Received: 13 May 2020 | Accepted: 23 April 2021

DOI: 10.1111/jvim.16148

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

Clinical safety of robenacoxib in cats with chronic musculoskeletal disease

Jonathan N. King[1] | Wolfgang Seewald[1] | Sophie Forster[2] | Gabriele Friton[1] | Derek E. Adrian[3,4] | B. Duncan X. Lascelles[3,4,5,6]

[1]Elanco Animal Health, Companion Animal Development, Basel, Switzerland

[2]Elanco Animal Health, Companion Animal Development, Basingstoke, UK

[3]Translational Research in Pain Program, Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina

[4]Comparative Pain Research and Education Center, North Carolina State University, Raleigh, North Carolina

[5]Thurston Arthritis Center, UNC School of Medicine, Chapel Hill, North Carolina

[6]Center for Translational Pain Research, Department of Anesthesiology, Duke University, Durham, North Carolina

Correspondence
Jonathan N. King, Elanco Animal Health, Companion Animal Development, Basel, Switzerland.
Email: jonathan.king@elancoah.com

Abstract

Background: Evaluate the clinical safety of robenacoxib in cats with chronic musculoskeletal disease (CMSD).

Animals: Four hundred forty-nine client-owned cats with CMSD.

Methods: Pooled analysis of safety variables from 4 prospective randomized blinded clinical trials of robenacoxib (n = 222) versus placebo (n = 227), administered orally once daily for 4 to 12 weeks. Safety was evaluated from reported adverse events (AEs) and abnormalities detected on hematology and serum and urine chemistry analyses.

Results: The number of cats with at least 1 AE was not significantly different ($P = .15$) with robenacoxib (n = 106, 47.8%) compared to placebo (n = 93, 41.0%). The relative risk of at least 1 AE (incidence robenacoxib/placebo) was 1.15 (95% confidence interval 0.93-1.43). There was no significant difference between groups in the number of clinical signs (range, 0-9) per cat ($P = .23$). Serum creatinine concentrations were higher during robenacoxib administration compared to placebo (+4.36 μmol/L, 95% confidence interval 0.21-8.50), but no related adverse clinical effects were detected. In the subgroup of 126 cats with evidence of chronic kidney disease, the relative risk of at least 1 AE (robenacoxib/placebo) was 1.09 (95% confidence interval 0.78-1.52, $P = .61$).

Conclusions and Clinical Importance: Robenacoxib was not associated with increased risk of AEs compared to placebo when administered for 4 to 12 weeks to cats with CMSD. The generalizability of the results to general practice is limited by the fact that cases with severe and uncontrolled concomitant diseases were not included.

KEYWORDS
adverse event, coxib, harm, NSAID

Abbreviations: AE, adverse event; CI, confidence interval; CKD, chronic kidney disease; CMSD, chronic musculoskeletal disease; CONSORT, Consolidated Standards of Reporting Trials; GLMM, generalized linear mixed model; IRIS, International Renal Interest Society; LMM, linear mixed model; NOS, not otherwise specified; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; PT, preferred terminology; Q-Q, quantile-quantile; RMANCOVA, repeated measures analysis of covariance; SOC, system organ class; SPERT, Safety Planning, Evaluation and Reporting Team.

1 | INTRODUCTION

Chronic musculoskeletal disease (CMSD), which includes osteoarthritis (OA) and degenerative joint disease, is an important cause of morbidity in cats. Nonsteroidal anti-inflammatory drugs (NSAIDs) are used in cats for the management of pain, inflammation and fever.[1] NSAIDs improve activity and behavior in cats with CMSD,[2-5] but there is a paucity of clinical safety data for these drugs in cats.[1] As of March 2021, only 2 NSAIDs, meloxicam and robenacoxib, are registered for long-term use in cats with CMSD in Europe and none are registered in the United States.

Robenacoxib has a good safety profile in healthy cats, with dosages up to 20 mg/kg per day for 6 weeks well tolerated in target animal safety studies.[6] Individual clinical field studies in companion animals are designed to evaluate effectiveness and field safety, but are usually underpowered to precisely detect harms. In cats with OA, administration of robenacoxib at the therapeutic dosage (1-2.4 mg/kg once daily) for 4 weeks was well tolerated compared to placebo, including in the subgroup of animals with evidence of concurrent chronic kidney disease (CKD).[7] As 95 cats were treated with robenacoxib, that study had 95% probability to detect adverse events (AEs) with a true incidence ≥3%, but only 62% probability to detect AEs with a true incidence of 1%.[7] Combining data from multiple studies is recommended, therefore, to improve the power and precision of safety assessments of therapeutic medications.[8]

The objective of the present study is to report results from a pooled analysis of clinical safety variables from 4 clinical trials comparing robenacoxib to placebo in cats with CMSD. The primary objective of all 4 studies was the evaluation of clinical efficacy (benefit) and assessment of safety (harms) was a secondary objective. The hypothesis for safety assessment for each study was that there would be no difference in safety outcomes between robenacoxib and placebo.

2 | MATERIALS AND METHODS

Four separate clinical trials were organized by the sponsor companies (Novartis Animal Health and Elanco Animal Health), referred to hereafter as studies 1 (conducted in France and the United Kingdom), 2, 3, and 4 (conducted in the United States). All were conducted in compliance with good clinical practice,[9] and after approval of the protocols by the sponsoring companies Ethics and Animal Welfare Committees, relevant regulatory authorities in the respective countries, and Institutional Animal Care and Use Committees. Informed written owner consent was obtained in all cases. The consent forms contained information on risks, including that robenacoxib is an NSAID and that NSAIDs as a class might have adverse effects, including to the gastrointestinal tract, kidney, and liver.

This report was prepared after consultation of the Safety Planning, Evaluation and Reporting Team (SPERT) recommendations for safety evaluation and reporting during drug development[8] and the extension of the Consolidated Standards of Reporting Trials (CONSORT) statement related to reporting of harms in randomized trials.[10] Both recommendations were designed for human studies.

2.1 | Inclusion and exclusion criteria

Criteria varied slightly among the 4 studies, and details are provided in Supplementary File 1.0. Cats were required to have CMSD based on the presence of signs of musculoskeletal pain and lesions in joints or the spine or both, and a history of owner-reported impaired activity for ≥12 weeks.

Exclusion criteria included concurrent use of other analgesics or presence of systemic disorders that precluded administration of an NSAID, or might have compromised activity of the cat, such as gastrointestinal hemorrhage or inflammation, impaired cardiac or hepatic function, or hemorrhagic disorders. Cardiovascular or endocrine diseases had to be judged by a clinician to be stable. Cats with international renal interest society (IRIS)[11] stages 1, 2, or 3 CKD (studies 1 and 2) or stages 1 or 2 (studies 3 and 4) could be included.

2.2 | Concomitant treatments

Administration of routine preventative anti-parasitic treatments, angiotensin-converting enzyme inhibitors, calcium channel blockers, diuretics, hyperthyroid medications, and insulin products was permitted. In studies 3 and 4, putative analgesic drugs such as amantadine, gabapentin, tramadol, tricyclic antidepressants (amitryptylline or clomipramine), or selective serotonin reuptake inhibitors (fluoxetine, paroxetine or sertraline) were allowed provided the cat had been receiving these drugs at a stable dose for at least 4 weeks before enrollment.

2.3 | Enrollment and randomization

After enrollment, cats were randomized to receive robenacoxib or placebo administered orally once daily for 12 weeks in study 1, 4 weeks in study 2, and 6 weeks in studies 3 and 4 (Figure 1). In studies 3 and 4, all cats received additionally placebo for 2 weeks in a baseline period (days −14 to 0).

Randomization sequences were generated, separately for each center in each of the 4 studies, by statisticians using computer software. There were no stratifications, including neither for severity of CMSD or the presence of CKD.

A "placebo, robenacoxib, placebo" sequence was also included in studies 3 (n = 36) and 4 (n = 9). Results from those groups were not included in the present safety analysis because attribution of AEs and clinical pathology results to either group was difficult or impossible, and inclusion of this group in the statistical analyses would have been problematic because the placebo and robenacoxib phases for each cat were not independent. Inclusion of data from those 45 cases had no impact on conclusions (AE data are shown in Supplementary File 3.0).

2.4 | Treatment and blinding

In all studies, investigators and owners were blinded to treatment from day 0 onwards. In studies 3 and 4, investigators and owners knew that the cats were receiving placebo in the baseline period.

Blinding was achieved by identical appearance of the formulation and packaging of the test items. Robenacoxib was administered orally once daily using Onsior™ 6 mg tablets (Elanco, Huningue, France) at a target dosage of 1 mg/kg (range, 1-2.4 mg/kg). The placebo tablets had identical appearance and content, except that 6 mg robenacoxib was replaced by lactose.

2.5 | Evaluation

The investigators (veterinarians) were trained on the efficacy and safety evaluations to optimize consistency within studies. Efficacy data are not reported in this paper. Safety was assessed by owner- and veterinarian-reported AEs plus blood hematology and serum and urine chemistry variables measured at various time points (Figure 1). AEs were classified according to the system organ class (SOC) and preferred term (PT) nomenclatures.[12] The severity and probable causal relation of the AEs to the test items were assessed.

All hematology (n = 21), serum chemistry (n = 30) and urine chemistry (n = 2) variables that were measured are listed in Supplementary Files 4.0 and 7.0.

Because CKD is common in cats with CMSD and might increase the risk of AEs, the effect of concomitant CKD was analyzed. Chronic kidney disease was defined as the presence of pre-treatment serum creatinine concentration ≥140 μmol/L (1.6 mg/dL) and urine specific gravity <1.035 for studies 2, 3, and 4, and serum creatinine ≥140 μmol/L for study 1 in which urinalysis was not conducted routinely. As noted in Supplementary File 1.0, IRIS stage 4 cases were excluded from enrollment in the studies and therefore all cases of CKD (n = 126) were IRIS stage 2 (n = 122) or 3 (n = 4).

2.6 | Study sample analyzed

Data from the 4 studies were pooled for analysis. Data were analyzed using the safety sample which consisted of all cats which were randomized and received at least 1 dose of the test items. This represents a subset of the all-randomized sample and is in alignment with CONSORT recommendations for reporting of harms.[10] No separate per-protocol analysis was made.

Study 1

Week	-2 to -1	0	2	4	8	12
Test item		Robenacoxib or placebo				
Examination	X		X	X	X	X
Blood/urine	X		X	X	X	X

Study 2

Week	-2	0	2	4
Test item		Robenacoxib or placebo		
Examination	X	X	X	X
Blood/urine	X			X

Studies 3 and 4

Week	-2	0	3	6
Test item	Placebo	Robenacoxib or placebo		
Examination	X	X		X
Blood/urine	X			X

Examination = clinical examination by investigator (veterinarian). 1 week = 7 days.

All 4 studies were blinded from day 0 onwards. The placebo treatment phase from week -2 to 0 in studies 3 and 4 was not blinded.

FIGURE 1 Summary of study designs relevant to safety evaluation

2.7 | Statistical methods

The data were analyzed according to the current guidelines on statistical reporting in the *Journal of Veterinary Internal Medicine* and *the New England Journal of Medicine*.[13] All reported *P*-values are 2-tailed. Because safety outcomes are reported, no correction for multiple tests was made, that is, the analyses were biased towards detecting differences between groups; *P*-values <.05 were considered significant and unadapted 95% confidence intervals (CIs) are reported. Missing data underwent no formal imputation. Sample sizes for the individual 4 studies were calculated based on the planned efficacy assessments (the primary objective of the studies). All analyses were performed using computerized software (SAS/STAT, Version 9.4, 2017, SAS Institute Inc, Cary, North Carolina).

2.7.1 | Primary analysis

The primary outcome was defined as the number of cats in each group with at least 1 AE; the frequencies were compared between the 2 groups using the Mantel-Haenszel test with stratification for study and the *P*-value is reported. In addition, the data were analyzed using a generalized linear mixed model (GLMM) and the relative risk (incidence robenacoxib divided by incidence placebo) and 95% CI were calculated. Treatment and the presence or absence of CKD and their interaction were included as effects in the model. Finally, the number of clinical signs for each animal was compared between groups using the Mann-Whitney *U* test with stratification for study and the *P*-value is reported.

2.7.2 | Secondary analyses

Secondary outcomes included the frequency of AEs according to individual SOCs and PTs plus results of hematology, serum and urine chemistry variables. No adjustments for multiple analyses were made; estimates of effect and 95% CIs are reported but not *P*-values.[13]

Frequencies of AEs for SOCs and PTs were analyzed using GLMM as for the primary outcome.

For hematology, serum and urine chemistry variables, data were standardized if units of measurement differed across studies (eg, creatinine mg/dL was converted to μmol/L). The data were then analyzed by a linear mixed model (LMM) for the repeated measures analysis of covariance (RMANCOVA; SAS procedure mixed) with treatment, study and visit (combined as a single variable), presence of CKD, baseline value, and interactions of treatment with study/visit and CKD as fixed effects; and site (within study) and an AR(1) correlation structure within subject as random effects. The response variable was log-transformed if that improved the normality distribution of the residuals, which was assessed using quantile-quantile (Q-Q) plots. The treatment effect (effect of robenacoxib minus effect of placebo) and 95% CI were calculated. For hematology and chemistry variables, values after treatment were compared to baseline using the Wilcoxon signed-rank test and *P*-values calculated. For serum creatinine, scatter plots were made of concentrations at baseline versus after treatment.

3 | RESULTS

Table 1 presents the number of cats, centers and dates for each study. All cats enrolled in studies 1 (n = 163 cats) and 3 (n = 73 cats) were included in the safety sample. One cat (placebo group) in study 2 (n = 194) and 1 cat (robenacoxib group) in study 4 (n = 21) were excluded since they were withdrawn before they received any test item, resulting in a total of 449 cases (222 in the robenacoxib group, 227 in the placebo group) in the safety sample.

Age, sex, breed, and CKD stage at enrollment are shown in Table 2.

Cats received robenacoxib (target dosage 1 mg/kg; range, 1-2.4 mg/kg) or a matched placebo orally once daily for 12 weeks (study 1), 4 weeks (study 2), or 6 weeks (studies 3 and 4). There were no events of unblinding of the investigators or owners.

3.1 | Primary analysis

The number (%) of cats with at least 1 reported AE (the incidence of harm) was 106/222 (47.7%) with robenacoxib compared to 93/227 (41.0%) with placebo and was not significantly different ($P = .15$) (Table 3; Supplementary File 2.0). The relative risk of an AE was calculated as 1.15 (95% CI, 0.93-1.43) ($P = .20$). The attributable risk (incidence robenacoxib minus incidence placebo) was 6.78% (95% CI, −2.39 to 16.0) and the number needed (to be treated) to harm (1/attributable risk) was 14.8 (95% CI, 6.27 to infinity).

There was no significant difference ($P = .23$) between the robenacoxib and placebo groups in the number of clinical signs reported as AEs for each cat, which ranged from 0 to 9.

3.1.1 | Effect of CKD on the primary outcome

In the GLMM model, there was no significant effect of CKD ($P = .22$) or treatment/CKD interaction ($P = .65$) for the number of cats with at least 1 AE (Supplementary File 2.0).

Of the 126 cats with evidence of CKD, the number (%) with at least 1 AE (the incidence of harm) was 29/58 (50.0%) with robenacoxib compared to 32/68 (47.1%) with placebo ($P = .99$). Estimates were 1.09 (95% CI, 0.78-1.52) ($P = .61$) for relative risk, 2.94% (95% CI, −14.6 to 20.4) for attributable risk, and 34.0 (95% CI, 4.89 to infinity) for number needed to harm. For the cats with CKD, there was also no significant difference ($P = .94$) between the robenacoxib and placebo groups in the number of clinical signs reported for each cat as AEs (range, 0-9 signs).

TABLE 1 Number of cats in the 4 studies

Study	Country	Number of centers	Date data collected	Number of cats						
				Enrolled	Included in safety sample			With CKD and included in safety sample		
				Total	Total	Robenacoxib	Placebo	Total	Robenacoxib	Placebo
1	France and UK	27	Nov 2006-Nov 2008	163	163	81	82	53	28	25
2	USA	26	Jul 2007-Nov 2008	194	193	95	98	48	22	26
3	USA	2	May 2014-Sep 2016	73	73	37	36	16	5	11
4	USA	6	Mar 2014-Dec 2015	21	20	9	11	9	3	6
Total	–	61	–	451	449	222	227	126	58	68

Abbreviation: CKD, chronic kidney disease.

TABLE 2 Demographic variables of cats at baseline

	Robenacoxib (n = 222)	Placebo (n = 227)	Total
Age (years)	11.6 (3.7, 0.8-19.5)	12.1 (4.1, 0.5-21.9)	
Sex			
Female intact	4 (1.8%)	2 (0.88%)	6 (1.3%)
Female spayed	114 (51.4%)	115 (50.7%)	229 (51.0%)
Male intact	1 (0.45%)	2 (0.88%)	3 (0.67%)
Male castrated	103 (46.4%)	108 (47.6%)	211 (47.0%)
Breed category			
Domestic short hair	171 (77.0%)	154 (67.8%)	325 (72.4%)
Domestic long hair	20 (9.0%)	25 (11.0%)	45 (10.0%)
Domestic medium hair	7 (3.2%)	9 (4.0%)	16 (3.6%)
Siamese/Siamese mix	5 (2.3%)	9 (4.0%)	14 (3.1%)
Maine Coon	5 (2.3%)	4 (1.8%)	9 (2.0%)
Persian/Persian mix	5 (2.3%)	5 (2.2%)	10 (2.2%)
Other	9 (4.1%)	21 (9.3%)	30 (6.7%)
Stage of CKD[a]			
IRIS stage 2	57 (25.7%)	65 (28.6%)	122 (27.2%)
IRIS stage 3	1 (0.5%)	3 (1.3%)	4 (0.89%)

Note: Data are mean (SD, minimum-maximum) for age, and number of cats (%) for sex, breed, and stage of CKD.
[a]No IRIS stage 4 CKD cases were included because that was an exclusion criterion.
Abbreviations: CKD, chronic kidney disease; IRIS, international renal interest society.

3.2 | Secondary analyses

3.2.1 | Frequencies of AEs according to SOC and PT

In Table 3, frequencies of AEs are shown for all SOC terms, and for PTs with frequency of AEs >1% (≥3 cats) in 1 or both groups or which might reflect possible adverse effects to the gastrointestinal tract, kidney or liver. All data are shown in Supplementary File 2.0. The 95% CIs for relative risk included 1 for every SOC or PT, suggesting no differences between groups.

The most common AEs (% frequency), in the robenacoxib|placebo groups respectively, were emesis 21.6|18.5, anorexia 6.8|4.4, diarrhea 4.5|5.3, and lethargy 2.7|6.6. The number of cats in the robenacoxib|placebo groups, respectively, with AEs typically associated with serious NSAID toxicity to the gastrointestinal tract, liver and kidney were anemia 1|1, digestive tract hemorrhage 0|2, hepatopathy 1|1, elevated liver enzymes 0|0, elevated serum creatinine or urea nitrogen 1|0, renal insufficiency 2|0, and renal failure 0|1.

A total of 5 cats died or were euthanized during treatment in the studies, 4 while receiving robenacoxib and 1 placebo. In the robenacoxib group, 1 cat in study 1 was euthanized after worsening of progressive stiffness and the onset of pain in the neck area; 1 cat in study 1 died after developing pitting edema of a hind leg; 1 cat in study 3 had worsening of pre-existing hind limb weakness and neurological deficits; and 1 cat in study 4 developed difficulty in breathing on day 19, judged probably secondary to heart failure caused by hypertrophic cardiomyopathy. In the placebo group of study 1, 1 cat was euthanized due to somnolence.

TABLE 3 Frequencies and estimated relative risk for reported adverse events

Variable (SOC or PT)	Robenacoxib (n = 222)	Placebo (n = 227)	Relative risk	
			Estimate	95% CI
Behavioral disorders	8 (3.6%)	9 (4.0%)	0.91	0.37-2.27
Behavioral disorder NOS	3 (1.4%)	4 (1.8%)	0.77	0.19-3.1
Inappropriate urination	3 (1.4%)	1 (0.4%)	3.06	0.59-15.80
Blood and lymphatic system disorders	3 (1.4%)	3 (1.3%)	1.24	0.31-4.93
Anemia NOS	1 (0.5%)	1 (0.4%)	1.02	0.28-3.66
Cardiovascular system disorders	1 (0.5%)	3 (1.3%)	0.34	0.04-3.29
Digestive tract disorders	56 (25.2%)	58 (25.6%)	1.00	0.73-1.38
Diarrhea	10 (4.5%)	12 (5.3%)	0.86	0.38-1.95
Digestive tract disorder NOS	3 (1.4%)	1 (0.4%)	3.07	0.32-29.60
Digestive tract hemorrhage NOS	0 (0.0%)	2 (0.9%)		
Emesis	48 (21.6%)	42 (18.5%)	1.26	0.85-1.87
Intestinal disorder NOS	3 (1.4%)	2 (0.9%)	1.85	0.82-4.18
Intestinal stasis	3 (1.4%)	2 (0.9%)	1.53	0.37-6.28
Ear and labyrinth disorders	4 (1.8%)	2 (0.9%)	1.85	0.31-11.11
Eye disorders	3 (1.4%)	4 (1.8%)	0.77	0.17-3.41
Hepatobiliary disorders	2 (0.9%)	1 (0.4%)	2.04	0.68-6.11
Hepatopathy	1 (0.5%)	1 (0.4%)	1.02	0.28-3.66
Immune system disorders	0 (0.0%)	1 (0.4%)		
Investigations	2 (0.9%)	0 (0.0%)		
Increased blood urea nitrogen or creatinine	1 (0.5%)	0 (0.0%)		
Metabolism and nutrition disorders	1 (0.5%)	0 (0.0%)		
Musculoskeletal disorders	8 (3.6%)	3 (1.3%)	2.72	0.79-9.38
Lameness	4 (1.8%)	1 (0.4%)	4.06	0.78-21.15
Musculoskeletal disorder NOS	3 (1.4%)	1 (0.4%)	3.07	0.32-29.60
Neurological disorders	5 (2.3%)	4 (1.8%)	1.24	0.37-4.18
Ataxia	3 (1.4%)	2 (0.9%)	1.45	0.25-8.44
Psychological disorders	1 (0.5%)	0 (0.0%)		
Renal and urinary disorders	12 (5.4%)	6 (2.6%)	1.88	0.69-5.14
Oliguria	2 (0.9%)	0 (0.0%)		
Polyuria	0 (0.0%)	1 (0.4%)		
Renal failure	0 (0.0%)	1 (0.4%)		
Renal insufficiency	2 (0.9%)	0 (0.0%)		
Urine abnormalities	4 (1.8%)	2 (0.9%)	1.85	0.31-11.11
Respiratory tract disorders	8 (3.6%)	6 (2.6%)	1.28	0.30-5.47
Sneezing	3 (1.4%)	0 (0.0%)		
Skin and appendages disorders	10 (4.5%)	8 (3.5%)	1.23	0.41-3.66
Pruritus	3 (1.4%)	2 (0.9%)	1.56	0.37-6.58
Skin lesion NOS	1 (0.5%)	3 (1.3%)	0.34	0.08-1.34
Systemic disorders	31 (14.0%)	32 (14.1%)	1.02	0.63-1.65
Abnormal test result	6 (2.7%)	7 (3.1%)	0.89	0.34-2.35
Anorexia	15 (6.8%)	10 (4.4%)	1.47	0.65-3.33
Death	5 (2.3%)	3 (1.3%)	1.51	0.30-7.68
Dehydration	0 (0.0%)	2 (0.9%)		
Lethargy	6 (2.7%)	15 (6.6%)	0.44	0.18-1.08
Polydipsia	3 (1.4%)	4 (1.8%)	0.74	0.21-2.59
Weight loss	4 (1.8%)	3 (1.3%)	1.32	0.26-6.67

(Continues)

TABLE 3 (Continued)

Variable (SOC or PT)	Robenacoxib (n = 222)	Placebo (n = 227)	Relative risk	
			Estimate	95% CI
Unclassifiable adverse event	3 (1.4%)	0 (0.0%)		
All adverse events	106 (47.7%)	93 (41.0%)	1.15	0.93-1.43

Notes: The relative risk of an adverse event (AE) (robenacoxib/placebo) and 95% CI were estimated using a generalized linear mixed model (GLMM) with no correction for multiple tests. For blank cells, not applicable. Data are shown for every SOC. For PT, variables are shown only if AEs occurred in ≥3 cats (>1%) in either group or if highly relevant to nonsteroidal anti-inflammatory drugs (NSAIDs) (anemia, digestive tract hemorrhage, hepatopathy, increased blood urea nitrogen or creatinine, oliguria, polyuria, renal failure, renal insufficiency, or dehydration).
Abbreviations: CI, confidence interval; NOS, not otherwise specified; PT, preferred term; SOC, system organ class.

TABLE 4 Estimates for selected hematology variables

Variable	Unit	Robenacoxib		Placebo		Difference (robenacoxib − placebo)	
		Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Red blood cell count	10^{12}/L	8.19	8.04-8.34	8.32	8.17-8.46	−0.13	−0.31 to 0.06
Hemoglobin	g/dL	12.31	12.11-12.51	12.43	12.24-12.63	−0.12	−0.38 to 0.14
Hematocrit	%	39.27	38.59-39.95	39.74	39.07-40.41	−0.47	−1.36 to 0.41
Mean corpuscular hemoglobin	pg	15.28	15.14-15.42	15.09	14.97-15.21	0.20	**0.01 to 0.38**
Platelet count	10^9/L	300.74	286.44-315.03	302.80	288.73-316.86	−2.06	−18.01 to 13.89
Reticulocyte count	10^9/L	18.15	16.00-20.29	18.54	16.28-20.81	−0.39	−3.04 to 2.25
White blood cell count	10^9/L	8.18	7.82-8.54	8.19	7.84-8.55	−0.01	−0.46 to 0.43
Basophil count	10^9/L	0.11	0.10-0.11	0.11	0.10-0.11	0.00	0.00 to 0.00
Eosinophil count	10^9/L	0.55	0.50-0.60	0.56	0.51-0.61	−0.01	−0.08 to 0.05
Lymphocyte count	10^9/L	2.19	2.06-2.32	2.14	2.02-2.27	0.05	−0.12 to 0.22
Monocyte count	10^9/L	0.29	0.27-0.31	0.30	0.28-0.32	−0.01	−0.04 to 0.01
Neutrophil count	10^9/L	5.00	4.72-5.27	5.02	4.75-5.30	−0.03	−0.36 to 0.31

Notes: Data show values for each variable after administration of robenacoxib or placebo, and the difference. Estimates and 95% CIs were calculated using repeated measures analysis of covariance (RMANCOVA), with no correction of CIs for multiple tests. CIs for the difference marked in bold do not include 0.
Abbreviation: CI, confidence interval.

A total of 3 cats died in the 14 days after cessation of treatment. In the robenacoxib group, 1 cat in study 2 was euthanized due to a perforated eye. In the placebo group, 1 cat in study 2 died due to uncontrolled hyperthyroidism, and 1 cat died due to a suspected oral malignant tumor.

The total number of deaths during treatment or in the 14 days after cessation of treatment was therefore higher with robenacoxib (5) than with placebo (3), but differences were not significant (relative risk, 1.51; 95% CI, 0.30-7.68) and deaths occurring in the robenacoxib group were diverse and not typical for NSAID toxicity.

3.2.2 | Hematology, serum and urine chemistry

Data from all variables are shown in Supplementary Files 4.0 to 9.0; results of selected variables of greatest clinical relevance are shown in Tables 4 and 5. Log transformation improved the distributions of the residuals for 30 of 53 variables, but deviations from normality (assessed visually using Q-Q plots) were judged to be relevant for 21 variables (Supplementary Files 4.0 and 7.0). Correlation structure analysis indicated repeated measurements within each subject were correlated.

Hematology

Results from all 21 variables are shown in Supplementary Files 4.0 to 6.0; results from 12 variables are shown in Table 4. For only 1 variable, mean corpuscular hemoglobin, did the 95% CI for the difference between groups not include 0. The content was higher in the robenacoxib group (estimate +0.20 pg; 95% CI, 0.01-0.38).

Serum chemistry

Results are shown in Supplementary Files 7.0 to 9.0; results from 26 variables are shown in Table 5.

TABLE 5 Estimates for selected serum and both urine chemistry variables

		Robenacoxib		Placebo		Difference (robenacoxib − placebo)	
Variable	**Unit**	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Albumin/globulin ratio		0.85	0.83-0.87	0.82	0.80-0.83	0.03	0.01 to 0.06
Albumin	g/L	32.60	32.24-32.95	32.76	32.41-33.12	−0.17	−0.59 to 0.26
Alkaline phosphatase	U/L	30.77	29.43-32.12	30.80	29.47-32.14	−0.03	−1.71 to 1.65
Alanine aminotransferase	U/L	56.70	53.58-59.82	56.06	53.01-59.11	0.65	−3.38 to 4.67
Amylase	U/L	1096.28	1064.16-1128.40	1088.90	1060.28-1117.51	7.40	−28.63 to 43.44
Aspartate aminotransferase	U/L	29.54	28.03-31.05	27.93	26.51-29.34	1.66	−0.21 to 3.53
Calcium	mg/dL	9.81	9.69-9.93	9.77	9.67-9.87	0.04	−0.08 to 0.17
Cholesterol	mg/dL	171.49	166.18-176.80	178.75	173.91-183.59	−7.11	**−14.03 to −0.19**
creatine kinase	U/L	192.04	164.47-219.60	164.31	143.34-185.27	30.08	−2.50 to 62.65
Creatinine	μmol/L	138.04	134.90-141.18	133.75	130.74-136.77	4.36	**0.21 to 8.50**
Fructosamine	μmol/L	256.49	250.23-262.74	254.49	247.97-261.01	1.99	−5.47 to 9.46
Gamma-glutamyltransferase	U/L	1.39	1.25-1.52	1.35	1.22-1.48	0.03	−0.13 to 0.20
Globulin	g/L	43.61	42.97-44.24	44.23	43.61-44.86	−0.63	−1.43 to 0.18
Glucose	mmol/L	5.38	5.13-5.63	5.53	5.27-5.78	−0.14	−0.42 to 0.14
Lipase	U/L	78.81	70.45-87.18	83.92	76.14-91.70	−4.95	−15.74 to 5.84
Inorganic phosphorus	mg/dL	4.55	4.39-4.72	4.37	4.22-4.52	0.19	0.00 to 0.37
Potassium	mmol/L	4.44	4.31-4.56	4.59	4.47-4.70	−0.15	**−0.28 to −0.02**
Sodium	mmol/L	152.94	152.26-153.62	153.15	152.55-153.74	−0.21	−1.11 to 0.70
Total bilirubin	μmol/L	1.00	0.89-1.12	0.94	0.83-1.04	0.07	−0.04 to 0.18
Direct (conjugated) bilirubin	μmol/L	0.51	0.45-0.57	0.54	0.47-0.60	−0.03	−0.10 to 0.04
Indirect (unconjugated) bilirubin	μmol/L	0.30	0.23-0.37	0.28	0.21-0.35	0.03	−0.04 to 0.09
Total protein	g/L	76.24	75.43-77.05	77.04	76.24-77.84	−0.80	−1.75 to 0.14
Triglycerides	mg/dL	70.76	63.22-78.30	74.47	67.53-81.41	−3.62	−13.38 to 6.15
Tri-iodothyronine (T3)	nmol/L	58.74	55.25-62.23	61.65	58.15-65.16	−2.85	−7.57 to 1.88
Thyroxine (T4)	nmol/L	22.91	21.20-24.62	23.88	22.06-25.71	−0.95	−2.75 to 0.85
Urea nitrogen	mmol/L	11.10	10.78-11.43	11.10	10.78-11.42	0.00	−0.38 to 0.39
Urine pH		6.58	6.43-6.73	6.64	6.51-6.78	−0.06	−0.23 to 0.11
Urine specific gravity		1.04	1.04-1.04	1.04	1.04-1.04	0.00	0.00 to 0.00

Notes: Data show values for each variable after administration of robenacoxib or placebo, and the difference. Estimates and 95% CIs were calculated using repeated measures analysis of covariance (RMANCOVA), with no correction of CIs for multiple tests. CIs for the difference marked in bold do not include 0.
Abbreviation: CI, confidence interval.

The 95% CI for the difference between groups did not include 0 for 4 variables; albumin/globulin ratio, cholesterol, creatinine, and potassium.

Although the albumin/globulin ratio was higher with robenacoxib (estimate, +0.03; 95% CI, 0.01-0.06), the effect was marginal and no difference between groups was detected for albumin or globulin.

Cholesterol concentrations were lower in the robenacoxib group (estimate, −7.11 mg/dL; 95% CI, −14.03 to −0.19), but this was related to a significant increase from baseline with placebo (mean ± SD from 180.8.5 ± 52.7 to 187.4 ± 52.8 mg/dL, $P = .0004$) with no significant change with robenacoxib (from 174.8 ± 48.6 to 175.7 ± 48.4 mg/dL, $P = .63$).

Creatinine concentrations were higher after treatment with robenacoxib (estimate, +4.36 μmol/L; 95% CI, 0.21-8.50), related to a significant increase from baseline with robenacoxib (mean ± SD from 139.0 ± 32.3 to 143.2 ± 35.3 μmol/L, $P = .003$) and no significant change with placebo (from 140.4 ± 37.8 to 141.2 ± 37.9 μmol/L, $P = .97$). There was no significant effect of CKD or treatment × CKD interaction for creatinine in the RMANCOVA model (Supplementary File 7.0). Scatter plots of baseline versus mean concentrations after treatment show no increase in risk of marked increases in serum creatinine with robenacoxib compared to placebo (Figure 2).

Potassium concentrations were lower in the robenacoxib group (estimate, −0.15 mmol/L; 95% CI, −0.28 to −0.02). Concentrations

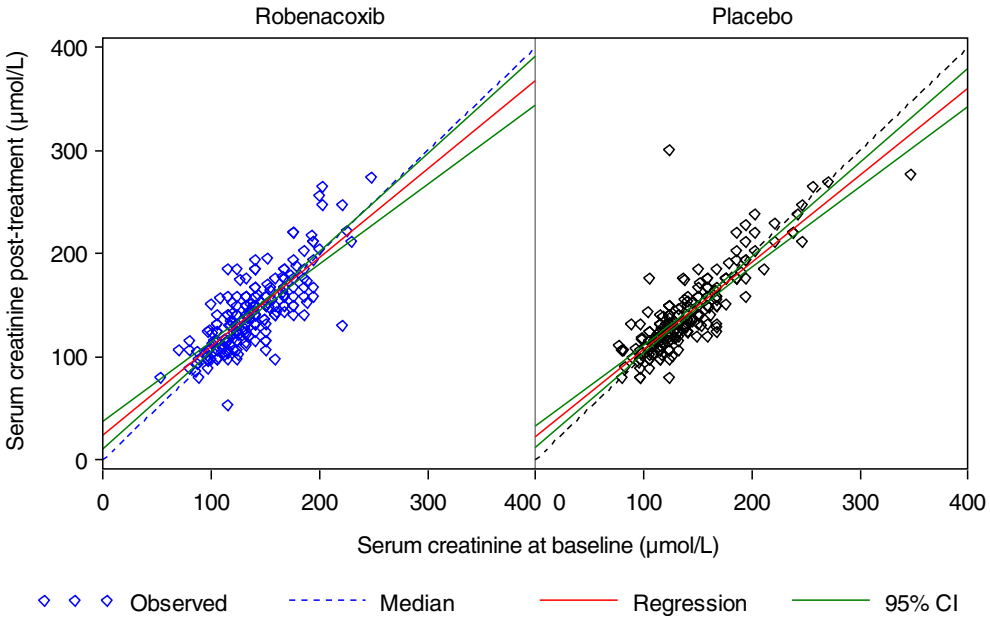

FIGURE 2 Scatter plots of serum creatinine concentrations at baseline versus post-treatment (weighted average) for each cat. The lines show the median line ($y = x$) and the regression line (y estimated from x, based on ordinary least squares regression) together with 95% confidence curves

increased from baseline in both groups, but with a larger increase with placebo (mean ± SD from 4.39 ± 0.45 to 4.58 ± 0.55 mmol/L, $P < .0001$) compared to robenacoxib (from 4.36 ± 0.48 to 4.44 ± 0.42 mmol/L, $P = .02$).

Urine chemistry

For both urine variables, urine specific gravity and pH, 95% CIs for the difference between groups did not include 0 (Table 5). There was also no significant effect of CKD or treatment × CKD interaction (Supplementary File 7.0).

4 | DISCUSSION

In this study, a pooled data analysis was made of safety variables from 4 clinical trials conducted with the NSAID robenacoxib in cats with CMSD. Randomized, placebo-controlled and blinded study designs were used in all 4 studies. A major limitation of many clinical trials in companion animals is their low power to detect adverse effects (harms), notably due to low numbers of subjects. The major strength of the present study, using a pooled safety data analysis approach, is the increase in power to detect harms due to the higher numbers of cats included in the analysis (robenacoxib n = 222, placebo n = 227) compared to the individual studies. Pooling of safety data from all studies in a drug development program is recommended.[8] The data presented suggest that robenacoxib was well tolerated when administered for 4 to 12 weeks to cats with CMSD. The dosage of robenacoxib tested was the same as registered in various countries globally for both acute and chronic indications in cats (target dosage, 1 mg/kg; range, 1-2.4 mg/kg, once per day). Nevertheless the study has important limitations which prevent definitive conclusions.

First, statistical analysis of safety variables is challenging. As is standard and recommended for safety assessments, all variables were analyzed with no correction for multiple tests in order to minimize the risk of false negative conclusions (type II errors).[8,10] Significant effects were concluded if (2-tailed) *P*-values were less than .05, or 95% CIs did not include 1 (for relative risk) or 0 (for effect difference). The inevitable consequence of this approach is a relatively high risk of false positive results (type I errors). In our study, we analyzed 53 clinical pathology variables, and for the AE reports there were 18 SOCs and 109 PTs.

Second, as is common in clinical trials, the primary objective of the 4 individual studies was the assessment of benefit (efficacy) while the evaluation of harm (safety) was only a secondary objective.

These limitations and the latest guidelines were taken into account for the statistical analyses, including presentation of results mainly as estimates of effect and 95% CIs, and limited reporting of *P*-values.[13]

The primary outcome was the frequency of cats in each group with at least 1 AE. All reported AEs are included in this endpoint, regardless of assessed causality, and no differentiation was made between mild and severe cases. The relative risk of cats having at least 1 AE while receiving robenacoxib compared to placebo was 1.15 (95% CI, 0.93-1.43). Because the 95% CI includes 1, differences between the groups were not significant at the 5% level using the classical null hypothesis significance testing approach. The null hypothesis of no difference between groups can be considered valid for the efficacy endpoints of the studies, but is not optimal for safety evaluation because the absence of proof of effect provides no assurance of absence of effect. The pooled analysis and the 4 individual trials were not designed as noninferiority studies, but it can be noted that the upper limit of the CI for relative risk (1.43) is greater than commonly used noninferiority limits, for example, 1.15 or 1.2, that is, noninferior safety of robenacoxib to placebo was not shown.[14] From a classical statistical testing perspective, the results are therefore inconclusive. Nevertheless, a 15% difference between robenacoxib and placebo in the frequency of cats with at least 1 AE is judged to be within clinically acceptable limits. There was no significant difference ($P = .23$) between groups in the number of clinical signs

per cat. Estimates were calculated for attributable risk (6.78%) and the number needed (to be treated) to harm (14.8), but are unreliable because the CIs were very wide (respectively −2.39 to 16.0, 6.27 to infinity).

The frequency of AEs according to individual SOCs and PTs were evaluated as secondary outcomes, and in all cases the 95% CIs for the relative risk included 1. It is also notable that the numbers of reported AEs for PTs of greatest concern for serious NSAID toxicity, related to the gastrointestinal tract, kidney, or liver, were not different between groups (see results section for details). Because data were analyzed from 222 cats exposed to robenacoxib, the study had reasonable (89%) probability to detect AEs with a true incidence ≥1%. However, the study included insufficient numbers of cats to make definitive conclusions, and was underpowered to detect AEs with a true frequency <1%.

The number of deaths during treatment or in the 14 days after cessation of treatment was higher with robenacoxib (5) than with placebo (3), but the 95% CI for the relative risk included 1 (0.30-7.68) and the deaths occurring in the robenacoxib group were diverse and not typical for NSAID toxicity (see Results section for details).

A total of 53 clinical pathology variables (hematology, serum and urine chemistry) were analyzed as secondary outcomes. Because the CIs were not adjusted for multiple tests, false positive outcomes would be expected by chance for 2 or 3 variables. For 5 of the 53 variables, 95% CIs for the difference between groups did not include 0, indicating a significant difference at the 5% level. For 4 of these variables, mean corpuscular hemoglobin, albumin/globulin ratio, cholesterol, and potassium, it is judged unlikely that robenacoxib was responsible for the observed differences from placebo (see Results section for details).

For serum creatinine, however, an effect of robenacoxib cannot be excluded. Serum creatinine concentrations increased from baseline in both groups, but there was a higher and significant increase with robenacoxib (+4.3 μmol/L, $P = .003$) and a smaller but not significant increase with placebo (+0.8 μmol/L, $P = .97$). The statistical model estimated +4.36 μmol/L higher concentrations with robenacoxib compared to placebo, with a 95% CI of 0.21 to 8.50. A 8.5 μmol/L higher serum creatinine concentration would represent a moderate effect with low clinical relevance. A scatter plot of change in concentrations from baseline provided no indication of increased risk of marked increases in serum creatinine with robenacoxib compared to placebo. Furthermore, the number of cases (respectively robenacoxib|placebo) with reported AEs related to renal insufficiency (2|0) or renal failure (0|1) was low and similar in the 2 groups. Additionally, no effect of CKD or CKD × treatment interaction was observed for serum creatinine in the RMANCOVA model. Robenacoxib had no effect on glomerular filtration rate in healthy cats.[15] It is judged unlikely, therefore, that robenacoxib caused clinically relevant increases in serum creatinine concentrations in the cats in our study.

Chronic kidney disease is relatively common in cats with CMSD,[16] and a total of 126 cats (28.1%) in our study had evidence of CKD (IRIS stages 2 or 3). The effect of concomitant CKD was assessed by including CKD effect and CKD × treatment interaction in the analyses, and in addition via analysis of the subgroup of 126 cats with CKD. Taking into account multiple analyses, there was no indication of any relevant effect of CKD, or the presence of a treatment × CKD interaction, on the results for AEs or clinical pathology variables. Only 4 cats were in IRIS CKD stage 3 at baseline, and stage 4 cases were excluded, however, and therefore the study did not allow meaningful evaluation of those stages.

In addition to the main issues discussed previously, the study had further limitations.

First, a common method for combining data from many studies is to perform a formal meta-analysis and weigh the contribution of the individual studies, based on the assessed quality of the data.[17] This was not attempted for this report since there were only 4 studies and their quality was judged to be equivalent. Nevertheless, the 4 component studies had differences, notably related to geographical location (1 in France and the United Kingdom, 3 in the United States), treatment times (4-12 weeks), timings and laboratories for analysis for blood and urine samples, and some of the definitions for reporting AEs. The potential impact of the 4 component studies (and sites) was incorporated into the statistical analyses; study, site (within study), and their interactions with treatment were included as effects in the parametric models, and stratification by study was included in the nonparametric Mantel-Haenzel tests. Study and site had no relevant impact on the results, although the heterogeneity between studies was not quantified. Conversely, the use of 61 sites in 3 different countries, combined with minor differences in inclusion and exclusion criteria and methods, can be considered a strength of this study and adds value to the generalizability of the conclusions for cats with CMSD. Because study had no relevant effect on outcomes, it can be concluded indirectly that treatment time, over the tested range of 4 to 12 weeks and which was confounded with study, also had no relevant effect.

Second, the owner consent forms contained information on potential harms of NSAIDs and specifically mentioned the gastrointestinal tract, kidney, and liver. The possibility exists, therefore, that both investigators and owners were "primed" to certain AEs, leading to overestimation of their relative frequency (confirmation bias), a phenomenon described in humans.[18] In human clinical trials, passive reporting of AEs typically leads to lower reporting rates than active surveillance.[10] In our studies, surveillance was both active and passive because the owners were prompted to report any changes in their cat's activity in the previous 24 hours in daily diaries and were specifically questioned by the investigators regarding AEs at visits.

Finally, the methods employed do not have high sensitivity for detection of some potential NSAID-related adverse effects, notably damage to the gastrointestinal tract or changes in renal function.

5 | CONCLUSION

It is concluded that robenacoxib, administered for 4 to 12 weeks, was well tolerated in cats with CMSD. With the possible exception of higher serum creatinine concentrations, no indication was detected of adverse effects of robenacoxib on owner or veterinarian-reported AEs, blood hematology, or serum or urine chemistry variables. No increased risk of AEs was detected to organs at most risk for NSAID toxicity, including

the gastrointestinal tract, kidney, or liver. The generalizability of the results to general practice is limited by the fact that cases with severe and uncontrolled concomitant diseases were not included.

ACKNOWLEDGMENT

No funding was received for this study. The authors thank the other investigators for managing the clinical cases, and colleagues from the sponsor companies and Contract Research Organizations for assistance managing or monitoring the studies.

CONFLICT OF INTEREST DECLARATION

The studies were supported by Novartis Animal Health, now owned by Elanco Animal Health, which manufactures and distributes robenacoxib (Onsior). Jonathan N. King, Sophie Forster and Gabriele Friton are employed by, and Wolfgang Seewald is retired from, Elanco Animal Health. Derek E. Adrian was employed by North Carolina State University during the study, but has subsequently joined Elanco Animal Health. B. Duncan X. Lascelles received payment from Elanco Animal Health in the past 5 years for consultancy and speaking engagements.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

The studies were conducted in compliance with the procedures and principles of good clinical practice (VICH GL9, CVMP: VICH/595/98, 2000), and after approval of the protocols by the sponsoring company Ethics and Animal Welfare Committees, relevant regulatory authorities in the respective countries, and IACUC. The IACUC protocol number at NCSU for study 3 was 14-009-O. All owners gave written informed consent before inclusion of their cat in each study.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study. All the adverse events described in the paper were reported to Regulatory Authorities in compliance with existing regulations.

ORCID

Jonathan N. King https://orcid.org/0000-0002-4194-9015
Sophie Forster https://orcid.org/0000-0001-9991-5531
Gabriele Friton https://orcid.org/0000-0003-2654-6717
Derek E. Adrian https://orcid.org/0000-0002-0226-6182
B. Duncan X. Lascelles https://orcid.org/0000-0002-2950-9009

REFERENCES

1. Lascelles BDX, Court MH, Hardie EM, Robertson SA. Nonsteroidal anti-inflammatory drugs in cats: a review. *Vet Anaesth Analg*. 2007;34:228-250.
2. Gruen ME, Griffith E, Thomson A, Simpson W, Lascelles BDX. Detection of clinically relevant pain relief in cats with degenerative joint disease associated pain. *J Vet Intern Med*. 2014;28:346-350.
3. Gruen ME, Griffith E, Thomson A, et al. Criterion validation testing of clinical metrology instruments for measuring degenerative joint disease associated mobility impairment in cats. *PLoS One*. 2015;10(7):e0131839.
4. Gruen ME, Alfaro-Córdoba M, Thomson AE, et al. The use of functional data analysis to evaluate activity in a spontaneous model of degenerative joint disease associated pain in cats. *PLoS One*. 2017;12(1):e0169576.
5. Guillot M, Moreau M, Heit M, Martel-Pelletier J, Pelletier JP, Troncy E. Characterization of osteoarthritis in cats and meloxicam efficacy using objective chronic pain evaluation tools. *Vet J*. 2013;196:360-367.
6. King JN, Hotz R, Reagan EL, et al. Safety of oral robenacoxib in the cat. *J Vet Pharmacol Therap*. 2012;35:290-300.
7. King JN, King S, Budsberg SC, et al. Clinical safety of robenacoxib in feline osteoarthritis: results of a randomized, blinded, placebo-controlled clinical trial. *J Feline Med Surg*. 2015;18:632-642.
8. Crowe BJ, Xia HA, Berlin JA, et al. Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the safety planning, evaluation, and reporting team. *Clin Trials*. 2009;6:430-440.
9. European Medicines Agency. Guideline on Good Clinical Practices. CVMP/VICH/595/98-FINAL; 2000. www.ema.europa. Accessed May 12, 2020.
10. Ioannidis JPA, Evans SJW, Gøtzsche PC, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med*. 2004;141:781-788.
11. IRIS staging of CKD (modified 2019). www.IRIS-kidney.com. Accessed 7 Nov 2019.
12. European Medicines Agency. Combined VeDDRA list of clinical terms for reporting suspected adverse reactions in animals and humans to veterinary medicinal products. EMA/CVMP/PhVWP/10418/2009-Rev.9; 2017. www.ema.europa. Accessed May 12, 2020.
13. Harrington D, D'Agostino RB, Gatsonis C, et al. New guidelines for reporting in the journal. *N Engl J Med*. 2019;381:285-286.
14. Freise KJ, Lin T-J, Fab V, et al. Evidence-based medicine: the design and interpretation of noninferiority clinical trials in veterinary medicine. *J Vet Intern Med*. 2013;27:1305-1317.
15. Pelligand L, Suemanotham N, King JN, et al. Effect of cyclooxygenase (COX)-1 and COX-2 inhibition on furosemide-induced renal responses and isoform immunolocalization in the healthy cat kidney. *BMC Vet Res*. 2015;11:296.
16. Marino CL, Lascelles BDX, Vaden SL, Gruen ME, Marks SL. Prevalence and classification of chronic kidney disease in cats randomly selected from four age groups and in cats recruited for degenerative joint disease studies. *J Feline Med Surg*. 2014;16:465-472.
17. Moninuola OO, Milligan W, Lochhead P, Khalili H. Systematic review with meta-analysis: association between acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) and risk of Crohn's disease and ulcerative colitis exacerbation. *Aliment Pharmacol Ther*. 2018;47:1428-1439.
18. Myers MG, Cairns JG, Singer J. The consent form as a possible cause of side effects. *Clin Pharmacol Ther*. 1987;42:250-253.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: King JN, Seewald W, Forster S, Friton G, Adrian DE, Lascelles BDX. Clinical safety of robenacoxib in cats with chronic musculoskeletal disease. *J Vet Intern Med*. 2021;35:2384–2394. https://doi.org/10.1111/jvim.16148