Field Comparison of Canine NSAIDs Firocoxib and Deracoxib.

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ABSTRACT

A multi-clinic, investigator blinded, randomized, prospective field trial enrolling 379 dogs compared deracoxib and firocoxib administered orally over 30 days to treat musculoskeletal disorders considered by the veterinary investigator as caused by osteoarthritis (OA). Over 60% of dogs improved within 7 days of treatment initiation (Day 0), and improvement over baseline was greater at Day 28 than at Day 7 based on veterinarian and owner assessments. For owners' assessments, statistically significantly (P=.003 to .0381) more dogs that received firocoxib than received deracoxib showed substantial improvement at Days 7 and 28, but differences in veterinarian assessments were not statistically significant. There were no serious adverse events and no significant difference between products in the rate of study non-completion.

INTRODUCTION

Firocoxib and deracoxib are active ingredients in two recently registered non-steroidal anti-inflammatory drugs (NSAIDs) indicated for use in dogs. Both are reported to have been developed to be cyclooxygenase (COX)-2 selective/COX-1 sparing.[1,2] In vitro studies support their greater COX-1 sparing property relative to other canine NSAIDs including etodolac and carprofen, and also data suggest that firocoxib is more COX-1 sparing than is deracoxib.[3,4] While the direct link between this property and an improved clinical response has not been established, published data provide evidence that COX-1 sparing drugs can provide measurable clinical efficacy benefits over their less COX-1 sparing NSAIDs counterparts. The evidence comes from two force plate studies using a urate crystal induced synovitis model of canine osteoarthritis (OA) and 2 field trials in which assessments were completed over 30 days.[1,5,6,7]

The synovitis model produces transient signs consistent with arthritis, and treatment effects are typically measured over a period of up to 1 day following induction of lameness. In one such study, deracoxib provided significant lameness improvement ($P < .05$) over carprofen at 4 hours after urate injection, while in the other synovitis model study, firocoxib provided significant improvement ($P < .05$) over carprofen at 3 and 7 hours post urate injection.[5,6] In one

field trial, firocoxib showed improved efficacy in some measurements over the less COX-1 sparing NSAID carprofen.[7] In the other field trial, dogs treated with firocoxib showed significantly greater (P< .05) improvement in OA-related pain and lameness, as assessed by dog owners and by veterinarians, and a significantly reduced (P= .0044) incidence of diarrhea relative to dogs treated with etodolac.[1]

A recent review highlighted the need for further data on the use of canine NSAIDs and the need for a comparison of the safety and efficacy of these drugs.8 In order to generate more clinical data on the use of COX-1 sparing NSAIDs in the amelioration of canine musculoskeletal pain and lameness considered to be caused by OA, a study was undertaken in client-owned dogs in the United States to compare firocoxib and deracoxib.

MATERIALS AND METHODS

Study Design

This was a multi-centered, positive-controlled, two-way comparative, investigator-blinded trial in client-owned dogs, in which the attending veterinarians considered etiology of musculoskeletal pain and lameness to be caused by non-infectious OA. The study was undertaken to compare the efficacy and safety of deracoxib (DERAMAXX® Chewable Tablets, Novartis Animal Health) and firocoxib (PREVICOX® Chewable Tablets, Merial) in dogs, when administered orally, once daily according to label directions, for 28 days (+/- 2 days). Within each participating practice, responsibility for enrollment of affected dogs lay with the diagnosing veterinarian, designated as the veterinary investigator (VI). The primary outcome variables consisted of five definitions of improvement, three based on the VI's assessment of Pain on Manipulation, and two on owners' assessments of improvement (or absence of improvement). Pain on Manipulation was evaluated on a 4-point scale (0=none, 1=slight, 2=moderate or 3=severe). Owner Overall Assessment was collected on Day 7 and Day 28 using a 7-point scale (+3 = great improvement, +2 = good improvement, +1 = a little improvement, 0 = same, -1 = a little worse, -2 = worse, -3 = much worse). Treatment effects were compared on two categories of improvement--"great improvement" and "great or good improvement." Secondary outcome variables were based on the VI's assessment of "overall lameness: walk," and "overall lameness: trot," and on the owners' global assessment of his or her dog's response to treatment under the headings of "Quality of Life" and "Dog Activity."

Owner assessments were obtained via prescheduled telephone calls conducted by a trained, blinded questioner using a format standardized for all owners. The telephone calls and follow-up visits were scheduled by a clinical coordinator (CC) at the enrollment visit and recorded on a calendar provided with other study materials. Telephone interviews were completed before the related clinic visit.

Veterinary Investigator Blinding

At the initial (enrollment) visit, the VI would make the presumptive diagnosis of OA based on signalment, history, and physical examination. The VI or CC would review trial procedures with the owner and obtain a signed informed consent. The CC would dispense treatment to each dog's owner (or caregiver) and was responsible for providing all needed trial education to owners of enrolled dogs. The CC was not involved in any evaluation aspect of the trial. At subsequent visits, the VI completed assessments on the dog with the assistance of a technician, not in the presence of the owner. Any owner wishing to have discussion with the VI was reminded to neither reveal the treatment that was being administered nor indicate his or her perception of the dog's treatment response.

At the conclusion of the study, the VI and CC in each clinic signed a state-

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***Table 1**: Inclusion and exclusion criteria for dog enrollment in comparative NSAID study*

Inclusion Criteria	Exclusion Criteria
• In overall good health	• Systemic disease or infectious arthritis
• Diagnosis of osteoarthritis based on history and clinical examination. Radiographs were optional to help confirm any diagnosis.	• NSAID treatment within 7 days prior to initial treatment in this trial (treatment with additional NSAIDs during the trial would be classified as a treatment failure).
• Score ≥2 lameness at a walk and/or at a trot	• Treatment at any time with deracoxib or firocoxib for OA-related pain and inflammation.
• Body weight in the range of 13–100 lbs	• Corticosteroid treatment within 42 days prior to initial treatment in this trial
• Dogs receiving glycosaminoglycans for >30 days prior to the trial could be included in the trial and the treatment continued during the trial (must be continued through the study)	• Treatment with glycosaminoglycans initiated within the 30 days of trial enrollment (disqualification if treatment initiated during the trial)
• At Clinical Investigator discretion, laboratory values outside normal range but within expectations for a given animal	• Dogs being considered for immediate breeding or those pregnant or lactating
	• Dogs having had adverse reactions to any NSAID registered for canine use
	• Owner refusal to accept the allocated drug
	• Dogs judged by the Clinical Investigator to be unsuitable for inclusion
	• Dogs that had orthopedic surgery within the previous 3 months or for which surgery was planned during the trial period
	• General anesthesia within 1 week prior to starting the study

ment confirming that VI blinding had been maintained throughout the study. Should any unblinding have occurred during the study, the reason for unblinding was to have been documented. The study was organized and monitored by an independent Contract Research Organization (AlcheraBio LLC), and participating clinics and their staffs were not informed of the identity of the study sponsor.

Study drugs were provided to each location in individual snap-close opaque plastic bags, clearly identified as study material and containing the FDA registered packaging. The bags were pre-numbered with a Case Identification Number in accordance with a randomization schedule. On enrollment of each dog, the VI would prescribe a dose rate for both drugs, according to label recommendations (deracoxib 1 – 2 mg/kg; firocoxib 5 mg/kg). At the time of product dispensing, the CC ensured that a given,

pre-labeled bag contained the drug specified by the Case Identification Number in the randomization schedule, provided the owner with written instructions containing information about the allocated drug's administration requirements, and dispensed the allocated plastic bag.

Estimation of sample size—Based on published studies and unpublished data, it was determined that at least 150 dogs would need to complete the study in each treatment arm to provide 80% power ($\alpha = .05$, 2-sided) of detecting differences in assessment of pain on manipulation between the groups of ≤10%.[1,7] To compensate for protocol deviations and losses to follow-up based on a non-completion rate of 15% (derived from earlier work), approximately 175 dogs would be randomly assigned to each of the 2 groups (total of 350 enrolled dogs).[9]

Inclusion/Exclusion Criteria

At the enrollment visit, a history was taken, and each dog was weighed and received a physical examination and lameness evaluation. To avoid or minimize owner bias in reporting the results, the protocol excluded all owners who had prior experience with either firocoxib or deracoxib as a treatment for OA. Other exclusions included recent treatment with any product that might affect study results, with the exception of glycosaminoglycans, for which dogs could only be included if treatment had started at least 30 days prior to the start of the study and the owner agreed to continue administration throughout the study (Table 1).

Whole blood and serum samples were taken for a standard CBC and serum chemistry analysis (including liver and kidney panels). If considered appropriate by the VI, a urine sample was collected and assessed for specific gravity. To be included in the study, dogs were required to have been diagnosed with lameness that had been evident for at least 2 weeks, as determined by client report and VI observation combined with clinical experience and/or radiographs. At the initial examination visit, dogs were evaluated by the VI and assigned an ambulatory lameness score of 0 (no lameness) to 4 (non-weight bearing lameness,–eg, dog touches toe to the floor on <50% of strides). For inclusion, dogs were required to score at least a 2 on either lameness at a walk or lameness at a trot. For convenience of dosing related to tablet size, dogs were required to weigh in the range of 13-100 lbs (Table 1).

Allocation and Treatments

Blocks of four enrolled dogs were formed on order of presentation of lameness, and a specific randomization schedule was created for each clinic. Randomization and blocking were performed using the Microsoft® Office Excel® 2003 Randomization and Data Sorting Functions. Within blocks, two dogs were randomly allocated to Group 1 and two to Group 2.

Owners of Group 1 dogs were dispensed deracoxib (protocol dose rate 1 – 2 mg/kg), and firocoxib (5 mg/kg) was provided to Group 2 owners. Day 0 for each dog was the day on which the owner administered the first treatment upon receiving instructions to proceed from the VI on the basis of satisfactory clinical pathology results (ie, no laboratory finding that might indicate NSAIDs to be contraindicated).

Statistical Analysis

Analysis of the primary and secondary outcome parameters was completed on a modified intent to treat (MITT) population, which included all dogs that received at least one dose of study drug and had at least one post-randomization outcome value. Dogs that did not complete due to an absence of improvement, deterioration of the diagnosed condition, or adverse events (AEs) were assigned the worst possible efficacy scores. For dropouts due to other or unknown reasons, the last post treatment scores were carried forward. All decisions regarding exclusion of subjects were documented prior to analysis of the study database.

All tests of significance, unless otherwise stated, were performed at $\alpha = .05$, two-sided. Assumptions of normality of

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Table 2: *Demographic information on enrolled dogs (MITT population) by treatment group.*

	Firocoxib (n=195)	Deracoxib (n=184)	p-value*
Male	87	81	0.9075
Male neutered	79	64	
Female	108	103	
Female spayed	104	98	
Mean Age (years)	9.20	10.45	0.0004
SD	3.41	3.38	
SEM	0.24	0.25	
Median	9.9	11.0	
Minimum, maximum	0.4, 15.9	0.7, 20.0	
Mean weight (lbs)	56.13	55.72	0.8718
SD	25.36	23.94	
SEM	1.82	1.76	
Median	59.3	56.8	
Minimum, maximum	10.0, 100.0	13.0, 100.0	

residuals and heterogeneity of variance were investigated for each response measurement. If the distribution could not be approximated by a normal curve, an analysis using ranks was performed. Values were ranked in ascending order with tied values being given a mean rank. All statistical analyses were generated using SAS®, version 9.1 or higher. Comparability between treatment groups for categorical variables was assessed by the $\chi 2$ test. For continuous variables, one-way analysis of variance (ANOVA) models implemented in SAS/STAT® PROC GLM were utilized to assess treatment group comparability for each study. For Pain on Manipulation, improvement (yes or no) from Day 0 to Day 7 and to Day 28 was calculated as change to a positive category of at least 1, "none" only (no pain), or "none or "slightly." For Owner Overall Assessment, improvement was defined for Day 7 and Day 28 as "great improvement" or "good or great improvement." Possible differences between treatment groups were assessed by logistic regression analysis using SAS/STAT PROC LOGISITIC. The initial models contained terms for treatment group, baseline pain, baseline lameness: walk, baseline lameness: trot, age, body weight, and dose received (more, according to label, less). Terms found not to be statistically significant ($p > .10$) were dropped from the final models using the method of backwards elimination. Odds ratios to compare treatment groups were generated based on the final models.

RESULTS

Animals

There were 195 dogs randomized to firocoxib treatment and 184 to deracoxib across 26 participating practices in 20 states of the USA. There was no report of VI unblinding during the study. Demographic characteristics for gender, weight, and diagnosis were not statistically significantly different between treatment groups. The most commonly represented breed was Labrador retriever. This plus the two other most commonly represented breeds, Golden retrievers and German shepherds, accounted for just over one third of the dogs enrolled in each treat-

ment group. The mean age of the deracoxib group (10.5 years) was significantly greater than that of the firocoxib group (9.2 years) (P= .0004) (Table 2). The statistical analysis plan stated that age would be a covariate in the logistic regression models. Therefore, the p-values assessing differences between treatment groups were adjusted for age. At baseline, most dogs experienced moderate Pain on Manipulation (firocoxib: 51.3%, deracoxib: 50.5%) and moderate lameness upon walk (firocoxib: 71.8%, deracoxib: 70.7%) and trot (firocoxib: 67.2%, deracoxib: 62.0%). Other factors, in addition to age, for which the analysis plan adjusted because of the significant effect of baseline values on treatment outcome were VI's assessments of Pain on Manipulation, Lameness at a Trot, and Lameness at a Walk (all P< .0001).

There were 10 dogs in the firocoxib group (5.1% of dogs enrolled in that group) and 9 in the deracoxib group (4.9%) that did not complete the study (Table 3). Of the non-completing dogs, two withdrawals in the firocoxib group and three in the deracoxib group were related to AEs that were considered to be possibly treatment related. In the firocoxib group, these were: intermittent vomiting, lethargy and melena seen in a 10 year old Labrador mix approximately 1 week into the study, with no safety signals observed in a CBC or blood chemistry panel. The dog subsequently recovered. There was also vomiting in an 11 year-old Labrador following 3 days of treatment, described over telephone to the VI by the owner, who elected to withdraw the dog from the study.

In the deracoxib group, AE-related withdrawals were: vomiting and diarrhea in a 16 year-old Scottish Terrier after 7 days of treatment; lethargy and reduced appetite in a 9 year-old cross breed after 7 days of treatment; and vomiting, melena and anorexia in a 5 year-old boxer approximately 3 weeks into study participation. Three dogs died during the study – a 9 year-old Rottweiler in the firocoxib group that was tentatively diagnosed with hypertrophic cardiomyopathy, and one dog in each group, a 15 year-old German Shepherd reported by the VI to not be treatment related, and a 15 year-old Australian Shepherd that was euthanized with no explanation provided. No statistically significant difference in discontinuation rate was found between treatment groups (P = .664).

Primary Variables

Over 60% of dogs in the study had shown improvement of at least one grade of Pain on Manipulation within 7 days of treatment initiation, with approximately one third of dogs having no pain detected at this time. Improvement over baseline levels was greater at Day 28 than at Day 7 for VI's as-

Table 3: *Number of non-completing dogs in each treatment group (percentage of total enrolled in that group) and reasons for non-completion.*

	Firocoxib (n=195)	**Deracoxib (n=184)**
Owner withdrew or lost to follow up	5 (2.6%)	3 (1.6%)
Withdrawn by Clinical Investigator (protocol violation or non-study related event)	1 (0.5%)	2 (1.1%)
Death‡	2 (1.0%)	1 (0.5%)
Adverse event (see text)	2 (0.5%)	3 (1.6%)

‡In the firocoxib group, death of a 9 year-old Rottweiler was attributed to postmortem diagnosis of hypertrophic cardiomyopathy, and for the other, a 15 year old German shepherd, no explanation was provided. In the deracoxib group, a 15 year-old Australian shepherd mix was humanely euthanized but no explanation was provided.

Table 4: *Primary outcome variables: Percentage of dogs by treatment group in each category of improvement for Veterinary Investigator assessment of Pain on Manipulation and for Owner Overall Improvement.*

	Study Day	Firocoxib (n=195)	Deracoxib (n=184)	Odds ratio (95% CI)	P-value*
Veterinary Investigator Assessment: Pain on Manipulation					
Improvement ≥1 grade	7	65.3%	62.3%		0.3918
	28	78.2%	73.8%		0.3770
None (no pain detected)	7	34.2%	31.1%		0.4837
	28	56.0%	48.1%		0.3416
Pain on Manipulation	7	78.2%	77.6%		0.8226
No pain or slight pain	28	90.2%	83.1%		0.2326
Owner Overall Assessment					
Great improvement	7	19.5%	9.2%	2.46 (1.27, 4.77)	0.0077
	28	38.5%	26.6%	1.70 (1.08, 2.69)	0.0220
Great or good improvement	7	49.7%	38.6%	1.57 (1.03, 2.41)	0.0381
	28	79.0%	64.7%	2.07 (1.28, 3.34)	0.0030

sessments for both treatments. There were no significant between-group differences for the VI's assessments.

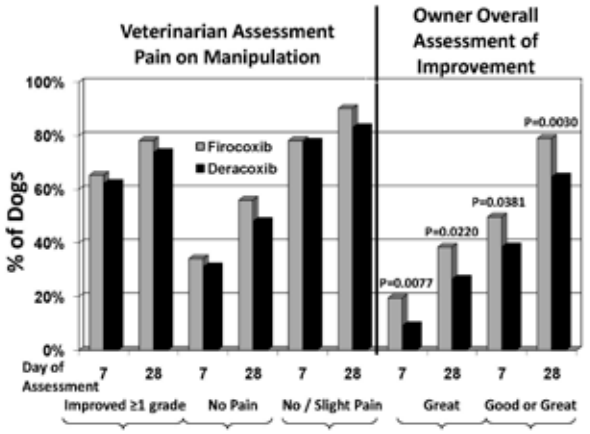
The proportion of dogs reported by owners to have improved at Day 7 and Day 28 was greater in the firocoxib group than the deracoxib group for each of the five primary definitions of improvement (Table 4). For the owners' overall assessments, relative to deracoxib, firocoxib elicited statistically significant improvements at Day 7 and Day 28 (P value range .0030 to .0381), yielding odds ratios for "great improvement" of 2.46 (95% confidence interval 1.27-4.77) and 1.70 (confidence interval 1.08-2.69), respectively. For "great or good improvement" odds ratios were 1.57 (confidence interval 1.03-2.41) and 2.07 (confidence interval 1.28-3.34) for Day 7 and Day 28, respectively.

The pattern of between-treatment differences was consistent between VI scoring of Pain on Manipulation, and Owner Overall Assessment of Improvement (Figure 1).

Secondary Variables

For all secondary outcome variables, the pattern of continuing improvement between Day 7 and Day 28 paralleled that seen with the primary variables. The proportion of dogs experiencing improvement at Day 7 and Day 28 was greater in the firocoxib group than the deracoxib group except "improvement of at least 1 grade" for overall lameness: walk. Statistically significant between-group differences were found at Day 28 for the owners' overall assessment of "much better" quality of life (P = .029), owners' overall assessment of "much better or better" quality of life (P = .013), and owners' overall assessment of "more or much more" activity (P = .003).

Figure 1: *Pattern of primary variable improvement during the study, according to change in veterinarian Pain on Manipulation assessments and Owner Overall Assessment of Improvement.*



DISCUSSION

Both NSAIDs used in this study are indicated for the control of pain and lameness associated with canine OA. While the inclusion criteria included the presence of OA, the means by which such diagnosis would be made was consciously not specified. In practice, diagnosis of canine OA can be made using one or more of the tools available to the clinician, including signalment, a client-provided history, observation of the dog at a walk or a trot, assessment of pain, crepitus, range of motion on manipulation, palpation of musculature for atrophy, lack of primary bone pain or neurologic signs, radiographs, and/or use of more sophisticated technologies, such as force plate assessment or magnetic resonance imaging. None of these techniques has been demonstrated to be completely diagnostic, and some may be beyond the practical limitations of clients. Therefore, the protocol for this field study was designed to reflect the real-world situation by allowing participating veterinarians to enroll a dog after the OA diagnosis had been made, based on signalment, history, and physical examination. Veterinarians then provided baseline pain and lameness assessments that could be used to measure improvements following initiation of NSAID treatment, with the aim of enrolling dogs that were sufficiently lame to allow reasonable assessment of whether there was subsequent improvement after treatment began. While the authors acknowledge that in some cases the diagnosis of OA may not have been definitive, all dogs presented with musculoskeletal pain and/or lameness, and the numbers of enrolled dogs was adequate to validate any significant between-treatment difference detected during the study.

A factor that can confound lameness assessment is that musculoskeletal problems, such as OA, may not necessarily present as "lameness." For instance, a dog in which a hip OA condition is bilateral may be equally uncomfortable in each hip, so that no limb appears to be favored when the dog is in motion. Another factor that may confound lameness assessment is that a patient adapts its gait over time, making a diagnosis of specific etiology more difficult. Finally, an anecdotal report from one VI illustrates that the behavior that allows an owner to identify a dog's discomfort may be masked when the dog is examined in the exam room.

In this case, the VI could not detect any lameness during the in-clinic examination, only to see the dog obviously lame as it returned to its owner's car. Thus, the methodology of VI evaluation of lameness and response to lameness has clear limitations. While force plate gait analysis has been demonstrated as an effective means of objectively describing lameness, resource constraints exclude the availability of force plates from use in large scale clinical trials investigating a response to NSAID treatment.[10,11] This variability raises the question of how to assess response to treatment in these studies.

The possible answer to such question links to the much-debated topic of the as-

sessment of chronic pain in dogs and of the determination of improvement over a baseline condition. There appears to be an expanding recognition that owners, even if untrained, are well qualified to assess chronic pain in their dogs, and they may be more qualified than veterinarians to assess pain, and response to management of pain, in their canine companions. This broad topic has been addressed by a number of authors who have found that owners may be more sensitive to subtle changes in their dogs' attitudes and demeanor and that observation of a dog in its home environment by a person who is familiar with that dog's behavior has advantages over observations made by a "stranger," however well qualified, in a veterinary clinic.[9, 12,13] Further support for the greater acuity of owners in chronic pain assessment of their dogs comes from a pivotal field study in which statistically significant ($P < .05$) differences in favor of deracoxib over placebo were found in force plate analysis and owner evaluation of quality of life, lameness, and level of activity. Despite the parallel between force plate findings and owner observations, there were no significant effects found in the veterinarian clinical evaluations. [14]

For our study, it was therefore decided to include one veterinarian measure (Pain on Manipulation) and one owner assessment (general assessment of improvement in the dog's condition) as primary variables for between-treatment comparisons. Consistent with the deracoxib pivotal study, the pattern of assessment of between-treatment differences was similar between veterinarians and owners with differences achieving significance only in the owner observations.

Because of the practical difficulties of implementing a double blind, this was undertaken as a single (veterinarian) blinded study. Owners were aware of which treatment they were giving their dog, but to avoid or minimize any potential for bias, none of the qualifying owners had any history of using either of the test products in their pets. Additionally, the patterns of improvement were similar between owners and veterinarians, indicating that this protocol stipulation appears to have achieved its objective.

The overall improvement reported by owners of dogs receiving deracoxib here (65% rated as "great or good") is similar to that reported in the pivotal study (60.2% rated as improved relative to baseline). For firocoxib, the owner evaluations of improvement seen in our study (79% at Day 28) are less than those reported by owners of firocoxib dogs in a European study (90% showing moderate or great improvement), similar to those found in an observational field study (74% "greatly" or "moderately" improved at Day 40), and greater than those reported in a USA field study (64% with "moderate" or "great" improvement), and perhaps give a broad range over which the response to a given NSAID would range.[1,7,15]

Few AEs were associated with use of either product in this study. For both groups, the reports of AE-related withdrawals described signs generally consistent with those of NSAID side effects; most were based only on owner reports; and none were life-threatening. For the three dogs that died during the study, one was not treatment related, and limited information was available for the other two (one in each group), but both were aged dogs and NSAID involvement in the deaths appears unlikely. With the caveat that field trials of this type are not powered to detect rare NSAID-caused AEs, the findings appear to endorse the safety of both firocoxib and deracoxib when used judiciously in a dog population which, because of its age, is likely to be susceptible to the potential adverse effects of any drug.

When considered with two other descriptions of comparative field studies with firocoxib (one a European study involving carprofen, the other a U.S. study with etodolac), this study is the third reported field study in which firocoxib has provided significant benefits over a less COX-1 sparing canine NSAID.[1,7] Whether the relative clinical benefit of firocoxib demonstrated

in these studies is due to its greater COX-1 sparing property or to other inherent characteristics of the molecule, such as its pharmacokinetic and/or pharmacodynamic properties, continues to be undetermined. It is believed that NSAIDs exert additional actions at the molecular level, and further research is needed to determine whether any clinical benefit of newer NSAIDs can be specifically linked to their COX-1 sparing properties.[16]

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