Nonsteroidal anti-inflammatory drugs are the most widely used analgesics in veterinary and human medicine. Although many NSAIDs are registered for use in dogs and humans, relatively few are licensed for use in cats.1 Carprofen, ketoprofen, and tolfenamic acid are registered for short-term use only (1 to 5 days) in cats. Meloxicam is registered in the United States for use as a single dose for postoperative pain in cats and has recently been registered in Europe for acute and chronic musculoskeletal disorders in this species.

**Objective**—To evaluate the efficacy and tolerability of oral administration of robenacoxib for treatment of acute pain and inflammation associated with musculoskeletal disorders in cats.

**Animals**—155 cats requiring relief of signs of pain and inflammation associated with acute musculoskeletal disorders.

**Procedures**—The study was a multicenter, prospective, randomized, masked, noninferiority field trial. Cats were allocated randomly to 1 of 3 treatment groups: group 1 (1.0 to 2.4 mg of robenacoxib/kg, q 24 h), group 2 (1.0 to 2.4 mg of robenacoxib/kg, q 12 h [daily dosage, 2.0 to 4.8 mg/kg]), and group 3 (ketoprofen [mean dosage, 1 mg/kg, q 24 h]). All cats were administered tablets PO for 5 or 6 days. The primary efficacy endpoint was the investigator global assessment score, which was the sum of scores of signs of pain, inflammation, and mobility assessed in a masked manner by veterinary investigators at baseline, day 2, and day 4 or 5. Cat owners monitored in a nonmasked manner secondary responses by observation of cats’ activity, behavior, appetite, and interactions. Safety was assessed by monitoring adverse events, clinical signs, and hematologic and plasma biochemical variables (before and after treatment).

**Results**—No significant differences were detected among the 3 treatment groups for any primary or secondary efficacy endpoints or for tolerability variables. Robenacoxib tablets administered once daily were significantly more palatable than ketoprofen tablets.

**Conclusions and Clinical Relevance**—Robenacoxib tablets administered once daily had noninferior efficacy and tolerability, and superior palatability, compared with the active control drug, ketoprofen, for the treatment of signs of acute pain and inflammation associated with musculoskeletal disorders in cats. (Am J Vet Res 2010;71:710–719)

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**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP</td>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>COX</td>
<td>Cyclooxygenase</td>
</tr>
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</table>

The paucity of licensed NSAIDs for use in cats may be attributable to a number of factors. One important issue is the relatively poor safety profile of some NSAIDs in cats.1 For acetaminophen (paracetamol), acetylsalicylic acid, and carprofen, this might be attributable to the fact that these drugs have longer terminal half-lives in cats, compared with dogs.1-3 An additional factor might be the difficulty in assessing pain in cats, compared with dogs and humans. Consequently, major efforts have been made in recent years to identify and validate subjective observer-based methods of assessing pain in cats.7-14 Those methods have been applied in studies7-11 designed to establish the analgesic efficacy of NSAID and opioid drug classes.
Robenacoxib is a novel highly selective inhibitor of COX-2. In rats, robenacoxib exerts the analgesic, anti-inflammatory, and antipyretic actions characteristic of NSAIIDs, while possessing a much wider safety margin for gastrointestinal and renal adverse effects than diclofenac, a drug of similar structure that is nonselective or, at most, only preferentially selective for COX-2, relative to COX-1. Analgesic, anti-inflammatory, and antipyretic actions of robenacoxib have also been reported in a kaolin model in cats, and pharmacodynamic and pharmacokinetic variables have been reported. Two pharmacological aspects of robenacoxib are of special relevance for its clinical use in cats. First, robencoxib is a highly selective and potent inhibitor of COX-2, which should result in reduced toxicosis caused by inhibition of COX-1. There is now a considerable body of evidence from preclinical animal and clinical studies suggesting that selective COX-2 inhibitors have improved gastrointestinal safety profiles, in comparison with classical NSAIIDs. In vitro blood assays in cats, the COX-1:COX-2 ratio for 50% enzyme inhibition for robencoxib was 502:1. Furthermore, robencoxib induces marked inhibition of COX-2 while sparing COX-1 ex vivo in cats, when administered at clinical dosages of 1 to 2 mg/kg. Second, in common with certain other NSAIIDs, robenacoxib distributes selectively in the body, leading to persistence at sites of inflammation but with transient exposure to the central body compartment and hence possible reduced potential for toxicosis in well-perfused organs such as the kidney. Therefore, our hypothesis was that robencoxib would have good efficacy and tolerability in cats. Nevertheless, it is known that COX-2–selective drugs are not devoid of risks, and therefore, as with any new drug, they must undergo extensive testing. Although COX-2 is induced at sites of tissue damage, it is known to occur constitutively as well (eg, in the CNS and kidney).

As part of the development program for use of robencoxib in cats, the objective of the present study was to evaluate the efficacy and tolerability of a tablet formulation of robencoxib for the treatment of signs of acute pain and inflammation associated with a range of musculoskeletal disorders (administered once or twice daily), compared with an active control, ketoprofen.

Materials and Methods

Animals and study design—The clinical trial was a prospective, randomized, masked, parallel-group comparison of 3 treatment groups: group 1, robencoxib administered once daily (q 24 h); group 2, robencoxib administered twice daily (q 12 h); and group 3, the positive control drug, ketoprofen, administered once daily. Ketoprofen was selected as the active control treatment for this study because it is licensed for oral use in cats for the relief of acute pain and inflammation associated with musculoskeletal and other painful disorders in Europe (as well as in Australia and Canada, but not in the United States) for up to 5 days. This was the longest treatment period for which any NSAID was registered in cats at the time of starting the study. To allow some flexibility for examination (eg, over weekends), the selected duration of treatment in the present clinical trial was 5 to 6 days.

The study was a multicenter and international study, involving 29 veterinary practices (20 in France and 9 in the United Kingdom) from differing geographic locations in each country. The study protocol was approved by the French (Agence Française de Sécurité Sanitaire des Aliments) and United Kingdom (Veterinary Medicines Directorate) regulatory authorities taking into account scientific, ethical, and animal welfare guidelines. Efficacy of the treatments was assessed in compliance with the Guideline for the Conduct of Efficacy Studies for Non-Steroidal Anti-Inflammatory Drugs. On the basis of this guideline, for ethical reasons, the study did not include a placebo or untreated group of animals.

The study was also conducted in compliance with the Procedures and Principles of Good Clinical Practice and the Guideline on Statistical Principles for Veterinary Clinical Trials.

Inclusion criteria were cats ≥ 6 weeks of age in France (any age in the United Kingdom), with a body weight ≥ 2.5 kg and ≤ 12 kg in France (≥ 3 kg and ≤ 12 kg in the United Kingdom), of either sex and any breed, and with signs of acute musculoskeletal pain and inflammation. A thorough investigation of the cat's clinical condition was performed by the investigator, and an owner's consent form was completed and signed. Musculoskeletal pain and inflammation were defined as the presence of signs of pain and inflammation affecting either the muscular or skeletal system or both systems.

Diagnosis was made on the basis of history, results of general physical examination, clinical signs, and, if required, additional analyses (eg, radiography).

Exclusion criteria were presence of signs of acute pain and inflammation associated with any of the following: neoplasia, a primary neurologic disorder, a known immunologic disorder, or any musculoskeletal disorder requiring surgery; pregnant or lactating female cats or cats intended for breeding; cats with severe concomitant disorders (eg, kidney or liver insufficiency or gastrointestinal disorders), the condition of which might have interfered with evaluation of response to treatment; cats that had received locally or systemically administered NSAIIDs within 7 days prior to inclusion; cats that had received corticosteroids within 30 days (short acting and systemically or locally administered) or 60 days (long acting) prior to inclusion; cats that could not be adequately examined because they became aggressive or excessively frightened in the veterinary practice; cats with only signs of chronic pain and inflammation affecting the musculoskeletal system (chronic was defined as a condition present for at least 8 weeks and not spontaneously resolvable within 2 weeks); and cats not available for the entire duration of the study.

Cats with the following criteria after inclusion were to be withdrawn from the study: an adverse event that required cessation of treatment, forbidden concomitant treatment, occurrence of a concomitant disorder that may have interfered with the evaluation of response to treatment, owners' failure to comply with the protocol, or withdrawal of owner consent.

Randomization and blinding procedures—After an initial examination on day 0, each cat was allocated randomly to 1 of the 3 treatment groups. A randomization-
tion list for each site was prepared by the statistician and was arranged in blocks of 3, with no stratification for age, sex, or etiology of disorders. There is no evidence of a sex or body weight difference with regard to pharmacological features of robenacoxib. Investigators were masked to the blocking schedule. Because robenacoxib is formulated as flavored tablets and ketoprofen is formulated as tablets with a different appearance, the treatments were identifiably different. Masking of veterinary assessments was therefore secured by use of the masking by function technique; the investigator was responsible for clinical assessments, and a separate dispenser was responsible for treatment delivery. Dispensers were veterinarians or veterinary nurses. Cat owners were not formally masked. Therefore, owner assessments were treated as secondary rather than primary endpoints. Lack of masking occurred on a single occasion, but corresponding data were included nevertheless in the analysis.

Drugs and administration procedures—The 3 treatment groups were group 1, robenacoxib (1 to 2.4 mg/kg, q 24 h); group 2, robenacoxib (1 to 2.4 mg/kg, q 12 h [daily dosage, 2.0 to 4.8 mg/kg]); and group 3, ketoprofen (1 mg/kg, q 24 h). The nominal dosage of robenacoxib was 1 to 2 mg/kg (actual dosage, 2 to 2.4 mg/kg for small cats weighing from 2.5 to 3 kg) administered once or twice daily. Dosages were achieved by use of a protocol. For robenacoxib, cats received 6-mg tablets once (group 1) or twice daily (group 2) as follows: 1 tablet for cats that weighed 2.5 to 6.0 kg and 2 tablets for cats that weighed >6 kg. For ketoprofen, cats received 3-mg tablets once daily as follows: 0.5 tablet for cats that weighed 2.5 to 3.5 kg, 1 tablet for cats that weighed 3.6 to 6.5 kg, 1.5 tablets for cats that weighed 6.6 to 9.5 kg, and 2 tablets for cats that weighed 9.6 to 12.0 kg.

The dosage for robenacoxib of 1 to 2.4 mg/kg was selected from a pharmacokinetic-pharmacodynamic study in a preclinical kaolin model of soft tissue inflammation and the dose predicted to provide 80% inhibition of COX-2 in a whole blood assay. It was recommended that robenacoxib should be administered either without food or with a small quantity of food (eg, hidden in a small amount of meat). Owners were asked to avoid giving a large quantity of food for 4 hours before or 1 hour after administration. If the cats were fed ad libitum, the instruction was not to feed a large quantity of food at the time of administration. Unpublished pharmacokinetic data in cats indicate reduced bioavailability when robenacoxib tablets are administered with the entire daily ration but not when administered with a third of the ration. Ketoprofen was recommended to be administered in compliance with the manufacturer’s recommendations (ie, with food). Owners were required to complete an owner compliance form at each administration, listing the number of tablets, date and exact time of drug administration, and time and type of food supplied.

The first administration of the test treatments on day 0 was performed by the dispenser. Subsequent doses were administered by the cats’ owners. For all groups, the total duration of treatment was 5 days (6 days if day 4 was not practicable for the owner or the investigator [eg, if day 4 were a Sunday]).

Assessment of efficacy—Each investigator (not the dispenser) carried out clinical assessments by use of observational efficacy criteria on days 0, 2, and 4 or 5 of treatment, whereas owner assessments were conducted once daily on each of the treatment days (0 to 4 or 5 inclusive). Assessments were made by use of numerical rating scales. For the investigator, the primary endpoint was the global assessment score, which was the sum of 3 secondary endpoints: signs of pain at palpation-mobilization, inflammation intensity, and mobility (Appendix 1). Overall response to treatment was an additional investigator secondary endpoint. Cat owners also assessed their cat on each day of administration by use of 4 criteria that were also secondary endpoints (Appendix 2). The time between administration and assessments (made by investigator and owner) was variable for each cat.

Concomitant treatments—Additional use of corticosteroids or analgesic drugs, including opioids or other NSAIDs, was prohibited because they might have affected assessment of the efficacy variables. Other concomitant treatments were allowed, provided they did not interfere with the objectives of the study. If anesthesia was required to facilitate analyses such as radiography, the use of sedatives or anesthetics was allowed, provided the sedation or anesthesia was performed before initiation of the treatment or after the last clinical examination of the study (eg, for blood sampling at the last visit).

Robenacoxib analyses—From each cat at the French sites, a single venous blood sample was collected into a tube containing EDTA for determination of blood robenacoxib concentration. Robenacoxib was quantified in blood rather than in plasma or serum because blood is easier to handle in field conditions and a smaller volume is needed. Blood is a valid medium for robenacoxib analysis because this compound does not enter erythrocytes. Samples were taken between 0 and 16 hours after final drug administration, and the precise time in relation to administration was noted. Samples were stored at <−18°C prior to analysis by use of a validated liquid chromatography–mass spectrometry method. The limit of quantification was 3 ng/mL.

Tolerability—Owners were asked to record all adverse events on the assessment forms, with particular attention paid to the occurrence of emesis, soft feces, diarrhea, and absence of blood in feces. Each adverse event was recorded with a description of clinical signs, duration, severity, and estimate of relationship to product administered (none, unknown, possible, or probable) together with treatment given (if any) and outcome.

Clinical biochemical and hematologic analyses—Blood samples for clinical biochemical and hematologic analyses were collected prior to treatment on day 0 and on day 4 or 5. Clinical biochemical plasma analyses included ALT, AST, ALP, creatine kinase, total protein, albumin, urea, creatinine, potassium, and sodium.
The hematologic analyses included RBC count, WBC count, differential WBC counts, platelet and reticulocyte counts, and Hct and hemoglobin concentration.

**Statistical analysis**—Data are presented as mean ± SD. Before analyzing data for efficacy or safety, all groups were compared to test for differences among treatment groups with respect to baseline and demographic variables.

For efficacy variables, means at day 2 and the final visit (investigator assessment) and between day 1 and the final visit (owner assessment) were determined. In addition, for efficacy variables and clinical biochemical and hematologic data, the change from baseline was analyzed.

Parametric analyses such as ANOVA and repeated-measures ANOVA were used when data were normally distributed. When the normality assumption of the residuals was not satisfied, data were transformed to give the best estimation of a normal distribution. Mann-Whitney U or Kruskal-Wallis tests were also used for analyses without change from baseline, and Wilcoxon tests were used for change from baseline analyses.

For efficacy variables, noninferiority analysis was applied. Noninferiority of robenacoxib administered once daily or twice daily; compared with ketoprofen, or robenacoxib administered once daily versus robenacoxib administered twice daily was proven if a 2-tailed 95% confidence interval for the parameter treatment-to-reference ratio included only values that were greater than a prespecified value (1 − δ). Noninferiority analysis was applied to sums of numerical rating scale values or individual numerical rating scale values obtained at day 2 and the final visit, weighted means over time, or both.

Individual values at the final visit (with and without change from baseline) were determined for hematologic and clinical biochemical variables, and differences among treatment groups were determined by use of Kruskal-Wallis and Mann-Whitney U tests. The prevalence of adverse events associated with robenacoxib treatment was compared with those for cats receiving ketoprofen by use of the Fisher exact probability test. Regression analysis was used to test the association between efficacy results and the time since last administration of the test treatments. The influence of etiology and use of antimicrobials on the efficacy results was examined further through subgroup analyses.

The study protocol defined a minimum of 150 cats to be included. Because limited knowledge was available on the between-animal variation for numerical rating scales or multidimensional scales in cats at the time of starting the study, it was not possible to perform an appropriate power calculation for the noninferiority analyses. However, 156 cats were included in the study and data from 155 cats were analyzed. These numbers were sufficient to fulfill the objectives of the study.

To determine significance, tests were 2-sided on a 5% level (α = 0.05). For noninferiority analyses, 95% confidence intervals were used; the δ value predefined for the noninferiority analysis was 0.25 with high and 0.20 with moderate or low between-animal variability. Because the variability was not high, δ = 0.20 was adopted. As defined in the protocol, the intention-to-treat population (all cats randomized without serious violation of inclusion criteria and for which there was at least 1 measurement after treatment) of 155 cats was used in the analysis. The per-protocol population consisted of 151 cats; 4 cats were withdrawn from the study for major protocol deviations. All statistical analyses were conducted with a commercial software.

**Results**

**Cats evaluated**—One hundred fifty-six cats were enrolled in the study between May 2004 and May 2006. One cat, with a fracture of the ulna identified via radiography after inclusion, was excluded from the analysis, leaving 155 cases (36 cats in group 1, 51 cats in group 2, and 48 cats in group 3). Distribution by sex was as follows: sexually intact females, 11 (7%); sexually intact males, 17 (11%); neutered females, 52 (34%); and neutered males, 75 (48%). Eleven breeds were represented. Mean ± SD age was 5.0 ± 4.1 years with body weight of 4.4 ± 1.1 kg. Mean ± SD duration of clinical signs was 30.5 ± 22.0 hours. The following musculoskeletal disorders were present in the following number (percentage) of cats: cat bites and scratches, 47 (30%); abscesses, 37 (24%); combined cat bites and scratches with abscesses, 7 (5%); joint luxation or subluxation, sprains (traumatic arthritis), strains (affecting ligaments, tendons, or muscles), and lumbosacral injuries, 53 (34%); and other, including acute flare-up of chronic degenerative joint disease, 11 (7%). A forelimb was affected in 65 cats, a hind limb in 52, the vertebral column in 10, and another area in 34.

Either anesthesia or sedation was used in 57% of cats. Treatment compliance in terms of reported frequency of administration relative to the schedule was good; 100% compliance was reported in 40 of 56 cats (group 1), 44 of 51 cats (group 2), and 35 of 48 cats (group 3). Cats were treated for a mean (range) of 5.2 (3 to 6) days (group 1), 5.3 (3 to 6) days (group 2), and 5.3 (4 to 6) days (group 3). One hundred three (66.5%) cats received antimicrobials, whereas 52 (33.5%) cats received no antimicrobials.

**Statistical comparisons among groups**—No significant differences were detected among groups at baseline for the frequencies of age (P = 0.14), body weight (P = 0.22), sex (P = 0.71), breed (P = 0.51), duration of signs (P = 0.15), affected area (P = 0.18), anesthesia or sedation (P = 0.64), concomitant treatment (P = 0.44), pattern of feeding (P = 0.72), investigator (P = 1.00), country (P = 0.86), investigator’s global assessment score (P = 0.77), or owner’s global assessment score (P = 0.45). The distribution of etiologies was significantly different among groups; however, in the repeated-measures ANOVA analysis, there was no significant effect of etiology on the efficacy assessments (P = 0.30 for investigator’s global assessment score and P = 0.17 for owner’s global assessment score). Therefore, it was concluded that the randomization procedures and other factors introduced no relevant bias into the comparisons among groups and were effective in producing matched groups.

**Investigator efficacy assessment**—Mean ± SD global assessment scores at the time of the initial pretreatment evaluation were similar in all groups: 3.89 ± 1.49 in group
1, 5.86 ± 1.34 in group 2, and 5.96 ± 1.44 in group 3. At the time of the final assessment (on day 4 or 5), mean values had decreased to 0.86 ± 1.14 in group 1, 0.76 ± 1.07 in group 2, and 0.81 ± 0.91 in group 3, reflecting mean percentage changes from baseline of −83.8%, −87.4%, and −86.0%, respectively. No significant differences were detected among groups, and therefore, the data indicated a good to excellent level of efficacy of similar magnitude in the 3 treatment groups. Additional analgesic or anti-inflammatory drugs, which were permitted in the protocol only as rescue therapy, were not needed in any cat.

Repeated-measures ANOVA was carried out with the following model effects: etiology, treatment group, treatment group X time interaction, country, baseline value, and subject (as random effect). Differences were not significant for etiology, etiology X time interaction, treatment group, treatment group X time interaction, and country. Time was significant (P < 0.001) for all variables.

In the noninferiority analysis (Table 1), the quotient values for each of the 2 robenacoxib treatment groups, relative to the ketoprofen group, were close to 1 for the primary and all 4 investigator secondary endpoints. The 95% confidence intervals were narrow, and because the lower margin of the confidence limit was > 0.80 for all primary and secondary endpoints, noninferiority to the active control group was concluded for groups 1 and 2. In fact, because the lower confidence limits were > 0.95 for the primary endpoint and > 0.90 for all secondary endpoints, noninferiority would have been determined if a higher limit (eg, 0.90) had been selected. Nonparametric analyses were performed in addition to the repeated-measures ANOVA. All 3 analyses revealed similar results, with no significant differences among the 3 groups for any endpoint.

An additional analysis was undertaken in robenacoxib-treated cats to compare responses in cats receiving the drug with ad libitum feeding and those receiving robenacoxib with feeding at regular times. Nonparametric comparison for primary and 4 secondary endpoints indicated no significant differences; P values were in the range 0.21 to 0.86.

In subgroup analyses, there were no significant differences in efficacy scores between the 103 cats that received antimicrobials and the 52 cats that did not receive them (eg, P = 0.22 for the investigator global assessment score). Noninferiority was proven for the comparison of groups 1 and 2 with group 3 for both subgroups of cats receiving or not receiving antimicrobials (lower margins of the 95% confidence intervals were > 0.90 for the primary endpoint and > 0.80 for all secondary endpoints). Analyses performed on subgroups determined via etiology revealed results similar to the full data set for subgroups of 47 cats with bite or scratch wounds, 37 cats with abscesses, and 53 cats with musculoskeletal injury. Noninferiority of groups 1 and 2, compared with group 3, was determined for all subgroups for the primary and secondary endpoints (with the exception of owner evaluation of activity in cats with musculoskeletal injury for group 1 vs group 3, in which the lower margin of the 95% confidence interval was 0.76). The subgroup of cats with other forms of trauma contained only 11 cats, so that firm statistical conclusions could not be drawn, although there were no obvious differences between this subgroup and the other subgroups.

Persistence of the actions of robenacoxib and ketoprofen for at least 24 hours was indicated by results of linear regression analysis for individual efficacy scores.
versus time elapsed since last administration. The times of administration and assessments made by the veterinarian at day 2 and the final visit were recorded. For all efficacy indices, slopes were shallow, indicating no biologically relevant change in efficacy during the 24-hour administration interval. This was illustrated by scatterplots and regression analyses of the primary endpoint, the investigator global assessment score (Figures 1 and 2).

**Owner efficacy assessment**—Assessment of efficacy by the owners was based on 4 separate numerical rating scales (Appendix 2) obtained at 1 pretreatment time and then once daily up to day 4 or 5 of treatment, with each numerical rating scale being scaled from 0 to 3 and therefore providing for minimum and maximum scores of 0 and 12, respectively, for the owner global assessment score. The initial mean ± SD values were similar: 5.96 ± 3.15 for group 1, 6.18 ± 3.08 for group 2, and 5.43 ± 3.20 for group 3. By day 4 or 5, mean values had decreased to <1.00 in all groups, and percentage changes relative to baseline at this time were –83.8% for group 1, –86.9% for group 2, and –87.0 for group 3, indicating that responses to this time were similar: 5.96 ± 3.15 for group 1, 5.43 ± 3.20 for group 2, and 5.96 ± 3.15 for group 3. Compared with group 3, group 1 had significantly (P = 0.031) higher palatability scores. Scores for groups 2 and 3 were not significantly different (P = 0.083).

**Palatability**—Palatability scores assessed by the owner at the final visit were classified as good or excellent as follows: 66% for group 1, 62% for group 2, and 44% for group 3. Palatability was classified as poor by 16% of owners for group 1, 18% of owners for group 2, and 31% of owners for group 3. The remainder were classified as satisfactory, so that mean palatability scores were 1.13 ± 1.13, 1.22 ± 1.10 and 1.62 ± 1.19, respectively, for groups 1, 2, and 3. Compared with group 3, group 1 had significantly (P = 0.031) higher palatability scores. Scores for groups 2 and 3 were not significantly different (P = 0.083).

**Tolerability**—Total numbers of all reported adverse events (whether or not attributable to the test treatments) over the 4- or 5-day observation period, expressed as a percentage of the number of cats treated, were 17% (group 3), 18% (group 1), and 22% (group 2). Differences among groups were not significant either for all adverse events (P > 0.60) or for individual clinical signs (P > 0.20). The commonest clinical signs were diarrhea (10 cats) and emesis (6 cats). Diarrhea and emesis were reported in the study more frequently in groups 1 (4 and 3 cats, respectively) and 2 (5 and 3 cats), compared with group 3 (1 and 0 cats), although differences did not approach significance (P > 0.20). However, pretreatment illnesses involving the gastrointestinal tract were more frequent in groups 1 and 2 (group 1, 5%; group 2, 4%), compared with group 3 (0%). In no cat in any group was blood detected in feces or vomitus.

The repeated-measures ANOVA analysis contained model effects similar to those used in assessing investigator scores. Treatment group, treatment group × time interaction, and country effects were not significant, but time was significant (P < 0.001) for all variables.

In the noninferiority analysis, the similarity of owner-assessed responses for the 2 robenacoxib treatment groups, compared with the control ketoprofen group, was indicated by the mean quotient values close to 1 and narrow 95% confidence intervals (Table 2). Because the lower confidence limit was set at 0.80, noninferiority of both robenacoxib groups was determined, compared with ketoprofen, for all endpoints. The lower confidence limit was ≥0.90 for the 5 assessed responses. Nonparametric analyses yielded similar conclusions, with no significant differences among the 3 treatment groups for any endpoint.

Table 2—Ratios (quotients) and 95% CI for a noninferiority analysis of cat owner scores comparing the efficacy of robenacoxib versus ketoprofen for treatment of acute pain and inflammation associated with musculoskeletal disorders in cats.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Robenacoxib (q 24 h)</th>
<th>Robenacoxib (q 12 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quotient</td>
<td>95% CI</td>
</tr>
<tr>
<td>Global assessment score</td>
<td>0.995</td>
<td>0.950–1.043</td>
</tr>
<tr>
<td>Level of activity</td>
<td>0.984</td>
<td>0.919–1.053</td>
</tr>
<tr>
<td>Behavior</td>
<td>0.997</td>
<td>0.946–1.049</td>
</tr>
<tr>
<td>Appetite</td>
<td>0.999</td>
<td>0.944–1.058</td>
</tr>
<tr>
<td>Interaction</td>
<td>0.992</td>
<td>0.946–1.040</td>
</tr>
</tbody>
</table>

Reciprocal scores of pain and inflammation were used to calculate the quotient and CIs; therefore, values >1 indicate superiority (numerical) of robenacoxib. All owner scores were secondary endpoints.
In addition to the gastrointestinal tract–related adverse event responses, other responses, all of low prevalence (≤ 5%), included hyperactivity, lethargy, and polydipsia (group 1); signs of abdominal pain, injection site abscess, and muscle pain (group 2); and anorexia, death, hepatic neoplasm, injection site alopecia, intestinal stasis, lethargy, skin abscess, and skin lesion (group 3). Most of these events were likely unrelated to treatment.

Hematologic values—For all 11 hematologic variables monitored, mean values for baseline samples were within reference ranges for cats. Compared with baseline values, changes were generally small, but values for the day 4 or 5 samples indicated, for groups 1, 2, and 3, differences of 31.0%, 18.6%, and 22.6% (platelet count); 17.8%, 35.8%, and 21.2% (reticulocyte count); –8.2%, 1.9%, and –8.2% (WBC count); –18.7%, –5.4%, and –15.9% (neutrophil count); 24.5%, 26.6%, and 12.9% (eosinophil count); and 33.2%, 27.3%, and 29.5% (lymphocyte count), respectively. None of the differences among groups was significant.

Clinical biochemical values—For the 10 biochemical variables monitored, mean baseline values were, in most instances, within reference ranges for cats. However, some plasma liver enzyme activities exceeded by more than 3 times the upper reference limit in the pretreatment samples, as follows: ALT (7/156 cats), AST (8/153 cats), and ALP (5/153 cats). Mean percentage increases from baseline for ALT, AST, and ALP were, respectively, 0.4%, –3.9%, and 6.3% in group 1; 11.9%, –1.4%, and 13.5% in group 2; and 14.0%, 1.8%, and 24.6% in group 3. From these data, it was concluded that, overall, liver enzyme activities were not affected by robenacoxib treatment administered once or twice daily.

Plasma protein and albumin concentrations were not changed in any drug treatment group. Small increases in plasma urea and creatinine concentrations occurred in all 3 treatment groups; mean percentage increases in urea concentration were 28.1% (group 1), 28.4% (group 2), and 23.6% (group 3), and corresponding percentage increases in creatinine concentration were 7.8%, 7.1%, and 5.7%, respectively. Small increases in plasma potassium and sodium concentrations were recorded for all 3 groups. Mean percentage increases from baseline for potassium and sodium concentrations, respectively, were 6.4% and 1.5% (group 1), 8.3% and 2.5% (group 2), and 8.8% and 1.7% (group 3).

No significant differences were detected among groups for any biochemical variable, except for plasma sodium concentration, for which the concentration in group 2 was significantly greater than that in group 1 (P = 0.012) or group 3 (P = 0.045). Although the normality assumption for the parametric ANOVA analysis was satisfied for most variables, a nonparametric analysis (Kruskal-Wallis and Mann-Whitney) was also performed and led to similar conclusions.

Blood robenacoxib concentrations—Blood concentrations of robenacoxib, normalized to a dosage of 1 mg/kg, in samples obtained between 0 and 16 hours after administration of the final robenacoxib doses were measured (Figure 3). Up to 6 hours, concentrations in most cats exceeded 10 ng/mL; after 8 hours, concentrations were generally < 10 ng/mL. Because the sampling strategy was sparse, accurate estimation of pharmacokinetic parameters was not possible. Approximate values were as follows: area under the curve was 757 ng·h/mL, maximum concentration was 226 ng/mL, and mean residence time was 2.46 hours.

Discussion

The principal result of this field trial was that the novel NSAID robenacoxib had noninferior efficacy and tolerability, compared with the reference product ketoprofen, for the treatment of signs of acute pain and inflammation associated with musculoskeletal disorders in cats. Noninferior efficacy and tolerability were determined in all cats as well as in various subgroups, including cats receiving or not receiving antimicrobials and cats with etiologies including musculoskeletal injury, wounds, and abscesses. In addition, there were no detectable differences in efficacy between robenacoxib administered either once or twice daily, and robenacoxib tablets administered once daily were significantly more palatable than were ketoprofen tablets. Therefore, robenacoxib tablets at a dosage of 1 to 2.4 mg/kg administered once daily can be recommended to reduce signs of acute pain and inflammation in cats with musculoskeletal disorders.

The main strengths of this study were that it was a multicenter, prospective, randomized, and masked field trial. The study had sufficient power, with 155 cats and only moderate between-animal variability, and significance was reached for the main statistical endpoints defined in the protocol (noninferiority for primary and secondary endpoints). A further strength of the study was the fact that the per-protocol population (151 cats) and intention-to-treat population (155 cats) were similar, indicating few major protocol deviations, which are important to minimize in noninferiority studies. As defined in the protocol, the intention-to-treat population was analyzed because this is usually the most conservative strategy and observed treatment effects should mirror those observed subsequently in practice.

The main limitation of the study was the absence of a negative control, so that determination of efficacy...
and tolerability of robenacoxib was reliant on proving noninferiority, compared with the positive control, ketoprofen. Ketoprofen is registered in Europe (as well as in Australia and Canada) for the indication tested (ie, treatment of pain). Further, measures should be similar to those used in the designed noninferiority studies, the methods and outcomes performed to support its registration. In optimally equivalent to those used in original ketoprofen studies performed to support its registration. In optimally designed noninferiority studies, the methods and outcomes should be similar to those used in the original studies of the active control drug. Therefore, the improvement in clinical signs was rapid and large with all 3 treatment schedules. Therefore, we concluded that the administered NSAIDs contributed to the observed improvement initially and possibly throughout the treatment period. An additional but unavoidable complication of the study was the fact that the robenacoxib and ketoprofen tablets were visibly different, and therefore, masking of veterinary assessments had to be secured by use of the masking by function technique by 2 persons: the first, the investigator, was responsible for clinical assessments, and the second, the dispenser, was responsible for treatment delivery. Cat owners were not formally masked, and for this reason, owner assessments were used as secondary endpoints. The primary endpoints were based on the investigators’ assessments. Additionally, the investigators were aware a priori that the study was a noninferiority trial, and therefore, we cannot exclude subtle bias to give all treatments the same rating.

A final limitation of the study was adoption of a noninferiority margin (δ) of 0.20, the same value as recommended in guidelines for bioequivalence studies. Noninferiority margins should be the largest margin that can be clinically acceptable, and to our knowledge, specific recommendations for veterinary NSAIDs have not been published. The choice of δ = 0.20 in the protocol was influenced by the presubmission expectation of variability in numerical rating scale scores used to assess signs of pain and inflammation in cats and the practical impossibility of recruiting large numbers of patients in veterinary field studies. In fact, results indicated that noninferior efficacy of robenacoxib, compared with ketoprofen, would also have been achieved if we had defined δ = 0.05 for the primary endpoint (ie, with a maximum of 5% difference in numerical rating scale scores among groups). Furthermore, the mean efficacy of robenacoxib administered once daily versus ketoprofen was 100.4% for the primary endpoint and ranged from 98.4% to 107.6% for the 9 secondary endpoints. Therefore, the data provided strong support for a conclusion of noninferior efficacy.

Duration of efficacy is an important consideration for any analgesic. In the present study, the duration of efficacy of robenacoxib tablets in cats was determined by use of 2 evaluations. First, there was no detectable increase in efficacy with twice-daily administration, compared with once-daily administration, supporting a conclusion that once-daily administration provided good efficacy over the whole dosage interval (24 hours). Second, the times of administration (usually by the owner) and efficacy assessment (by the investigator) were recorded. Regression analysis of efficacy scores versus time elapsed indicates no relevant change in efficacy occurred during the 24-hour interval (Figures 1 and 2). The relatively long duration of clinical efficacy of robenacoxib was not unexpected. Although robenacoxib has a short residence time in the blood (Figure 3), it persists for longer at sites of inflammation. Therefore, we concluded that robenacoxib tablets can be recommended with once-daily administration. Because longer dosage intervals (eg, administration every 48 hours) were not tested, the possibility that they would also provide adequate efficacy cannot be excluded. The NSAID treatments in the present study were administered for a mean of 5.3 days with a range of 3 to 6 days. Therefore, this study did not provide information regarding shorter treatment periods with these NSAIDs, which may also have provided adequate efficacy.

Although determination and outcome of use of antimicrobials was not one of the predefined objectives of the study, this factor was also analyzed. Two-thirds (66.5%) of the cats received an antimicrobial in addition to the NSAID. There were no significant differences in scores between cats receiving and those not receiving antimicrobials. Although these results indicated that antimicrobials probably did not make a marked contribution to the improvement in clinical signs, no definitive conclusions on the efficacy of the antimicrobials could be drawn because allocation of cats to antimicrobial treatments was not randomized. All 3 NSAID treatment regimens were well tolerated; treatment did not need to be interrupted or terminated in any cat. Moreover, there were no differences in frequency of adverse events among the 3 groups. Although diarrhea and emesis were numerically but not significantly more frequent in the robenacoxib groups, compared with the ketoprofen group, a causal relationship to robenacoxib seems unlikely for 2 reasons. First, the groups were not matched at baseline for previous gastrointestinal disorders (5% in group 1, 4% in group 2, and 0% in group 3). Second, gastrointestinal signs (including diarrhea) were not detected in cats receiving high dosages of robenacoxib (10 mg/kg, q 12 h) for 42 days in target species tolerance studies.
With the exception of plasma sodium results, which were concluded to be not biologically important and probably to have occurred by chance, there were no significant differences in plasma biochemical or hematologic variables among groups. Plasma concentrations of creatinine and urea increased in all groups during the study; this may have resulted from increased food intake of the cats as their appetite improved as pain and inflammation decreased.

No evidence of gastrointestinal, hepatic, or renal toxicity was detected with administration of either robenacoxib or ketoprofen. The rationale for developing COX-2 inhibitors is improved tolerability over older nonselective COX inhibitors, notably reduced inhibition of clotting and lesser damage to the gastrointestinal tract. The present study of treatment for 5 to 6 days did not prove superior tolerability of the COX-2 selective inhibitor robenacoxib, compared with the nonselective COX inhibitor ketoprofen. However, the treatment period of 5 to 6 days was possibly too short to reveal tolerability advantages of robenacoxib. The circumstances of this study (a clinical trial in client-owned cats) also did not permit detailed investigations (eg, gastroscopy or postmortem histologic examinations) that might have revealed differences between COX-2 selective and COX nonselective drugs, such as the kind reported in dogs by Luna et al.30 In humans, the COX-2 selective inhibitor lumiracoxib, which is an analogue of robenacoxib, induces significantly less frequent serious gastrointestinal damage (bleeding, perforation, or obstruction), compared with nonselective COX inhibitors30; however, specially designed studies are needed to test this point.

References

### Appendix 1

Summary of numerical rating scales used by investigators to assess cats in a study of treatment for acute pain and inflammation associated with musculoskeletal disorders in cats.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs of pain elicited on palpation-mobilization of the inflamed area</td>
<td>0: No reaction even after strong mobilization-palpation</td>
</tr>
<tr>
<td>(assessed by guarding movement, vocalization, or other reactions)</td>
<td>2: Reaction induced by minimal mobilization-palpation</td>
</tr>
<tr>
<td>Inflammation intensity (assessed by redness, heat, spontaneous signs of pain, or swelling of inflamed area)</td>
<td>0: None</td>
</tr>
<tr>
<td>Mobility (movement in consulting room or on examination table)</td>
<td>0: Normal; able to rise and walk normally</td>
</tr>
<tr>
<td>Overall response to treatment, compared with assessment on day 0</td>
<td>0: Excellent (clinical signs disappeared)</td>
</tr>
</tbody>
</table>

*Each assessment was made on a 4-point scale (0 to 3) on days 0, 2, and 4 or 5. The primary endpoint was the investigator global assessment score (0 to 9), which was the sum of the pain, inflammation, and mobility scores.

### Appendix 2

Summary of numerical rating scales used by owners to assess cats in a study of treatment for acute pain and inflammation associated with musculoskeletal disorders in cats.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of activity, compared with normal (assessed by jumping up or down, running, or playing with toys)</td>
<td>0: Normal</td>
</tr>
<tr>
<td>Behavior</td>
<td>0: Normal (interested in surroundings, alert, and content)</td>
</tr>
<tr>
<td>Appetite</td>
<td>0: Good (normal or improved from before disease)</td>
</tr>
<tr>
<td>Interaction-sociability with owner, other persons, or other animals</td>
<td>0: Good (normal or better than before disease)</td>
</tr>
<tr>
<td>Palatability of tablets†</td>
<td>0: Excellent (voluntary intake without food)</td>
</tr>
</tbody>
</table>

*All assessments were secondary endpoints made on 4-point scales (0 to 3). All assessments excluding palatability were summed to provide an owner global assessment score on a multidimensional rating scale (0 to 12). On days 0 and 4 or 5, the owner was interviewed by the investigator to establish activity, well-being, and response to treatment. Assessment forms were completed at the practice on days 0 and 4 or 5. The owner completed additional assessment forms at home on days 1, 2, 3, and (if the final visit was day 5) 4; on these days, all 4 efficacy criteria were assessed.

†Overall palatability throughout treatment was assessed at the final visit.