*Day 0*	*Day 29*	*Day 0*	*Day 29*
Total protein (g/dl)	6.7	6.4	6.6	6.0
Albumin (g/dl)	3.5	3.4	3.5	3.2
Globulin (g/dl)	3.2	3.0	3.1	2.8
Albumin:globulin ratio	1.1	1.1	1.1	1.2
Alanine aminotransferase (IU/L)	71	61	58	65
Alkaline phosphatase (IU/L)	175	163	96	92
Aspartate aminotransferase (IU/L)	31	26	29	33
Glucose (mg/dl)	99	105	99	104
Cholesterol (mg/dl)	240	238	241	235
Triglycerides (mg/dl)	159	168	133	142
Direct bilirubin (mg/dl)	0.13	0.10	0.11	0.12
Total bilirubin (mg/dl)	0.35	0.27	0.33	0.29
Creatinine (mg/dl)	1.0	1.1	1.0	1.0
Blood urea nitrogen (mg/dl)	17.6	23.7	17.0	17.4
Calcium (mg/dl)	11.0	10.7	11.0	10.5
Chloride (mEq/L)	113	113	113	112
Iron (µg/dl)	156	148	156	139
Phosphorus (mg/dl)	4.0	4.2	3.9	4.2
Potassium (mEq/L)	4.3	4.5	4.4	4.3
Sodium (mEq/L)	153	152	153	152

[a]Dogs were not required to be fasted before blood was collected, which may have affected variables on which diet (e.g., fat, protein) has an effect.

efficacy can be achieved with less risk of adverse reactions, particularly related to the gastrointestinal tract. In this study, use of firocoxib versus etodolac was associated with a nearly twofold reduction in potential abnormal events overall and a 10-fold reduction in cases with diarrhea. Differences in COX selectivity have been shown between firocoxib and etodolac, and these may contribute to the different performance of the two products in this study. Studies using in vitro canine whole blood assays have calculated the ratios of different NSAIDs for the concentrations that result in inhibition of 50% and 80% of COX activity (IC_{50} and IC_{80}, respectively). For firocoxib, the IC_{50} ratio of COX-1:COX-2 was calculated as 384, and for IC_{80} the ratio was 427.[5] In a different report, also based on an in vitro canine whole blood assay, the etodolac IC_{50} and IC_{80} COX-1:COX-2 ratios were 0.53 and 1.08, respectively, indicating that etodolac is COX-1 selective to nonselective in activity depending on the drug concentration.[9]

The results reported here are consistent with other field trial findings involving 218 dogs in which firocoxib was found to be significantly more effective than carprofen in reducing pain and lameness associated with canine osteoarthritis.[7] The percentage of dogs that had at least one abnormality during that study was greater in the carprofen group (P = .06). Calculated IC_{50} COX-1:COX-2 ratios from the whole blood as-

TABLE 9. Percent Incidence of Health Events Occurring at a Rate Greater Than 1% Reported during 30 Days of Dosing with Firocoxib or Etodolac, without Regard to the Relationship to Treatment

VEDDRA Term[a]	*Percent of Dogs Treated with Firocoxib* (n = *128)*	*Percent of Dogs Treated with Etodolac* (n = *121)*	P *Value*[b]
Any event	9.4	17.4	.0913
Diarrhea	0.8	8.3	.0044
Emesis	3.9	6.6	.4007
Melena	0.0	2.5	.1133
Anorexia	2.3	2.5	1.0000
Lethargy	0.8	2.5	.6131
Pain	1.6	0.8	1.0000

[a]Health events were recorded in daily diaries and then coded based on the Veterinary Medical Dictionary for Drug Regulatory Authorities (VEDDRA).
[b]*P* value based on a Pearson chi-square exact test comparing the treatments.

say for carprofen are reported to range from 6.5 to 16.8.[5,8,9] As with etodolac, comparison with carprofen lends support to the thesis that greater selectivity for COX-2 and greater sparing of COX-1 offer potential benefit.

Long-term inhibition of COX-2 in humans without concomitant inhibition of COX-1 has been associated with an increase in cardiovascular events. A prominent theory explaining why this occurs is based on the balance between COX-2–derived vascular endothelial prostacyclin and its role in offsetting the thrombogenic properties of COX-1–derived thromboxane.[14] Unlike in humans, cardiovascular disease in dogs is infrequently related to thromboembolic events. Use of COX-2–preferential or –selective drugs currently available for dogs (e.g., carprofen, deracoxib, meloxicam) has not been associated with an increase in cardiovascular events. The constitutive role of COX-2 in dogs is still being investigated. COX-2 mRNA has been detected in a number of canine tissues, including gastrointestinal tract, ovary, brain, kidney, and liver.[4] However, no expression of COX-2 protein was detected in these same tissues in healthy dogs, supporting its role as a proinflammatory inducible enzyme. The predominant side effects associated with NSAID use in dogs remain those typically linked to inhibition of COX-1, including vomiting, diarrhea, gastric ulceration, and renal damage.[15,16]

CONCLUSION

These data demonstrate that firocoxib in a chewable tablet formulation was effective, safe, and acceptable for the control of pain and inflammation associated with osteoarthritis in dogs under field-use conditions. Although similar numbers of dogs treated with firocoxib and etodolac met the basic definition for improvement, there were significantly greater levels of improvement for specific variables observed with firocoxib in osteoarthritic dogs.

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