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Efficacy and Safety of Injectable Robenacoxib for the Treatment of Pain Associated With Soft Tissue Surgery in Dogs

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Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are used routinely to control pain and inflammation after surgery in dogs. Robenacoxib is a cyclooxygenase-2 selective NSAID.

Hypothesis/Objective: Assess the clinical efficacy and safety of an injectable formulation of robenacoxib in dogs undergoing surgery.

Animals: Three hundred and seventeen client-owned dogs (N = 159 robenacoxib or N = 158 placebo).

Methods: In this prospective, multicenter, randomized, masked, placebo-controlled, parallel-group study, dogs received a SC injection of either robenacoxib, at a target dose of 2.0 mg/kg, or placebo once prior to surgery and for 2 additional days postoperatively. Pain assessments were performed using the short form of the Glasgow Composite Measure Pain Scale (CMPS-SF). The primary efficacy variable was treatment success/failure, with failure defined as the need for rescue therapy to control pain or withdrawal of the dog from the study due to an adverse event.

Results: Significantly ($P = .006$) more dogs administered robenacoxib were considered treatment successes (108 of 151, 73.7%) compared to dogs given placebo (85 of 152, 58.1%). Total pain scores ($P < .01$), pain at the surgery sites (response to touch, $P < .01$), and posture/activity ($P < .05$) were significantly improved at 3, 5, and 8 hours postextubation in dogs receiving robenacoxib versus placebo.

Conclusions and Clinical Importance: Robenacoxib administered by SC injection prior to surgery and for 2 additional days postoperatively was effective and well tolerated in the control of postoperative pain and inflammation associated with soft tissue surgery in dogs.

Key words: Analgesia; Cyclooxygenase-2; Nonsteroidal anti-inflammatory drug; Perioperative.

Soft tissue surgical procedures in dogs are associated with postoperative pain and perioperative analgesia is recommended as standard procedure.[1,2] The duration of pain control required varies between cases, but in some instances, it is needed for several days or longer.[1] The most frequently used analgesics for controlling pain and inflammation in the immediate postoperative period in dogs are opioids and nonsteroidal anti-inflammatory drugs (NSAIDs).[2] Robenacoxib[a] is an NSAID with several properties of interest for use in dogs undergoing surgery, including a fast onset of action and the availability of both injection and oral formulations.[3] Robenacoxib has a good safety index in healthy dogs, which is attributed to its pharmacodynamic and pharmacokinetic properties.[4] First, robenacoxib is highly selective for cyclooxygenase (COX)-2 in dogs, and at recommended dose inhibits COX-2 while sparing COX-1.[3,5] Second, robenacoxib is cleared rapidly from the central body compartment, but persists at sites of inflammation.[6,7]

In the European Union, robenacoxib injection is registered for the treatment of pain and inflammation associated with orthopedic or soft tissue surgery in dogs (www.ema.europa.eu).[8] Results from randomized, masked, positive-controlled clinical studies demonstrated that robenacoxib was at least as effective (ie, statistically noninferior) as meloxicam[b] when administered as a preoperative SC injection followed by postoperative oral tablets, for the management of pain and inflammation in dogs undergoing orthopedic and soft tissue surgery.[9,10]

To expand the range of registrations, this study was conducted in multiple sites in the United States, reflecting patient management conditions across a wider geographical area. The objective of this study was to investigate the clinical effectiveness and safety of injectable robenacoxib at a dose of 2.0 mg/kg for the control of postoperative pain and inflammation associated with various soft tissue surgeries in dogs.

Abbreviations:

AE	adverse event
ANCOVA	analysis of covariance
CMPS-SF	Glasgow Composite Measure Pain Scale—Short Form
COX	cyclooxygenase
GCPS	Glasgow Composite Pain Scale
LOCF	last observation carried forward
LSMean	least squares mean
NSAID	nonsteroidal anti-inflammatory drug
SC	subcutaneous
SD	standard deviation

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Materials and Methods

Study Design

The study was a prospective, multicenter, randomized, masked, placebo-controlled, parallel-group trial at 12 companion animal veterinary clinics located in Colorado, Illinois, Kansas, Louisiana, Michigan, Missouri, Pennsylvania, Tennessee, Texas, and Virginia.

The study was conducted in accordance with Guidelines for Good Clinical Practice,[c] Adequate and Well-controlled Studies,[d] and New Animal Drugs for Investigational Use.[e] The protocol was reviewed and approved by the company's Institutional Animal Care and Use Committee. All owners provided written consent at the pre-enrollment visit (Day −14 to −2) for their dog to enter the study. This manuscript was prepared after consideration of the CONSORT guidelines on randomized trials.[11]

Selection Criteria

The inclusion criteria comprised clinically healthy dogs aged ≥6 months, of any sex or breed, weighing at least 2.5 kg at the time of enrollment and scheduled to undergo soft tissue surgery (eg, ovariohysterectomy, cryptorchidectomy, splenectomy, cystotomy, or major external surgeries, such as mastectomy or skin tumor removal of mass ≥8 cm in size).

Dogs meeting any of the following exclusion criteria were not enrolled in the study: those that had a known hypersensitivity to NSAIDs or sulfonamide drugs; were being used for breeding, or were pregnant or lactating; were receiving anticonvulsant, behavioral, or cardiac medications; were dehydrated or were receiving concomitant diuretic therapy; had existing cardiovascular, gastrointestinal tract, hepatic, or renal dsyfunctions; had uncontrolled endocrine or systemic disorders such as diabetes mellitus, hypothyroidism, or other systemic disorders (dogs requiring treatment for diabetes mellitus or hypothyroidism had to be stabilized for at least 28 days prior to enrollment, stable status was documented by clinical pathology); within 14 days prior to enrollment had undergone invasive surgical procedures or procedures that would interfere with an accurate assessment of pain; had a concurrent painful condition other than the presenting condition which could have interfered with pain assessments; had been treated with topical or systemic anti-inflammatory products such as NSAIDs within 14 days prior to enrollment, short-acting (systemic or local) corticosteroids within 30 days prior to enrollment or long-acting corticosteroids within 60 days prior to enrollment; had been treated with anesthetics, sedatives, tramadol, or tranquilizers within 2 days prior to enrollment; exhibited aggressive or frightened behavior that caused difficulty in clinical examinations, collection of clinical specimens or administration of treatments; had a known intolerance to the anesthetics used in the study or had received alternative forms of pain relief (eg, acupressure, acupuncture, chiropractic manipulation, clinical therapy) within 14 days prior to enrollment. Dogs belonging to an employee of the sponsoring company or other animal health drug manufacturer, an investigator (or their spouse), or the Food and Drug Administration were not eligible for enrollment in the study.

Dogs meeting any of the following criteria after inclusion were withdrawn from the study: those that required pain intervention with a Glasgow Composite Measure Pain Scale-Short Form (CMPS-SF) score of ≥6 (considered a treatment failure); exhibited an adverse event (AE) that compromised their ongoing treatment or the integrity of the study data; were fractious and unable to continue in the study; received forbidden concomitant treatment; were affected by a protocol deviation(s) that compromised the integrity of the study or a disorder that could have interfered with the evaluation of their response to treatment, or for any other reason as determined by the investigator in consultation with the sponsor. Owners or investigators could also decide to withdraw the dog for efficacy or safety reasons and the study could have been stopped by the sponsor at any time point if required.

Anesthesia and Analgesia Protocol

All dogs were adequately hydrated prior to and during surgery. As an anesthetic premedication, all dogs received intravenous or intramuscular administration of butorphanol at a dose of 0.2 mg/kg body weight after dosing with robenacoxib or placebo approximately 45 minutes (±30 minutes) prior to surgery. Agents including propofol, thiopental, isoflurane, and sevoflurane were allowed to facilitate induction, maintenance, and recovery from anesthesia. Local anesthesia was not permitted for any dog.

Randomization and Treatment

Dogs were formally included on Day 0 and allocated randomly to treatment groups in a 1 : 1 ratio in blocks of 4 in order of enrollment. Dogs were administered either robenacoxib[a] solution for injection at a dose of 2 mg/kg of body weight (0.1 mL/kg) or the same volume 0.1 mL/kg of placebo[f] once daily for 3 days as SC injection in the dorsoscapular region. The dose administered to each dog was calculated from the pre-anesthetic body weight collected at Day −1 or Day 0. The first treatment was given approximately 45 minutes (±30 minutes) prior to surgery at the time of pre-anesthetic medication. Subsequent once daily injections were given at approximately the same time each day (Table 1).

The randomization list was computer-generated by the statistician using SAS/STAT software.[g] Blinding was accomplished by separation of function: a treatment administrator (ie, dispenser) at each clinic was responsible for dispensation and administration of test items and reconciliation of used and unused products. All study site personnel were masked to treatment assignment except the dispenser.

Clinical Examinations and Follow-Up

Clinical examinations were performed at enrollment, at scheduled study completion, in cases of early withdrawal, and for any animal which experienced a serious AE. The examination included a routine assessment of general appearance, major systems, and body weight.

Surgical Procedures

Surgery start time was defined as the time of first (skin) incision. If surgery start time was delayed and was ≥75 minutes after the first dose of robenacoxib or placebo administration, the investigator was instructed to stop study procedures, and observe at least a 2-day washout period prior to re-dosing and surgery.

Rescue Therapy

Intervention treatment ("rescue therapy") was administered at any time the investigator determined that a dog was excessively uncomfortable or in pain, had a score of ≥6 determined for the CMPS-SF[12,13] during pain assessment, or both. Intervention treatment could include any product (except other NSAIDs or corticosteroids) used to control pain.

Premature Completion and Follow-Up

Dogs could be withdrawn from the study, receive rescue therapy, or both, at any time at the discretion of the veterinarian.

Table 1. Assessment schedule for dogs administered robenacoxib or placebo.

Time	Day −14 to −2[a]	Day −1 to 0[b]	Day 0	Day 0[c]	Day 1[c]	Day 1[c]	Day 2[c]	Day 2[c]
Physical examination[d]		X						X
Body weight		X						X
Pain assessment (CMPS-SF)			X prior to treatment and surgery	X 1.5, 3, 5 hour (±30 minutes), 8 hour (±1 hour) postextubation	X 24 hour (±1.5 hour) after initial treatment, prior to 2nd treatment	X 2 hour (±30 minutes), 8 hour (±1 hour) postadministration	X 48 hour (±1.5 hour) after initial treatment, prior to 3rd treatment	X 2, 4 hour (±30 minutes) postadministration
Treatment			X		X		X	
Blood sample	X							X
Urine sample	X							X

CMPS-SF, Short Form of the Glasgow Composite Measure Pain Scale.
[a]Pre-enrollment visit.
[b]Acclimation start at least 2 hours before baseline CMPS-SF assessment.
[c]If pain intervention required: administer intervention treatment, perform exit examination, determine body weight, collect blood and urine, remove dog from study, and monitor in clinic for 24 hours.
[d]Examinations were also performed in cases of early withdrawal or serious AE.

Dogs receiving intervention treatment were observed in the clinic for a minimum of 24 hours postintervention and any potential AEs were documented. The owners of study dogs received a follow-up phone call approximately 3–10 days after normal or premature completion to assess the animal's general well-being.

Efficacy Assessments

Investigators were instructed that the same clinician (a veterinarian) should make all efficacy assessments for all cases at each site, whenever possible.

The primary efficacy variable was treatment failure, which was defined by the occurrence of either:

1 The need for rescue therapy to control postoperative pain. This was decided by the investigator based on either a score of ≥6 on the CMPS-SF[12,13] (Appendix) or if the investigator determined at any time that rescue pain therapy was needed.
2 Dogs withdrawn from the study prematurely due to AEs that compromised ongoing treatment and that were considered possibly or probably related to treatment.

Robenacoxib was compared to the placebo group on a success/failure basis.

Secondary efficacy variables included the total CMPS-SF score and the 6 individual components of the CMPS-SF (vocalization, attention to wound area, mobility, response to touch, demeanor, and posture/activity). A categorical score was assigned within each behavior category based on the severity of the behavior or response by the dog.

A baseline evaluation of the primary and secondary variables was performed on Day 0 after the dog had acclimatized for at least 2 hours in the clinic, and prior to administration of the test items or pre-anesthetic agents. Thereafter, evaluations were conducted on: Day 0 postsurgical extubation at 1.5, 3, 5 hours (±30 minutes), and 8 hours (±1 hour); Day 1 at 24 hours (±1.5 hour) after initial administration and prior to second treatment, and thereafter at 2 hours (±30 minutes) and 8 hours (±1 hour); Day 2 at 48 hours (±1.5 hour) after initial administration and prior to third treatment, and thereafter at 2 and 4 hours (±30 minutes) (Table 1).

Safety Assessments

Safety was analyzed in all dogs that had received at least 1 dose of robenacoxib or placebo. Data for safety assessments included reported AEs, owner follow-up findings, clinical pathology variables (serum chemistry, urinalysis, and hematology) collected prior to treatment and at study exit, changes in body weight and injection site observations (absence or presence [and severity] of erythema, heat, pain, and swelling). Any visible reaction of the dogs to the SC injection was classified as "pain on injection".

Statistical Analysis

The study was planned to include a minimum of 300 dogs with 150 dogs in each group, in order to yield approximately 80% power to detect a difference of 15% between the groups and assuming a success rate of 75% or greater in the robenacoxib group.

All analyses were performed using SAS/STAT software[g]. Unless stated otherwise, data are presented as mean (± standard deviation [SD]). Statistical significance was concluded with 2-tailed P values < .05. The experimental unit was each individual dog.

Primary Efficacy Variable

The primary efficacy variable was treatment success/failure, with superiority established by a statistically significant lower proportion of failures in the robenacoxib compared to the placebo group. A random effects generalized linear mixed model was utilized (SAS PROC GLIMMIX) with treatment as a fixed effect and site and "treatment by site" as random effects. The analysis involved a binary response; therefore, a binomial distribution with a logit link was utilized. The covariance was modeled using the variance components structure. All sites had multiple evaluable subjects in each treatment group (at least 2 cases per treatment group) and were therefore included in the primary efficacy analysis.

In addition, the "time to rescue therapy" for each dog was assessed via a Kaplan–Meier plot with comparison of groups using the log-rank, generalized Wilcoxon and likelihood ratio tests (SAS PROC LIFETEST). For this analysis, cases withdrawn from the study due to AEs were right censored.

Secondary Variables

A total pain score was calculated for each animal at each time point as the sum of the pain category scores at that time where total pain score = vocalization + attention to wound area (surgical site) + mobility + response to touch + demeanor + posture/activity scores (Appendix).

The last observation carried forward (LOCF) method was applied to the data through the first 8 hours after extubation for any animal that required rescue therapy on the day of surgery. Repeated measures analysis of covariance (ANCOVA) (SAS PROC MIXED) was utilized with treatment, time and "treatment × time" as fixed effects, and site and "treatment × site", "site × time", and "treatment × site × time" as random effects. The pretreatment total pain score was included in the model as a fixed covariate. Models incorporating the covariance structures Compound Symmetry and Heterogeneous Compound Symmetry were explored, with the structure yielding the lower Akaike Information Criterion selected for the final analysis.

Each of the individual components contributing to the total pain score was also analyzed using LOCF data from the day of surgery (extubation to hour 8) and the statistical model described for the total pain score analysis.

Body weight was evaluated statistically using ANCOVA (SAS PROC MIXED) with the pretreatment body weight used as a covariate. The model included the fixed effect of treatment. In addition, summary statistics for body weight at baseline and at study exit, and the difference between the study exit and baseline body weights, were calculated for each treatment group.

Serum chemistry, urinalysis, and hematology variables were evaluated statistically using ANCOVA (SAS PROC MIXED) with the pretreatment value as covariate. The model included the fixed effect of treatment, site, and the interaction "treatment × site" as random effects.

The frequency of AEs in the 2 groups was compared with Fisher's exact test (SAS PROC FREQ).

Observations on injection sites were described using injection site scores.

Results

Study Dogs and Doses Administered

A total of 318 client-owned dogs were included in the study. One dog was removed from the evaluation because surgery was postponed due to it being in estrus. Therefore, 317 animals (159 dogs received robenacoxib and 158 received placebo) were included in the demographic and safety analysis, including reports of AEs. A total of 303 dogs were analyzed for efficacy variables; 14 cases were excluded from the efficacy analysis due to inappropriate surgery type (N = 2) or no surgery conducted (N = 1), inclusion/exclusion criteria not met that could affect the integrity of the study (staff-owned dogs, N = 7), or inaccurate dosing (N = 4).

Demographic, breed, and surgery variables are shown in Table 2. Differences between groups were not significant, and it was concluded that the randomization had effectively created balanced groups.

The average (range) ages were 5.7 years (6 months to 15 years) in the robenacoxib group and 5.9 years (6 months to 15 years) in the placebo group. The weight range at pretreatment was 2.5–53.8 kg in the robenacoxib group and 2.5–66.9 kg in the placebo group.

The most common breeds were Labrador Retriever (N = 31), German Shepherd (N = 19), and Mix-Labrador Retriever (N = 16). The predominant soft tissue surgeries in both treatment groups were skin tumor removal of mass ≥8 cm in size (N = 99), ovariohysterectomy (N = 89), gastropexy (N = 36), and cystotomy (N = 30).

Butorphanol was used as preoperative medication in all dogs at a dose of 0.2 mg/kg body weight (intravenous or intramuscular). Of the cases evaluated for efficacy, 301 of the 303 dogs were administered propofol for induction, while 1 dog in the placebo group was administered isoflurane and 1 dog in the robenacoxib group was administered butorphanol tartrate. For maintenance, 282 dogs received isoflurane (141 in each treatment group), while 20 dogs received sevoflurane (10 in each treatment group) and 1 dog in the placebo group received propofol.

The most frequently used concomitant treatments included administration of analgesics, fluids, and antibacterials. Antibiotics were administered to 49.2% of dogs at the time of surgery.

Primary Efficacy Variable

During the study, a total of 193 dogs were considered treatment success with 108 of 151 cases (73.7%) in the robenacoxib group compared to 85 of 152 cases (58.1%) in the placebo group. The percentage of treatment failure was therefore 26.3% with robenacoxib and 41.9% with placebo. Most of the cases classified as treatment failures (43 with robenacoxib, 65 with placebo) received rescue therapy when their CMPS-SF score reached ≥6. Although it was permitted in the protocol, no cases with CMPS-SF <6 received rescue therapy. In the placebo group, 2 cases were designated treatment failures after they were prematurely removed from the study due to AEs that compromised ongoing treatment and were assigned, in a blinded review, a causality assessment of "possible" (Table 3). There was a significant difference ($P = .006$) in the proportion of success/failures in the robenacoxib group compared to the placebo group (Table 4).

Table 2. Demographic, breed, and surgery variables.

Variable	Robenacoxib	Placebo	Total	*P* Value*
Number of dogs (%)	159 (50.2)	158 (49.8)	317 (100.0)	
Age (years)	5.7 (4.2)	5.9 (4.1)	5.8 (4.1)	.71
Body weight (kg), pre-enrollment	22.0 (13.1)	22.3 (12.9)	22.1 (13.0)	.86
Sex and neutered status (%)				
Female intact	67 (42.1)	58 (36.7)	125 (39.4)	.31
Female spayed	40 (25.2)	55 (34.8)	95 (30.0)	
Male castrated	34 (21.4)	28 (17.7)	62 (19.6)	
Male intact	18 (11.3)	17 (10.8)	35 (11.0)	
Breed (%)				
Labrador Retriever	16 (10.1)	15 (9.5)	31 (9.8)	.48
German Shepherd	8 (5.0)	11 (7.0)	19 (6.0)	
Mix-Labrador Retriever	7 (4.4)	9 (5.7)	16 (5.1)	
Golden Retriever	3 (1.9)	9 (5.7)	12 (3.8)	
Basset Hound	6 (3.8)	4 (2.5)	10 (3.2)	
Various other breeds	119 (74.8)	110 (69.6)	229 (72.2)	
Type of surgery (%)				
Skin tumor removal (≥8 cm in size)	48 (30.2)	51 (32.3)	99 (31.2)	.56
Ovariohysterectomy	47 (29.6)	42 (26.6)	89 (28.1)	
Gastropexy	19 (12.0)	17 (10.8)	36 (11.4)	
Cystotomy	17 (10.7)	13 (8.2)	30 (9.5)	
Mastectomy (≥8 cm in size)	4 (2.5)	8 (5.1)	12 (3.8)	
Anal sacculectomy	3 (1.9)	7 (4.4)	10 (3.2)	
Other soft tissue surgery	21 (13.2)	20 (12.7)	41 (12.9)	

SD, standard deviation.
Data are mean (±SD) or number of dogs (%).
*Significance of differences between treatment groups (based on *t*-test for continuous variables and χ^2 test for categorical variables).

Table 3. Reasons for rescue analgesic therapy.

	Robenacoxib		Placebo	
Reason	N	% of Total (n = 43)	N	% of Total (n = 67)
CMPS-SF ≥6	43	100	65	97
Decision of investigator that dog required analgesia (with CMPS-SF <6)	0	0	0	0
AE compromising ongoing treatment	0	0	2	3

CMPS-SF, Short Form of the Glasgow Composite Measure Pain Scale.

Table 4. Frequency (row percent) of success and failure outcome by treatment.

	Outcome			
Treatment	Success (Completed study)	Failure (Withdrawn)	Total[a]	*P* value
Robenacoxib (%)	108 (73.7)	43 (26.3)	151	.006
Placebo (%)	85 (58.1)	67 (41.9)	152	
Total	193	110	303	

[a]Cases included in the efficacy analysis (N = 303).

A Kaplan–Meier plot for "time to rescue therapy" is presented in Figure 1. The 2 dogs in the placebo group removed prematurely due to AEs were considered right censored. The majority of rescues occurred at or before 8 hours postextubation, with 90/108 (83.3%) at ≤3 hours, 98/108 (90.5%) at ≤5 hours, and 101/108 (93.7%) at ≤8 hours. The number of dogs receiving rescue therapy at the 1.5, 3, 5, 8, 24, 26, and 32 hour time points (or in the interval since the previous time point) was, respectively, 30, 4, 2, 2, 4, 0, and 1 in the robenacoxib group (total 43) and 39, 17, 6, 1, 2, 0, and 0 in the placebo group (total 65).

In the time to event analysis, the log-rank, generalized Wilcoxon and likelihood ratio tests were all statistically significant ($P = .010$, $P = .015$ and $P = .001$) in favor of the robenacoxib group. The robenacoxib group had a lower probability of failures (rescues) beginning at 1.5 hours postextubation and at all subsequent remaining time periods than the placebo group.

Secondary Efficacy Variables

The least squares mean (LSMean) total pain scores showed statistically significant differences between groups and in favor of robenacoxib at 3, 5, and 8 hours postextubation ($P < .01$) with lower scores in the robenacoxib group (experiencing less pain), including

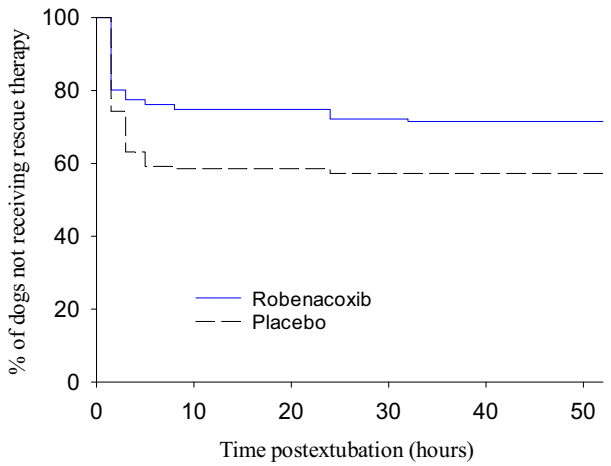

Fig 1. Kaplan–Meier plot of time to rescue analgesia therapy. Two cases in the placebo group were right censored at 26 and 48 hours after removal from the study due to AEs. Differences between groups were significant with log-rank ($P = .010$), generalized Wilcoxon ($P = .015$) and likelihood ratio ($P = .001$) tests.

the average total pain score (with LOCF) over time between both groups. Analyses for the 6 individual components contributing to the total pain score using analogous models, again utilizing LOCF through the first 8 hours after extubation, were conducted. Pain at the surgery sites (response to touch, $P < .01$) and posture/activity ($P < .05$) were significantly improved versus placebo at 3, 5, and 8 hours postextubation in dogs receiving robenacoxib (Table 5).

Safety—Adverse Events

The most commonly observed AEs in both groups were pain on injection and gastrointestinal tract disorders (particularly diarrhea and vomiting; Table 6). The total number of injections was 385 in the robenacoxib group and 338 in the placebo group.

Four AEs were classified as serious; 1 in a dog that received robenacoxib and in 3 dogs that received placebo. The serious AE in the robenacoxib-treated dog occurred after the first scheduled administration; surgery was not performed as severe bradycardia and moderate hypotension were observed after induction. The dog was withdrawn from the study, and the bradycardia and hypotension resolved after extubation. The AE was judged to be unrelated to treatment and the dog fully recovered. In the placebo group, 1 case developed serious diarrhea following surgery, another case showed an exacerbation of an underlying renal disease (hydronephrosis) after surgery, although the pretreatment examinations were considered acceptable for study inclusion. The third case received concomitant medication for pre-existing diseases (urinary incontinence and hypothyroidism) and developed severe "physiological stress" and mild hepatopathy after surgery.

A total of 8 dogs exhibited abnormal clinical signs during the postintervention period (6 dogs in the placebo and 2 dogs in the robenacoxib group). In the placebo group, 2 dogs regurgitated, 1 exhibited inappetence, 1 showed signs of nausea, 1 had mucous stool, and the final dog was lethargic and had increased liver enzymes and a swelling at the site of injection. In the robenacoxib group, 1 dog exhibited facial edema,

Table 5. Secondary efficacy variables (with LOCF).

Variable	Time Point (Day: Time)	Robenacoxib LSMean	Placebo LSMean	LSMean Difference	*P* Value
Total pain score	0: 1.5 hour	3.79	4.50	−0.744	.13
	0: 3.0 hour	3.37	4.76	−1.39	.006**
	0: 5.0 hour	3.23	4.69	−1.46	.006**
	0: 8.0 hour	3.14	4.71	−1.57	.004**
Vocalization	Overall[a]	0.233	0.328	−0.094	.24
Attention to wound/ Surgical site	Overall[a]	0.139	0.168	−0.029	.58
Mobility	Overall[a]	0.616	0.765	−0.148	.31
Response to touch	0: 1.5 hour	0.976	1.26	−0.279	.14
	0: 3.0 hour	0.857	1.44	−0.586	.002**
	0: 5.0 hour	0.896	1.47	−0.573	.002**
	0: 8.0 hour	0.889	1.49	−0.605	.001**
Demeanor	Overall[a]	0.954	1.12	−0.164	.28
Posture/Activity	0: 1.5 hour	0.662	0.771	−0.110	.38
	0: 3.0 hour	0.596	0.851	−0.256	.039*
	0: 5.0 hour	0.577	0.846	−0.269	.030*
	0: 8.0 hour	0.513	0.809	−0.296	.017*

LOCF, last observation carried forward; LSMean, least squares mean; LSMean difference, LSMean of the robenacoxib group − LSMean of the placebo group.

[a]"Treatment × time" interaction was not statistically significant ($P > .05$). Therefore, results for the main effect of treatment are presented.

*Statistically significant at $P < .05$.

**Statistically significant at $P < .01$.

Table 6. Adverse events (AE) reported during the study.

AE[a]	Robenacoxib N	Robenacoxib % of Total (n = 159)	Placebo N	Placebo % of Total (n = 158)	*P* Value
Pain on injection[b]	18	11.3	8	5.1	.06
Diarrhea	15	9.4	8	5.1	.19
Vomiting	10	6.3	6	3.8	.44
Bradycardia	6	3.8	1	0.6	.12
Decreased appetite	5	3.1	2	1.3	.45
Hypotension	2	1.3	0	0.0	.50
Facial edema, hypersensitivity	1	0.6	0	0.0	>.99
Increased incisional bleeding	1	0.6	0	0.0	>.99

P values were calculated with the Fisher's exact test.
[a]Dogs may have experienced more than 1 type or occurrence of an event during the study.
[b]Most often occurred as a single event. Any visible reaction of the dogs to the SC injection was classified as "pain on injection".

while constipation and inflammatory leukocytosis were reported in the second dog.

Based on results from follow-up phone calls, owners reported abnormal findings in 35 dogs (14 dogs that received robenacoxib and 21 dogs that received placebo). The most common observations were findings related to postoperative recovery such as systemic disorders (decreased appetite, pain and incisional swelling; N = 14) and gastrointestinal tract disorders (vomiting, soft stools and diarrhea; N = 8).

Safety—Clinical Pathology

Summary data are shown for selected serum chemistry variables in Table 7 and for urinalysis and hematology variables in Table 8. In both treatment groups, mean values for all serum chemistry and urinalysis variables were within normal reference ranges at pretreatment and study exit, with the exception of urine pH which was slightly increased at pretreatment in the robenacoxib group. Differences between groups were not significant with the exception of serum potassium (higher in robenacoxib group at study exit, $P = .018$) and urine pH (higher in the placebo group at study exit, $P = .001$). The LSMean urine pH at study exit was 6.55 for robenacoxib versus 6.84 for placebo. Mean values for all hematology variables at pretreatment and study exit were within normal reference ranges in both groups. There were no significant differences between groups with the exception of absolute lymphocytes ($P = .035$) and absolute monocytes ($P = .021$), with the robenacoxib group having higher LSMeans at study exit for both variables. Mean counts for both variables remained within normal ranges. LSMeans in the robenacoxib and placebo groups were, respectively, 2,392.59 and 2,086.44 cells/μL for absolute lymphocytes and 813.24 and 725.79 cells/μL for absolute monocytes.

Safety—Body Weight Change

The change in body weight was similar between treatment groups (ie, body weight at study exit minus body weight at baseline). There were no significant ($P = .750$) differences in LSMean study exit body weight between

Table 7. Selected serum chemistry variables at pretreatment and study exit (mean±SD).

Variable (Laboratory Reference Range)	Time	Robenacoxib (n = 159) Mean (±SD)	Robenacoxib Cases[a] High	Robenacoxib Cases[a] Low	Placebo (n = 158) Mean (±SD)	Placebo Cases[a] High	Placebo Cases[a] Low	*P* Value
Serum								
Urea nitrogen, mg/dL (6–31 mg/dL)	Pretreatment	18.0 (5.5)	3	1	17.8 (5.9)	3	0	.55
	Study exit	15.7 (5.0)	1	0	15.0 (10.2)	5	3	
Creatinine, mg/dL (0.5–1.6 mg/dL)	Pretreatment	0.96 (0.25)	2	1	0.98 (0.27)	2	0	.82
	Study exit	0.88 (0.23)	0	3	0.88 (0.55)	2	1	
Alkaline phosphatase, U/L (5–131 U/L)	Pretreatment	104.7 (166.2)	29	0	79.2 (83.7)	25	0	.13
	Study exit	117.6 (170.7)	30	0	110.2 (165.8)	30	0	
Alanine aminotransferase, U/L (12–118 U/L)	Pretreatment	45.0 (28.3)	8	0	51.2 (59.5)	6	0	.72
	Study exit	50.2 (99.1)	4	3	60.8 (121.3)	13	0	
Aspartate aminotransferase, U/L (15–66 U/L)	Pretreatment	29.0 (10.3)	1	1	29.1 (8.3)	0	1	.08
	Study exit	33.4 (18.3)	12	4	43.8 (72.3)	14	1	
Total bilirubin, mg/dL (0.1–0.3 mg/dL)	Pretreatment	0.13 (0.05)	0	0	0.14 (0.05)	0	0	.26
	Study exit	0.14 (0.08)	1	0	0.15 (0.14)	1	0	
Total protein, g/dL (5.0–7.4 g/dL)	Pretreatment	6.61 (0.59)	15	0	6.60 (0.60)	12	0	.55
	Study exit	6.42 (0.60)	9	0	6.45 (0.66)	9	1	
Albumin, g/dL (2.7–4.4 g/dL)	Pretreatment	3.53 (0.37)	1	5	3.51 (0.39)	2	4	.28
	Study exit	3.37 (0.38)	0	8	3.38 (0.41)	0	8	

SD, standard deviation.
P values were obtained from an ANCOVA of the study exit values for each variable, with the pretreatment value for each variable used as a covariate.
[a]Number of cases with values higher and lower than the reference range pretreatment and at study exit.

Table 8. Selected urinalysis and hematology variables at pretreatment and study exit (mean±SD).

		Robenacoxib (n = 159)			Placebo (n = 158)			
			Cases[a]			Cases[a]		
Variable (Laboratory Reference Range)	Time	Mean (±SD)	High	Low	Mean (±SD)	High	Low	*P* Value
Urine								
Urine specific gravity (1.015–1.050)	Pretreatment	1.04 (0.01)	24	18	1.04 (0.01)	21	8	0.12
	Study exit	1.04 (0.02)	60	4	1.04 (0.02)	38	13	
Hematology								
Hemoglobin, g/dL (12.1–20.3 g/dL)	Pretreatment	16.9 (2.0)	9	2	16.7 (2.0)	2	3	0.60
	Study exit	15.6 (2.0)	1	6	15.3 (1.8)	0	11	
Hematocrit, % (36–60%)	Pretreatment	50.2 (5.7)	6	0	49.4 (5.6)	2	2	0.34
	Study exit	47.2 (5.9)	1	4	46.1 (5.6)	1	5	
Red blood cell count, 10^{12}/L (4.8–9.3 $\times$ 10^{12}/L)	Pretreatment	6.9 (0.82)	0	0	6.8 (0.85)	0	1	0.57
	Study exit	6.5 (0.86)	0	4	6.3 (0.77)	0	1	
White blood cell count, 10^{9}/L (4.0–15.5 $\times$ 10^{9}/L)	Pretreatment	11.1 (4.3)	20	0	10.7 (3.4)	7	1	0.38
	Study exit	14.1 (5.5)	46	0	13.4 (5.5)	43	0	

SD, standard deviation.

P values were obtained from an ANCOVA of the study exit values for each variable, with the pretreatment value for each variable used as a covariate.

[a]Number of cases with values higher and lower than the reference range pretreatment and at study exit.

the robenacoxib and placebo groups after adjusting for pre-enrollment body weight.

Safety—Injection Site Reaction

Injection site reactions were recorded rarely. Swelling was noted in 1 dog in the robenacoxib group at the 24-hour follow-up assessment to the Day 0 injection, but not subsequently. Injection site reactions were recorded in 2 dogs in the placebo group; in the first case, heat was observed at 24 hours following the Day 0 injection, in the second case, pre-existing erythema and swelling due to dermatitis in the intrascapular region were observed and persisted until Day 2.

Discussion

In this clinical trial, dogs undergoing soft tissue surgery received presurgical analgesia with butorphanol and agents for induction and maintenance to facilitate recovery from anesthesia. The addition of robenacoxib administered by SC injection approximately 45 minutes prior to surgery and then for 2 subsequent days (not to exceed more than 1 treatment per day) was well tolerated and provided better control of postoperative pain compared to placebo. The superior efficacy of robenacoxib compared to placebo was evidenced from the significantly ($P = .006$) higher frequency of treatment success (respectively, 73.7% versus 58.1%, the primary variable). For the secondary variables, the LSMean total pain scores showed statistically significant differences between groups and in favor of robenacoxib at 3, 5, and 8 hours postextubation ($P < .01$). Pain at the surgery sites ($P < .01$) and posture/activity ($P < .05$) were significantly improved in dogs receiving robenacoxib versus placebo at 3, 5, and 8 hours postextubation. Although specific inflammation endpoints were not included in this study, anti-inflammatory effects of robenacoxib have been shown previously in rodents[7] and dogs.[3]

The dogs enrolled were of various breeds, and the types of surgery performed were representative of those commonly encountered in veterinary practice. The study was designed as a prospective, multicenter, randomized, masked, placebo-controlled field trial, thereby providing the highest level of evidence possible for assessing the clinical efficacy of robenacoxib. The use of a placebo has high scientific rigor due to the risk of caregiver placebo responses, especially with use of subjective methods to assess pain as used in this study.[14] Furthermore, the use of placebo raises ethical and welfare questions, but these were mitigated by frequent observation time points during the study (with multiple assessments in the first 8 hours postsurgery) and the option to provide rescue therapy immediately when it was judged to be needed. In addition, all dogs received preoperative administration of the analgesic butorphanol. Opioids are most commonly used as analgesics in perioperative pain management[1,2] and butorphanol is one of the most commonly used drugs.[15] However, butorphanol has a short duration of effect in dogs and repeated administration may be required during prolonged surgical procedures. To provide optimal analgesia and minimize adverse effects, recent guidelines recommend combining drugs that act at different sites of the pain pathway, such as opioids and NSAIDs.[16]

The perioperative pain management effect of various NSAIDs has been investigated in clinical studies in dogs.[9,10,17,18] Comparison of results between studies is difficult due to different study designs, anesthetic procedures, concomitant drugs, NSAID treatment durations, types of surgeries as well as pain assessment methods. In 2 previous studies, the efficacy of robenacoxib and meloxicam was investigated in dogs undergoing soft

tissue and orthopedic surgery. The efficacy of robenacoxib was statistically noninferior to the positive control, meloxicam.[9,10] In the soft tissue study,[10] pain and inflammation were assessed subjectively by clinicians using the Glasgow Composite Pain Scale (GCPS);[13] unweighted results were reported because weighting factors for the indices had not been published at the time the study was initiated.[1,19] There were no specific criteria defined when rescue therapy should be used and no dog received such therapy. The effect of 2 other NSAIDs, administered as a single oral dose presurgery followed by 2 days postsurgery, for the control of pain and inflammation in soft tissue surgery in dogs was investigated in the following studies. For firocoxib,[h] superior efficacy versus a negative control was reported with comparable design to our study and pain assessment using CMPS-SF.[17] The frequency of rescue therapy was 16.4% for the active and 50.0% for the negative control. For deracoxib,[i] superior efficacy versus a placebo control was reported. The frequency of rescue therapy was 12.5% (2/16) with deracoxib compared to placebo 56.3% (9/16).[18] However, in that study, pain was assessed using a different method (GCPS). The incidence of rescue therapy (range 12.5–26.3%) in clinical trials testing NSAIDs in dogs undergoing soft tissue surgery indicates that NSAIDs alone will not produce optimal control of pain in all cases, and therefore, multimodal therapy is needed for optimal control of pain.[2,16]

The assessment of pain in animals is challenging and veterinary pain assessments must be made in the absence of the communication skills of the patient; therefore, appropriate pain assessment tools need to be selected.[20] Additionally, effective management of pain in the perioperative period remains challenging despite the recognition of its importance to patient welfare and healing.[21] In this study, the primary efficacy variable was a clinical investigator's assessment of perioperative (acute) pain by using the CMPS-SF, which is a validated composite scale for assessing acute pain in dogs in the hospital setting based on observations of behavior.[12,13] The choice of CMPS-SF appeared justified as intervention level scores were similar across different clinics and different observers.[12] Additionally, CMPS-SF provides guidance with regard to analgesic requirement; that is, rescue medication is required if the total score is 6 or greater. Therefore, it was considered that CMPS-SF was an appropriate standard for the assessment of the efficacy.

The results of the primary efficacy variable were supported by 6 secondary endpoints. The analysis of the secondary efficacy variables was challenging due to the unequal frequency of withdrawal of cases after administration of rescue therapy between the 2 groups, with the placebo group having more rescues within the first 8 hours than those dogs treated with robenacoxib. The data were therefore analyzed using the LOCF method. The LOCF method[22] has limitations, but was justified in this study because it was used for cases proactively withdrawn due to treatment failure and for a limited period (up to 8 hours postextubation).

Reported AEs, clinical pathology variables, results of examinations by clinical investigators, and injection site observations indicated that robenacoxib was well tolerated. Although a range of AEs was reported in both groups, these were all mild and benign (except for 1 AE that was judged not to be treatment-related in the robenacoxib group and 3 AEs in the placebo group) and most were judged either not related or only questionably related to treatment. The most frequently reported AEs were pain on injection, diarrhea, and vomiting. Robenacoxib has a good safety index in healthy dogs, producing no biologically relevant toxicity at oral doses as high as 40 mg/kg daily for 1 month and up to 10 mg/kg daily for 6 months.[4] There was no evidence from this study of any toxicity of robenacoxib to target organs that are most sensitive to NSAID toxicity (gastrointestinal tract, kidney, and liver). Although some statistically significant differences in clinical chemistry (potassium), urinalysis (pH), and hematology (absolute lymphocytes and monocytes) variables were found between groups, the means of all these variables remained within normal clinical ranges at the end of the study and differences were not considered to be clinically relevant.

Conclusion

Robenacoxib administered by SC injection at a target dose of 2.0 mg/kg once daily for 3 days was effective and well tolerated in the control of postoperative pain and inflammation in dogs undergoing soft tissue surgeries.

Footnotes

[a] Onsior, Elanco Animal Health Inc, Greenfield, IN
[b] Metacam, Boehringer Ingelheim Animal Health GmbH, Ingelheim, Germany
[c] VICH GL9, FDA/CVM Guidance for Industry 85, 2001
[d] 21 CFR 514.117
[e] 21 CFR 511.1
[f] 0.9% sodium chloride injection, USP
[g] SAS, Version 9.2, SAS Institute Inc, Cary, NC
[h] Previcox, Merial, Duluth, GA
[i] Deramaxx, Elanco Animal Health Inc, Greenfield, IN

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Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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Appendix: The short form of the Glasgow Composite Measure Pain Scale (CMPS-SF) used by the clinicians to assess the dogs.

Circumstance	Assessment and Scale
Look at the dog in kennel	*Vocalization: Is the dog:*
	[0] quiet
	[1] crying or whimpering
	[2] groaning
	[3] screaming
	Attention to wound area: Is the dog:
	[0] ignoring any wound or painful area
	[1] looking at wound or painful area
	[2] licking wound or painful area
	[3] rubbing wound or painful area
	[4] chewing wound or painful area
Dog out of kennel on lead	*Mobility: When the dog rises/walks is it:*
	[0] normal
	[1] lame
	[2] slow or reluctant
	[3] stiff
	[4] it refuses to move
Response to touch	*Response to touch: Does the dog:*
	[0] do nothing
	[1] look around
	[2] flinch
	[3] growl or guard area
	[4] snap
	[5] cry
Overall assessment	*Demeanor: Is the dog:*
	[0] happy and content or happy and bouncy
	[1] quiet
	[2] indifferent or nonresponsive to surroundings
	[3] nervous or anxious or fearful
	[4] depressed or nonresponsive to stimulation
	Posture: Is the dog:
	[0] comfortable
	[1] unsettled
	[2] restless
	[3] hunched or tense
	[4] rigid