Evaluation of oral administration of firocoxib for the management of musculoskeletal pain and lameness associated with osteoarthritis in horses

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Objective—To generate data on the effects of firocoxib administration to horses with osteoarthritis.

Animals—Client-owned horses with signs of lameness and joint pain associated with osteoarthritis.

Procedures—Firocoxib was administered as an oral paste (0.1 mg/kg, q 24 h) for 14 days. Assessments were performed on day 0 (baseline) and days 7 and 14.

Results—390 of 429 horses from 80 sites in 25 states met the criteria for analysis. Quarter Horse and Thoroughbred were the 2 most commonly represented breeds, comprising half of the study population. Signs of musculoskeletal pain or lameness attributed to osteoarthritis were diagnosed in a single joint in 197 (197/390 [50.5%]) horses and in multiple joints in 193 (193/390 [49.5%]) horses. In those with involvement of a single joint, the tarsus was the most frequently affected joint (79/197 [40.1%]). Among the 390 horses with complete lameness data, improvement was reported in approximately 80% by day 14. Investigators rated 307 (78.7%) horses as improved, whereas owners or handlers rated 316 (81.0%) horses as improved at the termination of the study. Horses treated with firocoxib paste had significant improvement in lameness scores from baseline values. Improvement was most rapid within the first 7 days after starting treatment and continued, albeit at a slower rate, through treatment day 14.

Conclusions and Clinical Relevance—Firocoxib significantly improved lameness scores throughout the 14-day period with few adverse effects. Firocoxib can be a safe cyclooxygenase-2–specific NSAID for the treatment of musculoskeletal pain and lameness associated with osteoarthritis. (Am J Vet Res 2012;73:664–671)
large number and broad cross section of horses with signs of musculoskeletal pain or lameness associated with osteoarthritis. Clinical assessments were conducted 3 times during an approximately 14-day period by each horse's primary-care veterinarian and by each horse's daily caregiver. Furthermore, we examined the data to identify clinically relevant associations and patterns, including determining the types of affected horses most or least likely to have a positive outcome (ie, improvement in comfort and function). Our hypothesis was that lameness scores would improve after treatment with a COX-2–specific NSAID for 14 days.

Materials and Methods

**Animals**—Client-owned horses were selected for inclusion in the multicenter study by equine veterinarians across the United States. The American Association of Equine Practitioners membership listing of equine veterinarians was used to contact equine veterinarians to request their participation in the study reported here. Written approval was required, including informed consent and agreement by each horse's owner, trainer, or other principal caregiver that the designated individual would administer any treatments as prescribed and complete required forms and log books as described in the protocol. Approval by an institutional animal care and use committee or similar oversight entity was not required.

Qualifying horses were selected and enrolled in the present study on the basis of the following inclusion criteria: horses were required to be > 1 year old and have lameness and signs of joint pain attributed to osteoarthritis; the lameness had to be of moderate severity (grades 2 to 4 on a scale of 0 to 5) and evident for at least 4 weeks. Radiographic confirmation of the diagnosis of osteoarthritis was advised but not required as a condition of enrollment. There was no limit to the number of horses that could be enrolled in the present study; enrollment included all horses that met the criteria for enrollment. Horses were excluded from the study on the basis of several criteria. Horses typically were excluded if they had been administered an NSAID or antiarthritic drug within 5 days preceding the study or a corticosteroid within 30 days preceding the study. However, if a veterinarian elected to include a horse that had been administered an NSAID or corticosteroid within the defined period, a washout period was required before the horse could be included in the present study. Other exclusion criteria included horses that had recently undergone surgery within 45 days preceding the study or underwent surgery during the study; were < 1 year old; were being bred during the study; were pregnant or lactating; had systemic disease, infectious arthritis, or gastrointestinal bleeding; had a known allergy to aspirin, firocoxib, or other NSAIDs; were in competitions that required collection of urine or blood samples; or had other predisposing conditions (eg, renal or hepatic disease).

**Participating veterinarians**—Equine veterinarians who agreed to participate in the present study signed a participation form. Then, they participated in a protocol training session presented live or via an archived electronic webcast. After completion of the Web-based training session, participating investigators were provided with a commercial preparation of firocoxib® for use in the study reported here. All participants received the oral paste formulation of firocoxib; an unmedicated placebo paste was not administered to the horses.

**Procedures**—The trial required 3 scheduled visits by veterinarians and examinations performed by veterinarians at the time of enrollment (baseline; day 0), middle of the study (day 7), and end of the study (day 14). At the time of enrollment, each investigator conducted a detailed physical and lameness examination, completed an enrollment form, and instructed the caregiver on proper drug administration and requirements of the study, including instructions for completing a form for recording the caregiver's daily interpretation of the horse's lameness status. Caregivers were then provided a 14-day supply of firocoxib paste for that horse. Firocoxib was administered at a dosage of 0.1 mg/kg, PO, every 24 hours for 14 consecutive days1 (days 1 through 14). Examinations were conducted on days 7 and 14; on those days, the investigator repeated the lameness examination, completed a lameness evaluation form, and then asked the caregivers to provide an overall assessment of the horse's lameness. The lameness evaluation form had a space for additional comments by the veterinarians regarding observations or findings not included on the study form. During the assessment on day 7, investigators also ensured that each caregiver was completing the daily record (ie, lameness status form). At the conclusion of the study, investigators collected each caregiver's daily record and questioned the caregiver's impression of changes in the horse's lameness, palatability of the oral product, and ease or difficulty of product administration.

Investigators graded lameness using the American Association of Equine Practitioners scoring system6 from 1 (mild lameness) to 5 (severe). This system is based on whole numbers for each grade; however, some investigators graded horses in half-grade increments. For data analysis, half-grade increments were rounded up to the more severe lameness option (eg, a recorded grade of 2.5 became a grade of 3).

**Statistical analysis**—Descriptive statistics were completed for lameness scores recorded by veterinarians on days 0, 7, and 14 and for the changes between assessments. Because a placebo paste was not included in the present study; a transitional probability model was chosen to eliminate the potential for bias in the data analysis. The transitional probability model was used to quantify the transitional rate of lameness among the various lameness states and the mean persistence or duration of lameness in these states for the 14-day treatment period.2 This statistical method was chosen to characterize the recovery process for the population and how that process may vary with time. The model was a function of the beginning and the end lameness states (grades 1, 2, 3, or 4) and time. The model form used was as follows:

\[ F'(I,t) = -L(J,I,t), F(I,t) = F(I,0) = IC(I) \]

the initial number of horses with lameness grade 1
where \( F'(I,t) \) is the rate of increase in the number of horses in lameness state \( I \), \( F(I,t) \) is the number of horses in lameness state \( I \) at time \( t \), \(-L(J,I,t)\) is the time-varying fractional transfer rate (which accounts for the fact that recovery rate changes over time) of horses from lameness state \( J \) to lameness state \( I \) at time \( t \), \( I(t) \) is the number of horses (or occupancy) in lameness state \( I \) at time \( t \), and \( IC(I) \) is the initial number of horses in lameness state \( I \). Instantiating this equation, \(-L(J,I,t)\) for a change from lameness grade \( 2 \) to lameness grade \( 1 \) at time \( t \) would be the fractional transfer rate of horses improving from lameness grade \( 2 \) to \( 1 \) at time \( t \). Selection of the analytic form of the temporal component of the transitional probability parameters \(-L(J,I,t)\) was governed by parsimony and plausibility. It was important that no fractional transfer value became negative and that none became overly dependent on time. This statistical method meant that all horses go through each lameness grade in the process of reaching the final lameness state. In principle, it could be recorded or observed as having improved >1 lameness grade when, in actuality, the lameness grade between the recorded lameness scores was an unobserved event that must have taken place.

Estimates of the parameters for the various lameness scores were developed with the aforementioned equation, and the transitional probability model was used to quantitate the movement of horses entering with baseline lameness state \( I \) and progressing through the various lameness scores during the study period.

Data were analyzed by use of statistical software, and dynamic modeling software was used to develop and fit the transitional probability models. Values of \( P < 0.05 \) were considered significant.

**Results**

**Sample**—Eighty veterinary investigators in 25 states enrolled 467 horses, of which 390 met the criteria for inclusion in the statistical analysis (Figure 1). Data for lameness at the beginning and end of the study were available for 429 horses. Of these, 29 were disqualified because initial lameness grades were \(<2 \) or \( >4 \), and an additional 10 horses had a primary or concurrent lameness clearly unrelated to osteoarthritis (eg, muscle laceration, tendon or ligament injury, or other bone lesions not localized to a joint). Of the 390 qualifying horses, 135 (35.7%) had a starting lameness grade of 2, 160 (41.0%) had a starting lameness grade of 3, and 75 (19.2%) had a starting lameness grade of 4 (percentages do not sum to 100% because of rounding). No horses with grade 5 lameness were included in the study population.

Qualifying horses comprised 244 (62.6%) geldings, 129 (33.1%) mares, and 17 (4.4%) stallions. Horses ranged from 18 months to 32 years of age (mean, 13.3 years; median, 12.0 years), with 242 (242/390 [62.1%]) horses between 7 and 20 years of age. Measured or estimated body weight recorded for 389 horses ranged from 190 to 909 kg, and approximately half of the horses weighed \( \leq 300 \) kg. The 2 most commonly represented breeds were Quarter Horse and Thoroughbred, which together comprised greater than half of the study population. The remainder consisted of a variety of other breeds, which included Standardbred, Appaloosa, Tennessee Walking Horse, and crossbreds.

Osteoarthritis was diagnosed in a single joint in 197 (50.5%) horses and in multiple joints in 193 (49.5%) horses. Among those with involvement of a single joint, the tarsus (distal intertarsal and tarsometatarsal joints) was the most frequently affected joint (79 [40.1%] horses), followed by the metacarpophalangeal and metatarsophalangeal (fetlock) joints (40 [20.3%] horses), carpus (antebrachio carpal and middle carpal joints; 37 [18.8%] horses), stifles (femoropatellar, lateral femorotibial, and medial femorotibial joints; 15 [7.6%] horses), proximal interphalangeal joint (pastern; 10 [5.1%] horses), and distal interphalangeal joint (collar joint; 8 [4.1%] horses). In 4 (2.0%) horses, the distal sesamoid bone (navicular bone) was identified as the single site involved, and in the remaining 4 (2.0%) horses, the shoulder or hip joints were involved.

**Horses removed from the study**—Of the 467 enrolled horses that received at least 1 administration of firocoxib paste, 4 (0.9%) had adverse events that resulted in removal from the study. An 11-year-old warm-blood-crossbred horse developed edema of the lips and gums soon after the first dose of firocoxib was administered; the horse improved following treatment with flunixin meglumine and antihistamine but was immediately withdrawn from the study. A 9-year-old cross-bred mare developed several minor episodes of colic, which resulted in withdrawal before day 7. A 20-year-old Quarter Horse gelding with a long-term history of NSAID administration (phenylbutazone and naproxen) was removed on day 7 because of mild oral ulcers and an episode of colic that improved after treatment with flunixin meglumine. After removal of that horse from the study, the oral ulcers resolved without treatment. Finally, an 11-year-old Selle Français was removed on day 10 because of signs of lethargy and sedation.

Two caregivers each withdrew a horse because they did not observe improvement in the horse’s lameness. One of these was an 11-year-old Percheron-crossbred gelding with mild osteoarthritis of the metacarpophalangeal joint and a problem with the forelimb suspensory ligament. The horse, which was withdrawn from the study on day 10 because of signs of lethargy and sedation, resulted in removal before day 7. A 20-year-old Quarter Horse gelding with a long-term history of NSAID administration (phenylbutazone and naproxen) was removed on day 7 because of mild oral ulcers and an episode of colic that improved after treatment with flunixin meglumine. After removal of that horse from the study, the oral ulcers resolved without treatment. Finally, an 11-year-old Selle Français was removed on day 10 because of signs of lethargy and sedation.

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old Thoroughbred gelding with grade 4 lameness and involvement of the carpal joint. Subsequent to this horse’s withdrawal, it was determined that despite the mandated washout period, the horse had been receiving phenylbutazone up to the day before beginning firocoxib treatment.

**Caregiver responses**—Among the caregivers who responded to the questions concerning palatability (n = 420) and convenience of administration (422) of the firocoxib paste, 406 (406/420 [96.7%]) reported that it was palatable for their horse and 407 (407/422 [96.4%]) rated it as convenient to administer.

**Lameness improvement**—At the assessment on day 7, clinical investigators provided lameness grades for 389 horses. Of these, 275 (70.7%) had improvement in lameness of ≥1 grade and 3 (0.8%) had lameness that was worse. At the end of the study (day 14), 307 of 390 (78.7%) horses had improvement in lameness of ≥1 grade and 10 (2.6%) horses had lameness that was worse. From investigator ratings, improvements in lameness were significantly different from day 0 to 7, from day 0 to 14, and from day 7 to 14 (Table 1). At the assessment on day 7, caregivers rated 297 (297/390 [76.2%]) horses as improved, and by day 14, investigators assessed that lameness had improved in 316 (316/390 [81.0%]) horses. Among the caregivers who responded to the question, 87.6% reported an improvement of gait. The assessments of lameness by caregivers and veterinarians were similar on days 7 and 14.

**Results for the transitional probability model**—By use of the transitional model, the percentages of horses that improved from one lameness grade to the next lower grade per unit of time were calculated. There were too few horses with a starting lameness grade of 4 on day 0 to incorporate into the model. The transitional model established that 34 of 160 (21.3%) horses with grade 3 lameness transitioned to grade 2 lameness, 49 of 155 (31.6%) horses with grade 2 lameness transitioned to grade 1 lameness, and 7 of 75 (9.3%) horses with grade 1 lameness transitioned to no clinical lameness. The probability of an improvement of 1 lameness grade within a specific time was greatest for horses that initially had the most severe lameness (grade 3), as in—

### Table 1—Lameness score and changes in lameness scores as assessed by study investigators (ie, equine veterinarians) in horses with osteoarthritis that received firocoxib (0.1 mg/kg, PO, q 24 h for 14 days).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Day 0</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Days 0 to 7</th>
<th>Days 0 to 14</th>
<th>Days 7 to 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of horses</td>
<td>390</td>
<td>389</td>
<td>390</td>
<td>389</td>
<td>390</td>
<td>389</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2.78 ± 0.74</td>
<td>1.84 ± 1.06</td>
<td>1.50 ± 1.14</td>
<td>-0.95 ± 0.82</td>
<td>-1.29 ± 1.01</td>
<td>-0.34 ± 0.75</td>
</tr>
<tr>
<td>Median</td>
<td>3.00</td>
<td>2.00</td>
<td>1.00</td>
<td>-1.00</td>
<td>-1.00</td>
<td>0</td>
</tr>
<tr>
<td>Range</td>
<td>2.00 to 4.00</td>
<td>0 to 4.00</td>
<td>0 to 4.00</td>
<td>-4.00 to 1.00</td>
<td>-4.00 to 2.00</td>
<td>-2.00 to 3.00</td>
</tr>
<tr>
<td>P value*</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Improvement in lameness (No. [%] of horses)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>275 (70.5)</td>
<td>307 (78.7)</td>
<td>358 (41.3)</td>
</tr>
</tbody>
</table>

*Results represent the P value determined with the Wilcoxon signed rank test. †For days 7 to 14, results represent horses in which the lameness was the same or there was improvement.
dictated by the slope of the line for the transition from grade 3 to grade 2 (Figure 4). These recovery data and the percentages per unit of time allowed a projected recovery trajectory to be created, and the estimated rate of improvement of horses could be plotted. Analysis of the resulting projected recovery graph obtained by plotting data from horses with a starting lameness grade of 3 suggested a rapid initial progression (improvement) to the next lower lameness grade after treatment commenced. The model estimated that full recovery (no clinical lameness) for horses began within 2 days after administration of firocoxib, with one-third of horses having no lameness after treatment for 14 consecutive days. The slope of the line for improvement from grade 3 to grade 2 indicated that more horses would be likely to progress from grade 1 to fully recovered (no lameness), whereas the slope of the line for the most severe lameness indicated that few horses that did not respond by day 7 would respond by day 14.

Results for the model indicated a continuation of improvement between days 7 and 14. The transitional probability model revealed rapid initial improvement from treatment initiation to day 7, followed by a slower rate of improvement during the second half of the treatment period (ie, days 7 to 14).

Improvement was detected regardless of the starting lameness grade. Approximately 80% of horses within each grade had improvement by the end of the treatment period (ie, days 7 to 14).

Figure 4—Projected recovery trajectory for horses with a starting lameness grade of 4. The lines are model predictions for recovery, and the dots are the actual number of horses in each of the recovery lameness grades (ie, 1, 2, or 3). Improvement of horses to lameness grade 3 is complete by approximately 6 days. Improvement to lameness grades 2 and 1 follows an almost linear trajectory, with improvement to grade 2 having the more rapid increase. The more rapid increase indicates that horses were transitioning to grade 2 more quickly than they were to grade 1 (grade 1 was considered full recovery from lameness). Day 0 is the day before treatment with firocoxib was initiated; firocoxib was administered on days 1 through 14.

Figure 5—Schematic diagram of the transitional probability model describing the improvement of horses entering the present study with a starting lameness of grade 3 and progression through lameness grades (numbered ovals) during oral treatment with firocoxib. In the model, L(J,I,t) is the time-varying fractional transfer rate (which accounts for the fact that recovery rate changes over time) of horses from lameness grade J to lameness grade I at time t. For the 155 horses of the study, the value for L(3,2,t), which indicates a change from lameness of grade 3 to lameness of grade 2, was 42.3%/d on day 0 and 7.1%/d by day 7. In contrast, L(2,1,t), which indicates a change from lameness of grade 2 to lameness of grade 1, was approximately 5%/d by day 7 and 21%/d by day 14.

Table 2—Summary of parameters for grade 3 and 4 lameness scores.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter or function</th>
<th>Value or functional form</th>
<th>Function dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial lameness grade</td>
<td>IC(3)</td>
<td>157</td>
<td>NA</td>
</tr>
<tr>
<td>No. of transition</td>
<td>L(3,2)</td>
<td>0.4228 ± 0.0259</td>
<td>*G(3)</td>
</tr>
<tr>
<td>Probability rates</td>
<td>L(2,1)</td>
<td>0.0269 ± 0.0024</td>
<td>*G(1)</td>
</tr>
<tr>
<td>Ancillary parameters</td>
<td>P(3)</td>
<td>0.1170 ± 0.0238</td>
<td>NA</td>
</tr>
<tr>
<td>Probability rates</td>
<td>P(2)</td>
<td>0.2735 ± 0.0024</td>
<td>NA</td>
</tr>
<tr>
<td>Ancillary equations</td>
<td>G(1)</td>
<td>1 + P(1)*T</td>
<td>L(2,1,T) = L(2,1)*G(1)</td>
</tr>
<tr>
<td></td>
<td>G(2)</td>
<td>e^(-G(1)*T)</td>
<td>L(3,2,T) = L(3,2)*G(2)</td>
</tr>
<tr>
<td>Initial lameness grade</td>
<td>IC(4)</td>
<td>157</td>
<td>NA</td>
</tr>
<tr>
<td>No. of transition</td>
<td>L(4,3)</td>
<td>0.2131 ± 0.0048</td>
<td>*G(3)</td>
</tr>
<tr>
<td>Probability rates</td>
<td>L(3,2)</td>
<td>0.1382 ± 0.0038</td>
<td>*G(4)</td>
</tr>
<tr>
<td>Probability rates</td>
<td>L(2,1)</td>
<td>0.0944 ± 0.0023</td>
<td>*G(4)</td>
</tr>
<tr>
<td>Ancillary parameters</td>
<td>P(3)</td>
<td>-0.0399 ± 0.0022</td>
<td>NA</td>
</tr>
<tr>
<td>Probability rates</td>
<td>P(4)</td>
<td>-0.0678 ± 0.0021</td>
<td>NA</td>
</tr>
<tr>
<td>Ancillary equations</td>
<td>G(3)</td>
<td>1 + P(3)*T</td>
<td>L(4,3,T) = L(4,3)*G(3)</td>
</tr>
<tr>
<td></td>
<td>G(4)</td>
<td>1 + P(4)*T</td>
<td>L(3,2,T) = L(3,2)*G(4)</td>
</tr>
</tbody>
</table>

IC(j) is the number of horses with the initial lameness grade j for IC(3) and grade 4 for IC(4). L(J,I,j) is the time-varying fractional transfer rate (which accounts for the fact that recovery rate changes over time) of horses from lameness state J to lameness state I; thus, L(3,2) indicates a change from lameness grade 3 to lameness grade 2, L(2,1) indicates a change from lameness grade 2 to lameness grade 1, and L(4,3) indicates a change from lameness grade 4 to lameness grade 3. *P(x) converts L(J,I,j), which is a constant, to L(J,I,t), which is a time-varying transition probability. G(x) is the lameness grade; therefore, G(1), G(2), G(3), and G(4) indicate lameness grades 1 through 4, respectively. P(x) is ancillary parameters; therefore, P(1), P(2), P(3), and P(4) indicate ancillary parameters 1 through 4, respectively. T is time. RMS is the gradewise estimate of the residual mean square for the fit to lameness models developed in conjunction with the admission of horses with lameness state I. NA = Not applicable.
study. Complete resolution of lameness was detected in 28 of 78 (36.0%) horses that started with grade 2 lameness but in only 21 of 155 (13.5%) horses that started with grade 3 lameness and 9 of 157 (5.7%) horses that started with grade 4 lameness. Even in the most severely affected group (lameness grade 4), improvement of ≥ 2 lameness grades was reported in more than half of that study group (38/75 [50.7%] horses). Dynamic modeling of the lameness data from the 3 assessments revealed good agreement between the model and the observational data. The fitted transitional probability models in which the initial number of horses with lameness grade 1 denoted the initial occupancy state for the 2 lameness grades were summarized (Table 2; Figure 5). Transitional probability rates provided estimates (values and errors) for each model. Ancillary parameters provided estimates of the parameters and errors of the time-varying components of the transitional probability models. Ancillary equations provided the analytic form for the time-varying component of each transitional probability model.

Discussion

Several aspects of the methods used in the study reported here must be addressed. The first is the absence of a negative control group. The benefits of placebo or placebo-like treatments administered to humans have been reported; as a result, clinical field studies often include a placebo control group that receives a treatment with no expected therapeutic effect. Thus, inclusion of a placebo group in a study is intended to help separate an observed clinical response into placebo and treatment components. In consideration of this point, our conclusions were based on the clinical improvement detected after starting the treatment, rather than assigning the response only to the treatment. Therefore, the design reflected the response that might be expected in any clinical situation, which is likely attributable to a combination of treatment and placebo effects. To minimize the effect of a lack of a control group on the outcome, the study was designed to be performed at multiple centers by a large number of veterinarians and caregivers as separate evaluators and incorporated a transitional probability model to eliminate the potential for bias in the analysis.

Another aspect of the study design that should be considered is that the medication was provided to the caregivers at no cost. It is our impression that this second aspect is counterbalanced by 2 competing considerations. One is that free product would favorably exacerbate any placebo effect. Alternatively, with no financial stake in the product, there would be no need for the investigators or horse caregivers to have an investment in the results, which could make their assessments less favorable. Nonetheless, an accurate measure of the effect of free product cannot be easily or completely resolved but is another factor for readers to consider.

Firocoxib oral paste was tolerated well by most horses of the present study when used daily for 14 days to attenuate lameness. For the lameness grades used in the present study, there were only 10 horses in which lameness worsened. Therefore, only recovery, or forward progression through lameness grades, was incorporated into the model, with no regressive transitions. More than three-fourths of treated horses had improvement in lameness, as determined on the basis of caregiver and veterinarian assessments and records, which supported our hypothesis that lameness scores would improve from the baseline grade after treatment with a COX-2–specific NSAID for 14 days.

Safety is a concern with NSAID use in horses, and results of the present study were in agreement with those of another study in which investigators found that firocoxib has a low risk of adverse effects in horses when used as prescribed (0.1 mg/kg, PO, q 24 h). Adverse events were detected in only 4 of 467 (0.9%) horses that received firocoxib in the study reported here. Similar to results of the other study, the adverse events were all considered mild and resolved after discontinuation of the medication.

As a further point of reference, in another study that involved > 1,000 dogs administered firocoxib, the withdrawal rate associated with adverse effects was 2.9%, and this withdrawal rate was not significantly different between dogs that had been receiving another NSAID before the trial and those that had not. No serious illness or deaths directly attributable to firocoxib were reported in that study, which involved daily administration for a period of 40 days.

Overall, approximately 80% of the present study population had improvement in lameness, lameness score, or qualitative degree of comfort and mobility. In general, improvement was consistent, regardless of sex, breed, age, body weight, location and number of joints affected by lameness, and starting lameness grade. However, several interesting patterns were detected. Perhaps not surprisingly, there was typically less improvement in lameness in heavier horses (> 636 kg) and older horses (> 20 years).

The results for the transitional model may provide a basis for developing estimates of improvement after starting treatment with firocoxib. Important features of this model include that it provides group-level as opposed to subject-level modeling, permits the exploration of time-varying recovery rates, allows for state-space probability transitional modeling, allows management of smaller data sets of information, adjusts for the lack of a placebo-controlled study, and enables evaluation beyond the ordinary application of kinetics. Furthermore, no subject can skip a lameness grade (improvement or worsening of lameness) during treatment administration. Finally, the clinical assessment of lameness is accurate and consistent. For example, analysis of the data indicated that approximately 1 in 5 horses with a starting lameness grade of 3 will improve to a lameness grade of 2 with each day of treatment. The finding that horses that weigh less (< 636 kg) and are younger (< 20 years) might respond more quickly than would horses that weigh more and are older indicated that horses that weigh less and are younger are more likely to have earlier improvement in lameness. In horses that began the study with a lower grade of lameness, improvement was slower and it was difficult to differentiate improvement for horses that started with a grade 2 lameness from those that began with a grade 3 lameness. Clearly, other factors, such as rest and the amount and type of activity performed by a
horse as well as the severity of the osteoarthritis, need to be considered for individual horses. Nonetheless, complete recovery of some horses began within 2 days after starting treatment, and one-third of treated horses were not clinically lame after treatment with firocoxib for 14 days.

Another interesting pattern detected in the data of the study reported here was the continuation of improvement between days 7 and 14. One would expect that if the lameness were primarily caused by inflammation, improvement would be seen within the initial days after starting treatment, perhaps even after the first dose. Beyond that, it could be reasoned that continued use might not be associated with further gains in comfort or mobility. Plasma firocoxib concentrations considered sufficient to suppress at least 50% of COX-2 activity are achieved in horses within 8 hours after a single orally administered dose of firocoxib (0.1 mg/kg). In a clinical study of horses with chronic lameness attributed to osteoarthritis, significant improvement in lameness score and peak vertical force when trotting over a force plate was detected within 10 hours after the first dose of firocoxib. Furthermore, repeated oral administration of firocoxib at 24-hour intervals maintains a therapeutic plasma concentration for the duration of treatment. Thus, it appeared unlikely that the observed improvement between days 7 and 14 in the present study was attributable solely to a sustained anti-inflammatory effect.

An explanation for continued improvement is the time to achieve peak plasma firocoxib concentrations or the structural and functional changes to pain pathways that are commonly found in chronic pain states, including arthritis. In the specific case of firocoxib, plasma steady-state concentrations with daily oral administration are not reached until day 7, and at steady state, the drug’s half-life in horses is >36 hours; thus, the peak plasma concentration after 7 or 12 daily doses is higher than that after the first dose. However, in the aforementioned study in which investigators used force plate analysis at 10 hours after treatment, there was no significant benefit in the osteoarthritis during the time the firocoxib was administered, but this could not be determined from the data collected in the study reported here.

It must also be mentioned that the opposite pattern (worsening of lameness between days 7 and 14) was detected in a small number of horses. Five horses that had major improvement (2 to 3 lameness grades) by day 7 had dramatically worse lameness at the end of the study reported here. This phenomenon has been reported in a previous study on pain control and activity of human athletes, especially those with early osteoarthritis. It appears that effective pain management allows a greater amount of activity, including activity beyond the patient’s current level of fitness and muscle tone. This observation highlights the importance of client education whenever one is initiating pain control. Owners of horses with osteoarthritis should be directed to control their horse’s activity for the first few weeks after initiating treatment in an effort to reduce the risk of overexertion and potential further injury to joints and other supporting structures weakened by chronic disease. A plan for physical therapy that gradually strengthens and returns the muscles and connective tissues to full function in a controlled manner is advised.

We detected good agreement between assessments of clinical investigators (veterinarians) and caregivers on days 7 and 14, although typically, the clinical investigators were slightly less inclined to designate a horse as improved than were the caregivers. Agreement between the assessment by the veterinarians and caregivers was high at an overall rate of 44.1% versus what would routinely be an expected agreement rate of only 22.9%. The higher-than-expected agreement between veterinarians and caregivers was surprising because lameness scoring was performed separately; we do not have an explanation for this finding. For 42 horses, the caregivers rated the horse as improved, whereas the clinical investigators recorded the lameness as unchanged or worse between days 0 and 14. Also interesting was the fact that a greater percentage of caregivers reported that the horse was moving better at the end of the study (87.6% of respondents) than the percentage who rated the horse as improved (81.0%) when required to rate the response to treatment as good, very good, or excellent. Horse owners, trainers, and other caregivers seemed to take quality of life into consideration when evaluating treatment effectiveness, which may help to explain the good compliance with treatment throughout the study.

It is worthwhile to mention the limits of a 14-day treatment period. Firocoxib is approved for treatment for up to 14 days; however, with a chronic and pain-inducing condition such as osteoarthritis in horses, most owners do not want to discontinue treatment at

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the end of a 14-day period, particularly if a horse has responded well to the drug. Many horses with moderate to severe osteoarthritis require an NSAID or other analgesic medication for a longer duration; many or some of them may require it for the rest of their lives. Thus, long-term safety and efficacy studies of oral firocoxib in horses are needed.

For the study reported here, we concluded that administration of firocoxib paste (0.1 mg/kg, PO, q 24 h) significantly improved lameness scores and comfort and mobility in most horses treated because of naturally occurring osteoarthritis. Improvement was detected within the first 7 days after starting treatment, and typically the improvement continued, albeit at a slower rate, between days 7 and 14 of treatment. Adverse effects were infrequent (< 1% of horses); they were mild and resolved after discontinuation of the drug. Palatability and convenience of use were rated high by the caregivers who administered the drug daily to the horses during the study.

References