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The pharmacokinetics of mavacoxib, a long-acting COX-2 inhibitor, in young adult laboratory dogs

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The pharmacokinetics of mavacoxib were evaluated in an absolute bioavailability study, a dose-proportionality study and a multi-dose study in young healthy adult laboratory Beagle dogs and in a multi-dose safety study in Beaglesized laboratory Mongrel dogs. When administered as the commercial tablet formulation at 4 mg/kg body weight (bw) to fasted dogs, the absolute bioavailability (F) of mavacoxib was 46.1%; F increased to 87.4% when mavacoxib was administered with food. Following intravenous administration, the total body plasma clearance of mavacoxib was 2.7 mL·h/kg, and the apparent volume of distribution at steady-state was 1.6 L/kg. The plasma protein binding of mavacoxib was approximately 98% in various in vitro and ex vivo studies. The dose-normalized area under the plasma concentration-time curve was similar in Beagle and Beagle-sized Mongrel dogs when mavacoxib was administered with food. Mavacoxib exhibited dose-proportional pharmacokinetics for single oral doses of 2-12 mg/kg in Beagle dogs and for multiple oral doses of 5-25 mg/kg in Beagle-sized Mongrel dogs. Only minor accumulation occurred when mavacoxib was administered at doses of 2-25 mg/kg bw orally to laboratory dogs with a 2-week interval between the 1st two doses but with a monthly interval thereafter. Across all three Beagle studies (n = 63) the median terminal elimination half-life $(t_{\frac{1}{2}})$ was 16.6 days, with individual values ranging 7.9–38.8 days. The prolonged $t_{\frac{1}{2}}$ for mavacoxib supports the approved regimen in which doses are separated by 2-4 weeks.

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INTRODUCTION

Market research demonstrates that about 20% of all dogs are presented at some time during their life with clinical signs of osteoarthritis (OA) at veterinary practices (Johnston, 1997). Over the last 15 years nonsteroidal anti-inflammatory drugs (NSAIDs) have become the choice of treatment to control pain and inflammation associated with OA (Sanderson *et al.*, 2009). Most of these NSAIDs have relatively short plasma elimination half-lives and require once a day or twice a day dosing. These daily medicines are predominantly administered to control so-called flare-ups (i.e. episodes of acute pain associated with OA). It is postulated that continuous control of pain and inflammation will increase the functionality of the OA affected joints (Pelletier *et al.*, 2000; Fiorentino *et al.*, 2008). Mavacoxib (TrocoxilTM) is a member of the coxib class of cyclooxygenase-2 (COX-2) inhibitors. It is approved in the European Union for the treatment of pain and inflammation in canine OA where continuous treatment exceeding 1 month is indicated. The approved dosing regimen consists of a loading dose of 2 mg/kg bw to be repeated after 14 days, thereafter the dosing interval is 1 month. Chemically, mavacoxib is described as 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide and the chemical structure of the molecule can be generically termed as a diarylsubstituted pyrazole. Mavacoxib is structurally related to celecoxib (Penning *et al.*, 1997). The primary locus of metabolism in dogs for celecoxib is a metabolically labile aromatic methyl substituent (Paulson *et al.*, 2000), which has been replaced in mavacoxib with a metabolically stable fluoro substituent. This change resulted in a

compound with low clearance and a prolonged $t_{\frac{1}{2}}$ (Pfizer internal data). The molecular structures of mavacoxib and celecoxib are illustrated below:



This study describes four pivotal laboratory dog studies that were performed to support the registration of mavacoxib, as well as a study to assess the *in vitro* plasma protein binding of mavacoxib. Of the four dog studies, three were pharmacokinetic studies in Beagle dogs, and the fourth study was a safety study with a toxicokinetic component in Mongrel dogs. Studies on disposition and metabolism of mavacoxib, and on the population pharmacokinetics of mavacoxib are described elsewhere (Cox *et al.*, 2010; Hummel *et al.*, 2010).

MATERIALS AND METHODS

Dog studies

The pharmacokinetic studies utilized parallel group study designs, in part, because the long $t_{\frac{1}{2}}$ of the compound resulted in an impractical washout period for crossover studies. The laboratory Beagle and Mongrel dog studies were conducted in compliance with Good Laboratory Practice (OECD, 1998) standards. In each study there were 8–10 dogs per group. Objectives of the studies are listed below.

Study 1: to determine the absolute bioavailability and the effect of feeding on bioavailability following single oral administration at a nominal dose of 4 mg/kg bw; with separate groups for intravenous administration, fed administration and fasted administration.

Study 2: to assess the dose-proportionality at nominal single oral doses of 2, 4, and 12 mg/kg bw.

Study 3: a single group study to evaluate the multiple-dose pharmacokinetics following oral administration of a nominal dose of 4 mg/kg bw on study days 0, 14, 42, and 70.

Study 4: to assess safety in Mongrel dogs treated orally with seven doses of mavacoxib on study days 0, 14, 42, 70, 98, 126, and 154 at nominal dosages of 0 (placebo), 5, 15, and 25 mg/kg bw. The toxicokinetic data from the study are discussed in this article, but safety aspects of this study are reported elsewhere (Krautmann *et al.*, 2010).

The dogs in these studies were intact, experimentally naïve, and an equal mix of males and females with predose (before 1st dose for the multiple-dose studies) body weights ranging 5.5–14.2 kg for the Beagle dogs and 5.3–13.8 kg for the

Mongrel dogs. The dogs were generally young adults, with ages for the Beagle dogs on the first day of dosing ranging from approximately 12-26 months. The corresponding median age of the Mongrel dogs was 24 months, with ages of 21 of the 24 dogs ranging from approximately 14-44 months. Three female Mongrel dogs in the safety study were older, with ages of 73-93 months. Before inclusion of dogs in any of the studies, the dogs were judged by the attending veterinarians to be in excellent general health based on physical examination and the results of haematology, clinical chemistry and coagulation-time tests. General health observations were performed at least daily during all of the studies. In addition, the dogs and cages were observed after each dosing event for signs of emesis. Treatment of the dogs was in accordance with regulations outlined in the USDA Animal Welfare Act (9 CFR parts 1, 2, and 3) and the conditions specified in Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington, DC, 1996). Before the initiation of the studies, the protocols, amendments or procedures involving the care or use of the dogs were reviewed and approved by Institutional Animal Care and Use Committees.

Mavacoxib was administered as the commercial oral tablet formulation with tablet strengths ranging between 6 and 120 mg. The mavacoxib dosage was based on each dog's bw, which was generally collected on either the day before dosing or the morning of dosing. For the oral treatments in the Beagle dog studies, 1 or 2 tablets were administered by hand by placing the tablets near the back of the mouth. The dose was immediately followed by approximately 10-20 mL tap water to facilitate passage of drug to the stomach. Intact tablets were administered to the Beagle dogs except for one instance when a dog with a relatively light body weight was assigned to receive 2 mg/kg in the dose-proportionality study and a 30 mg tablet was split and shaved to achieve the desired dose. Across all of the Beagle dog studies, the actual range of doses receiving the nominal 4 mg/kg oral dose was 3.88-5.45 mg/kg bw. In the dose-proportionality study, the actual doses with nominal doses of 2 and 12 mg/kg ranged 1.92-2.87 and 11.2-14.6 mg/kg, respectively. In the safety study with Mongrel dogs, various combinations of tablets were administered to the dogs, so that the actual doses were within the range of -5.6% to +2.9% of the nominal doses. On one occasion in the safety study, a subject was re-dosed with a tablet that was expelled in vomit within 20 min of drug administration. In the absolute bioavailability study (study 1), the reference intravenous solution contained mavacoxib 6 mg/mL in a vehicle containing PEG 400^{1} : normal saline (80:20 v/v) and was administered into a cephalic vein over approximately 1 min.

Except for the assessment of the effect of food on bioavailability in study 1, the subjects in the Beagle dog studies were fasted overnight prior to dosing and fed at approximately 4 h postdose. To maximize systemic drug exposure in the safety study (study 4), the subjects were allowed access to food within approximately 1–2 h before each dose. In all four studies, the dogs were acclimated for 14–39 days before the start of the studies. For

¹Polyethylene glycol, average molecular weight 400.

study 1 (the absolute bioavailability study), the dogs became acclimated to having their food ration being available for only 1 h each morning. Food consumption was monitored and by the end of the acclimation phase all dogs assigned to the fed treatment were judged to consume at least 50% of their food during the 1 h of availability. When mavacoxib was administered with food in this study, 50% of the dogs' daily food ration was presented to the dogs at approximately 1 h before drug administration and the remainder of their food was presented ad libitum immediately after dosing. The food provided to the dogs in all of these studies was Certified Canine Diet no. 5007 (PMI Feeds Inc, St. Louis, MO, USA), which contained $\geq 25.0\%$ crude protein and $\geq 9.0\%$ crude fat. Water was provided ad libitum. Serial blood samples (2 mL) were collected for mayacoxib plasma concentrations before dosing and at repeated intervals after dosing from each dog via jugular venipuncture with K3EDTA as the anticoagulant. In the single-dose studies (i.e. studies 1 and 2), blood samples for mavacoxib plasma concentration determination were collected for 70-84 days after dosing, with 6-8 samples in the 1st 24 h, eight samples at 2-28 days postdose, and then sampling every 2 weeks until the end of the studies. In the multiple-dose Beagle dog study 3, the blood samples were similarly collected throughout each of the first three dosing intervals and during the 70 days after the last (4th) dose, with 12–17 postdose blood samples for each dose. In multiple-dose safety study 4, serial blood samples were collected throughout the 182 day in-life portion of the study, but the blood sampling scheme was necessarily more limited in this study than in the Beagle dog studies. For the 1st dose, the blood samples were collected predose and at 1, 7, and 14-days postdose. For the subsequent doses, the blood samples were collected at 1, 7, 14, and 28 days postdose.

Analytical methodology

The plasma samples were analyzed for mavacoxib content by high performance liquid chromatography (HPLC) with tandem mass spectrometry detection (LC-MS/MS). In this assay, 100 μ L plasma was fortified with the internal standard (4H²-mavacoxib) and mixed with 200 μ L acetonitrile to precipitate plasma proteins. The acetonitrile extract (20 μ L) was injected onto a gradient HPLC system with a Zorbax Extend C18 column (5 μ m particle size, 2.1×50 mm) with a Phenomenex Security Guard cartridge. The mobile phase flow rate was 0.3 mL/min and the initial mobile phase was 5 mM ammonium formate buffer: 5 mM ammonium hydroxide in acetonitrile (90:10 v:v). The mobile phase was changed to 100% 5 mm ammonium hydroxide in acetonitrile over 0.50 min and held there for an additional 2.0 min. Detection was accomplished with a PE Sciex API 3000 with Turbo-Ion Spray source, negative ions monitored in MRM mode with Precursor \rightarrow Product ion pairs for mavacoxib of $384.0 \rightarrow 319.758$ and for the internal standard of $388.0 \rightarrow 324.355$. The limit of detection for mavacoxib was 1.6 ng/mL, and the calibration range of the assay was 5.0 ng/mL (the lower limit of quantification) through at least 2000 ng/mL. Quality control samples at three mavacoxib concentrations (generally 50, 500, and 2000 ng/mL) were included in each analytical run. In validation work for the assay, the mean relative errors of the assay ranged from -6.0 to -0.8% and the precision ranged 1.8-5.1%. For the assays conducted to support the mavacoxib dog studies, the mean relative errors of the quality control samples ranged from -0.2% to 3.4% and coefficients of variation were $\leq 3.9\%$. Stability of mavacoxib was demonstrated in plasma for up to 192 days when stored at ≤ -10 °C and for at least 58 h when stored at room temperature.

Pharmacokinetic analysis

Noncompartmental pharmacokinetic analysis of the concentration data was performed with Watson LIMS, v6.4.0.04 (Thermo Scientific, Philadelphia, PA, USA). Pharmacokinetic variables estimated for the single-dose oral treatments were the observed peak plasma mavacoxib concentration (C_{max}) , the time of the peak concentration (t_{max}) , area under the plasma concentration-time curve through the time of the last quantifiable concentration (AUC_t) , total extrapolated area under the plasma concentration-time curve (AUC_w), the terminal elimination rate constant (λz), and terminal elimination half-life ($t_{1/2}$). In the multi-dose studies, the pharmacokinetic variables calculated for each dosing interval were the area under the plasma concentration-time curve over the dosing interval (AUC_{τ}), C_{max}, t_{max} and the trough concentration at the end of the dosing interval (C_{τ}) . The AUC_t and AUC_t values were calculated with linear trapezoidal rule, and the extrapolation of AUC_t to obtain AUC_{∞} was performed using the observed concentration at the last time point. Estimates of λz and $t_{\frac{1}{2}}$ were collected in the multi-dose study in Beagle dogs from the concentrations at extended time points after the last dose. Additional pharmacokinetic variables calculated from the intravenous treatment of the absolute bioavailability study were the total body plasma clearance (CLiv), mean residence time (MRT) and apparent volume of distribution at steady-state (Vss).

Statistical design of studies and analysis

In the absolute bioavailability and dose-proportionality studies in Beagle dogs (studies 1 and 2) and the multi-dose safety study in Mongrel dogs (study 4), the dogs were blocked within sex based on body weight and cage location, and randomly assigned to a treatment or dose group. For the multiple-dose study in Beagle dogs (study 3), no randomization was required. The plasma mavacoxib concentration data were normalized to the nominal dose for the treatment, log-transformed and modeled statistically using an appropriate mixed linear model that accounted for the fixed and random factors and their interactions for each study. Back-transformed least squares (LS) mean were reported for each sample time. A minority of Beagle dogs had postdose dosenormalized concentrations below the lower limit of quantification (BLQ, 5 ng/mL), and the BLQ values were coded in this statistical analysis of the concentration data as half of the lower limit of quantification.

Least squares mean and 95% confidence intervals (CI) of the pharmacokinetic variables were estimated with statistical models analogous to those used for the concentrations. The C_{max} and *AUC* variables were log-transformed, and t_{ν_2} was inversely transformed before analysis, and the back-transformed LS mean and 95% *CI* were reported for each group. The absolute bioavailability of the oral treatments in the absolute bioavailability study was estimated from log-transformed AUC_{∞} by taking the difference between the LS mean log-values of the oral treatments and the intravenous treatment. The LS mean differences of the log-values and their 90% *CIs* were back transformed to provide the bioavailability estimates.

To test for dose-proportionality (studiers 2 and 4), an assumption for the statistical analysis was that the logarithm of the pharmacokinetic variables (AUC_t , AUC_∞ , AUC_τ , C_{max} , C_τ) was proportional to the logarithm of the dose. The following model was fit to the data for the pharmacokinetic variables:

Log2(Y) = $\alpha + \beta \cdot \text{Log2}(\text{dose})$, which after back-transformation gives Y = $2^{\alpha} \cdot \text{Dose}^{\beta}$, where Y is the pharmacokinetic variable, α is dependent on other terms in the model and β is the proportionality constant and under dose-proportionality is equal to 1. The statistical model included fixed effect terms such as log2(dose) and sex, and random effect terms such as block. The β parameter was estimated and a 90% *CI* determined. A test for lack of fit of the linear model was conducted by including an additional term for a quadratic dose effect; this term was dropped from the model to test for dose-proportionality. Dose-proportionality was concluded if the 90% *CI* on the estimate of β included 1 and the test for lack of fit was not significant (P > 0.05).

Data for $t_{\frac{1}{2}}$ were pooled from all of the Beagle dog studies (n = 63 dogs), and a histogram for the distribution of the $t_{\frac{1}{2}}$ values was prepared. All of the statistical calculations were performed using SAS, version 8.2 or 9.1 (SAS Institute Inc., Cary, NC, USA).

In vitro and ex vivo plasma protein binding of mavacoxib

Equilibrium dialysis studies were performed using a 96-well equilibrium dialysis apparatus (HTDialysis, LLC, Gales Ferry, CT, USA) with Spectra/Por membranes (12 000-14 000 molecular weight cut off). The plasma protein binding of mavacoxib was determined with a variety of samples: (i) control canine plasma samples fortified with mavacoxib, (ii) single postdose samples from 20 Mongrel dogs in study 4, and (iii) single trough samples from 26 mixed-breed osteoarthritic dogs in a field trial receiving a nominal mavacoxib dose of 4 mg/kg bw. Details of the field trial are reported elsewhere (Payne-Johnson et al., 2009). All of these samples had been subjected to at least one freeze-thaw cycle before assessment of plasma protein binding. The plasma samples (150 μ L) were added to the donor chamber, and the opposite chamber contained 150 μ L of 0.01 M phosphate buffered saline, pH 7.4 (PBS). Dialysis was performed at approximately 37 °C with shaking in a humidified incubator for 4 h. Following dialysis, 75 μ L aliquots from both buffer and plasma chambers were assayed for mavacoxib content by an LC/MS/MS procedure modified from the plasma procedure. In preliminary work, the time to reach equilibration was assessed by monitoring the mavacoxib concentrations in both chambers separated by a membrane. In this work, dog plasma was fortified with 2 μ g/mL mavacoxib and dialyzed against PBS for times ranging 0–24 h. Studies were also performed to estimate recovery of mavacoxib from the dialysis apparatus. In the recovery studies, mavacoxib concentrations ranging 0.1–10 μ g/mL in either PBS or plasma were placed in both chambers of the apparatus and dialyzed for 4 h.

The recovery of the mavacoxib from the dialysis cells was estimated using the following equation:

$$\% \text{Recovery} = \frac{C_{\text{donor}} + C_{\text{acceptor}}}{C_{\text{donor}}(0)} \times 100$$

where: $C_{\text{donor}} = Concentration$ in the donor chamber after dialysis

 $C_{acceptor}$ = Concentration in the acceptor chamber after dialysis $C_{donor}(0)$ = Concentration in the donor chamber prior to dialysis

The percent of binding to plasma proteins was calculated as shown in the equation below:

% Protein binding =
$$\frac{C_{\text{donor}} - C_{\text{acceptor}}}{C_{\text{donor}}} \times 100$$

For each plasma sample, protein binding was determined in triplicate and mean and standard error were reported.

RESULTS

Beagle dog study 1 (absolute bioavailability study)

No adverse drug experiences were noted during the study. LS mean plasma mavacoxib concentration data from the study are shown in Fig. 1. Several dogs had multiple peaks in their plasma mavacoxib concentration—time profiles, even after intravenous administration, and the LS mean concentration data in Fig. 1 were generally consistent with the profiles of individual dogs. The secondary peaks were most pronounced at 5 days postdose,



Fig. 1. Least squares mean plasma mavacoxib concentration data from study 1, the absolute bioavailability study.

 Table 1. Mavacoxib pharmacokinetic variables from study 1, the absolute bioavailability study

Variable	Treatment	n	LS mean (95% CI)	Range of individual values
$AUC_t (\mu g \cdot h/mL)^*$	i.vFasted	10	1420 (1150, 1760)	818-1790
	Oral-Fasted [†]	10	643 (521, 793)	297-1120
	Oral-Fed	10	1240 (1000, 1530)	973-1990
$AUC_{\infty} (\mu g \cdot h/mL)^*$	i.vFasted	10	1480 (1190, 1850)	822-1890
	Oral-Fasted [†]	10	683 (548, 852)	303-1190
	Oral-Fed	10	1290 (1040, 1610)	983-2480
$C_{\rm max}^*$ (µg/mL)	i.vFasted	10	3.12 (2.60, 3.74)	2.56-3.78
	Oral-Fasted [†]	10	1.04 (0.87, 1.25)	0.57-1.90
	Oral-Fed	10	2.46 (2.05, 2.95)	1.94-3.09
$t_{\nu_2}^{\dagger}$ (days)	i.vFasted	10	17.3 (15.0, 20.5)	11.5-25.4
	Oral-Fasted	10	19.3 (16.5, 23.4)	15.2-33.1
	Oral-Fed	10	15.5 (13.6, 18.0)	9.6-38.6
t_{\max} (h)	i.vFasted	10	0.55 (-25.3, 26.37)	0.17-4.00
	Oral-Fasted	10	67.40 (41.58, 93.22)	2.00-120.0
	Oral-Fed	10	17.40 (-8.42, 43.22)	1.00-120.0

 C_{max} and *AUC* variables were normalized to the nominal 4 mg/kg bw dose for the treatments. [†]For these parameters, the treatment effect was statistically significant (P < 0.001) and the Oral-Fasted value was significantly different than the values from the other treatments (P < 0.001), but the values from the i.v.-Fasted and Oral-Fed treatments were not statistically significant (P > 0.05). [‡]No significant treatment effect on t_{V_2} (P > 0.05).

and there was no indication that these late peak concentrations were analytical artifacts.

Least squares mean pharmacokinetic variables for the study are listed in Tables 1 & 2. The blood sampling scheme was adequate to characterize AUC_{∞} , as judged by mean extrapolation beyond AUC_t for the three groups of <6%. The LS mean absolute bioavailability (90% CI) of mavacoxib when administered to fasting and fed dogs was 46.1% (33.6-63.2%) and 87.4% (63.7-119.7%), respectively. Based on AUC_∞, administration of mavacoxib with food resulted in an LS mean increase in relative bioavailability of 89.5%, with a 90% CI of 38.3-159.8% (P < 0.001). Administration of mavacoxib with food significantly increased mavacoxib bioavailability and resulted in nearly complete absorption. Absorption of mavacoxib began soon after dosing, and the LS mean plasma mavacoxib concentration from the fed treatment at 1 h postdose was 2.05 μ g/mL and >80% of C_{max} . Following administration of the i.v. dose, the LS mean values of Vss, CL, and MRT were 1.6 L/kg, 2.7 mL·h/kg (0.0648 L day/kg), and 25.8 days, respectively. LS mean values of half-life ranged 15.5–19.3 days for the three groups and did not differ significantly (P > 0.05). Individual plasma elimination

Table 2. Mavacoxib apparent volume of distribution at steady-state (Vss), clearance (CL), and mean residence time (MRT) from the i.v. treatment of study 1, the absolute bioavailability study

Variable	Treatment	n	LS mean (95% CI)	Range of individual values
Vss (L/kg)	i.vFasted	10	1.64 (1.41, 1.87)	1.28–2.41
CL (mL·h/kg)	i.vFasted	10	2.7 (2.1, 3.3)	2.1–4.8
MRT (days)	i.vFasted	10	25.8 (22.8, 28.9)	14.7–31.2

half-life values across the three groups ranged from 9.6–38.6 days.

Beagle dog study 2 (dose-proportionality study)

No adverse drug experiences were noted during the study. Two dogs had aberrantly high concentrations at 4 h, and these high concentrations were excluded in the calculation of the PK variables. The blood sampling scheme was adequate to characterize AUC_{∞} , as judged by mean extrapolation beyond AUC_t for the three groups of <7%. Mavacoxib had relatively variable pharmacokinetics, with AUC values within each dose group spanning a range of approximately 2–5 fold, and with C_{\max} values spanning a range of approximately 2.4–2.9 fold. The LS



Fig. 2. Least squares mean plasma mavacoxib concentration data from study 2, the dose-proportionality study.

 Table 3. Mavacoxib pharmacokinetic variables* from study 2, the dose-proportionality study

Variable	Treatment (mg/kg)	n	LS mean (95% <i>CI</i>)	Range of individual values
AUC_{t}^{*} (µg·h/mL)	2	8	387 (286, 523)	295-572
	4	8	890 (659, 1203)	480-1220
	12	8	2824 (2089, 3817)	1083-5339
AUC_{∞}^{*} ($\mu g \cdot h/mL$)	2	8	405 (291, 563)	299-606
	4	8	956 (687, 1329)	483-1707
	12	8	2931 (2107, 4077)	1102-5584
C_{\max}^* (µg/mL)	2	8	0.89 (0.71, 1.12)	0.43 - 1.22
	4	8	2.19 (1.74, 2.76)	1.16 - 2.94
	12	8	6.50 (5.17, 8.17)	3.48-8.46
$t_{\frac{1}{2}}^{\dagger}$ (days)	2	8	14.6 (11.5, 20.2)	9.3-19.7
	4	8	13.8 (10.9, 18.5)	7.9-38.8
	12	8	12.5 (10.1, 16.4)	9.5-23.0
$t_{\rm max}$ (h)	2	8	11 (4, 29)	1-48
	4	8	16 (6, 41)	4-72
	12	8	43 (17, 108)	24-168

* C_{max} and *AUC* variables were normalized to the nominal dose for the treatment, i.e. 2, 4, or 12 mg/kg. For each of these parameters, the overall dose effect was statistically significant (P < 0.001) and the value at each dose concentration was significantly different from the values for the other two dose concentrations (P < 0.001). *No significant dose effect on t_{V_0} (P > 0.05).

mean plasma mavacoxib concentration data for study 2 are shown in Fig. 2, and pharmacokinetic variables for the three doses are summarized in Table 3. LS mean t_{max} values for the three doses ranged from 11–43 h, with individual values ranging 1–168 h. This broad variability in t_{max} was a common finding in each of the Beagle dog studies. LS mean $t_{\frac{1}{2}}$ values for the 3 doses were similar and ranged 12.5–14.6 days. Across dose groups, individual $t_{\frac{1}{2}}$ values ranged 7.9–38.8 days. Doseproportionality was demonstrated for AUC_t , AUC_{∞} , and C_{max} over the dosage range of 2–12 mg/kg; slopes of the regressions for the logarithms of the parameter values against the logarithms of dose were 1.10 for all three variables, with 95% CI of approximately 0.91–1.3.



Fig. 3. Least squares mean (95% *CIs*) plasma mavacoxib concentration data from study 3, the multiple-dose study.

Beagle dog study 3 (multiple-dose study)

During the course of the study one female dog died on study day 35. The pathologist noted a marked hypertrophy of the left ventricle of the heart and concluded that cardiac pathology was the most likely cause of death. Because the dog did not complete the study, the data from the dog were excluded from the calculation of descriptive statistics for both the concentrations and the pharmacokinetic variables. No other adverse drug experiences were noted during the study.

Least squares mean mavacoxib concentration-time data are shown in Fig. 3 and pharmacokinetic variables are summarized in Table 4. There were no statistically significant differences in trough concentrations over the duration of the study (P > 0.05), LS mean C_{τ} values ranged from 0.96 μ g/mL after the 1st dose to 0.77 μ g/mL after the last dose. The lowest individual C_{τ} values from the four doses ranged 0.50-0.57 ng/mL. LS mean peak mavacoxib concentrations increased significantly from 1.66 to 3.32 μ g/mL between the first and second doses (*P* < 0.001), but without significant changes between doses 2 and 4 (P > 0.05). With the shorter dosing interval after the 1st dose than after the other doses, the \textit{AUC}_{τ} from the 1st dose was approximately 35% of the values from doses 2 to 4 (P < 0.001), but the AUC_{τ} values from these later doses were relatively constant and not significantly different. These data collectively indicate that steady-state pharmacokinetics were achieved after the 2nd dose with the regimen in which the first two doses were separated by 2 weeks but with a 4 week dosing interval thereafter. The LS mean $t_{\frac{1}{2}}$ after the last dose was 16.3 days, with a 95% CI of 14.5-18.6 days. The individual variability in pharmacokinetic variables was moderate, with a 1.7-3.3 fold range of individual values in C_{τ} , C_{max} , AUC_{τ} , and $t_{\frac{1}{2}}$ after the fourth dose.

Values of $t_{\frac{1}{2}}$ pooled from the three Beagle dog studies

Sixty-three Beagle dogs were treated with mavacoxib in the three studies, with individual t_{ν_2} values ranging 7.9–38.8 days. The median t_{ν_2} was 16.6 days (Fig. 4). Three dogs (approximately 5%) had prolonged t_{ν_2} values that were greater than 30 days (values of 33.1–38.8 days) and approximately twice the median t_{ν_2} .

Mongrel dog safety study

One dog in the 25 mg/kg bw group developed a GI perforation and died approximately midway through the study. Plasma mavacoxib concentrations for this dog were within the range of concentrations for the other dogs in the dose group. Because this dog did not complete the study, the data from the dog were excluded from the calculation of descriptive statistics for both the concentrations and the pharmacokinetic variables. A second dog in the same dose group completed the study, but pathology evaluation revealed that it too had suffered a GI perforation and made an apparent recovery. Its plasma mavacoxib concentrations also were within the range of concentrations for the other **Table 4.** Mavacoxib pharmacokinetic vari-ables from study 3, the multiple-dose study

Variable	Dose number (dosing study day)	п	LS mean (95% <i>CI</i>)	Range of individual values
<i>AUC</i> _τ * (μg·h/mL)	Dose 1 $(day 0)^{\dagger}$	9	389 (271, 559)	211-688
	Dose 2 (day 14)	9	1170 (928, 1470)	724-1840
	Dose 3 (day 42)	9	1140 (913, 1410)	726-1690
	Dose 4 (day 70)	9	1000 (850, 1180)	750-1310
C_{\max}^* (µg/mL)	Dose 1 (day 0) [†]	9	1.66 (1.20, 2.28)	0.84-2.83
	Dose 2 (day 14)	9	3.32 (2.70, 4.08)	2.34-5.08
	Dose 3 (day 42)	9	2.86 (2.15, 3.82)	1.38-4.26
	Dose 4 (day 70)	9	2.71 (2.06, 3.58)	1.66-3.99
$C_{\tau}^{*^{\ddagger}}$ (µg/mL)	Dose 1 (day 0)	9	0.96 (0.72, 1.28)	0.50 - 1.78
	Dose 2 (day 14)	9	0.89 (0.67, 1.18)	0.54-1.25
	Dose 3 (day 42)	9	0.83 (0.62, 1.10)	0.54-1.33
	Dose 4 (day 70)	9	0.77 (0.60, 0.99)	0.57 - 1.14
$t_{\frac{1}{2}}$ (days)	Dose 4 (day 70)	9	16.3 (14.5, 18.6)	13.3-22.2
t _{max} (h)	Dose 1 (day 0)	9	24 (8, 41)	2-72
	Dose 2 (day 14)	9	25 (8, 41)	2-72
	Dose 3 (day 42)	9	22 (5, 38)	2-72
	Dose 4 (day 70)	9	18 (1, 34)	2-72

 C_{max} , C_{τ} , and AUC_{τ} were normalized to the nominal dose for the treatment, i.e. 4 mg/kg bw. [†]The overall effect of dose number was statistically significant (P < 0.001), and the LS mean value from dose number 1 was significantly different from the values for dose numbers 2, 3, and 4 (P < 0.001), but there were no significant differences between any of the values for dose numbers 2, 3, or 4 (P > 0.05).

[‡]No significant effect of dose number on C_{τ} (P > 0.05).



Fig. 4. Histogram of mavacoxib $t_{\frac{1}{2}}$ values from 63 adult laboratory Beagles. Bars indicate the percentage of dogs with $t_{\frac{1}{2}}$ values within 5 day intervals. Three dogs (approximately 5%) had $t_{\frac{1}{2}}$ values >30 days.

dogs in the dose group. A more thorough discussion of the safety aspects of the study are described elsewhere (Krautmann *et al.*, 2010). Least squares mean plasma mavacoxib concentration data from the study are depicted in Fig. 5, and LS mean



Fig. 5. Least squares mean plasma mavacoxib concentration data from study 4, the safety study.

pharmacokinetic variables from the last dose are summarized in Table 5.

In all of the groups, C_{max} was numerically greater after the second dose than after the first dose, and the difference was statistically significant for the 5 and 15 mg/kg bw dose groups. The C_{max} values remained relatively constant thereafter, however, and there were few statistically significant differences in C_{max} within a dose group for the subsequent doses. There were similarly few changes in AUC_{τ} values within each dose group from doses 2–7, especially for doses 5–7. These comparisons indicate that the data summarized in Table 5 represent the steady-state pharmacokinetics mavacoxib. Trough mavacoxib concentrations were >0.4 μ g/mL after all doses for 7 of the 8 dogs in the 5 mg/kg bw group. For one dog in the group, trough

Variable	Dose concentration (mg/kg bw)	п	LS mean (95% <i>CI</i>)	Range of individual values
AUC_{τ}^{*} (µg·h/mL)	5	8	1930 (1660-2260)	1210-2540
	15	8	5330 (4560-6220)	4040-8180
	25	7	8820 (7480-10 400)	7950-10 500
C_{\max}^{*} (µg/mL)	5	8	4.6 (4.0-5.2)	3.3-5.8
	15	8	13.5 (11.9-15.4)	11.4-16.0
	25	7	21.8 (19.1-24.9)	19.0-25.8
<i>C</i> _τ * (μg/mL)	5	8	1.8(1.3-2.3)	0.78 - 2.8
	15	8	4.7 (3.6-6.1)	2.3-9.8
	25	7	7.2 (5.5–9.5)	5.3-11.7

Table 5. Mavacoxib pharmacokinetic variables from the last dose of study 4, the safetystudy in Mongrel dogs

 C_{max} , C_{τ} , and AUC_{τ} were normalized to the nominal dose for the treatment, i.e. 5 mg/kg bw. For each of these parameters, the overall effect of dose was statistically significant (P < 0.001) and the LS mean value at each dose level was significantly different from the values for the other dose levels (P < 0.05).

concentrations exceeded 0.4 µg/mL after doses 1, 6, and 7 but ranged 0.28–0.37 µg/mL for doses 2–5. Dose-proportionality was concluded across the 5–25 mg/kg bw dose concentrations for the first and last dose values of $C_{\rm max}$, C_{τ} , and AUC_{τ} . LS mean slope parameters for these three pharmacokinetic variables ranged 0.88–1.09, with 95% *CIs* for each regression including 1.0. Normalization of the last dose LS mean AUC_{τ} to a 4 mg/kg dose resulted in values from the three dose concentrations of 1380–1528 µg·h/mL, which are similar to the single-dose LS mean AUC_{∞} of 1290 µg·h/mL from the oral-fed group of the absolute bioavailability study (study 1).

In vitro and ex vivo plasma protein binding of mavacoxib

In preliminary work to establish the equilibration time for mavacoxib, the measured percent binding for a 2 μ g/mL plasma sample consistently decreased from 99.7% to 98.3% as equilibration time increased from 2 to 24 h. The total recovery of mavacoxib from the dialysis apparatus also decreased over this time period 96.8-87.5%, and time to equilibration could not be established. In recovery studies in which mavacoxib solutions in PBS at initial concentrations of 0.1–10 μ g/mL were placed in both chambers and dialyzed for 4 h, recovery of mavacoxib from the apparatus ranged 46–68% relative to the nondialyzed solutions and appeared to be independent of concentration. In similar recovery experiments with plasma, recovery was $\geq 84\%$ and also independent of concentration. These findings were consistent with time-dependent sorption of unbound mayacoxib to the dialysis apparatus. The 4-h incubation time was selected to standardize conditions for further studies, recognizing that the 4-h period represented a compromise regarding attainment of equilibrium and optimal recovery. With the 4-h incubation time, the plasma protein binding of mavacoxib was independent of concentration for mean postdialysis donor (plasma) compartment mavacoxib concentrations of 0.26–6.0 μ g/mL, with mean percent binding values ranging 98.2-98.4%. For the 26 plasma samples from study 4, with mean postdialysis donor compartment concentrations ranging 0.67–10.2 μ g/mL, the median percentage bound was 98.1% with a range of 97.2–98.7%. Of the 20 samples from the field trial, three samples had postdialysis acceptor compartment concentrations BLQ of the assay. For the other 17 samples with mean postdialysis donor compartment concentrations ranging $0.59-5.1 \ \mu g/mL$, the median percentage bound was 98.5%, with a range of 98.0–98.8%. The *ex vivo* plasma protein binding of mavacoxib is therefore independent of concentration over the range of therapeutic concentrations and similar in laboratory Beagle and Mongrel dogs.

DISCUSSION

Mavacoxib is unique among NSAIDs because its combination of low clearance (CLiv of 2.7 mL·h/kg) and relatively large apparent volume of distribution (Vss of 1.6 L/kg). Some NSAIDs (e.g. carprofen, celecoxib, deracoxib) have CLiv values at therapeutic analgesic or osteoarthritic doses in laboratory dogs that are more than six-times that of mavacoxib (Priymenko et al., 1998; Paulson et al., 2001; Novartis Animal Health, 2007). Mavacoxib and the NSAIDs as a class are highly bound to plasma proteins, and this extensive plasma protein binding is presumably manifest, at least in part, in typically small Vss values. For example, carprofen and robenacoxib have values of Vss that are less than 12% of the mavacoxib Vss (Priymenko et al., 1998; EMEA, 2008a). Despite being highly bound to plasma proteins, other coxib class NSAIDs (e.g. celecoxib, deracoxib) have apparent volumes of distribution that are similar to that of mavacoxib (Paulson et al., 2001; Novartis Animal Health, 2007). Because of its combination of low CLiv and relatively large Vss, mavacoxib has a $t_{\frac{1}{2}}$ that is much longer than those of other NSAIDs. The prolonged $t_{\frac{1}{2}}$ for mavacoxib supports the approved regimen in which doses are separated by 2-4 weeks. Compliance with this regimen was better than with a once-daily NSAID (EMEA, 2008b; Payne-Johnson et al., 2009), and because of the prolonged $t_{1/2}$, a continuous therapeutic response may be more likely in instances when there are problems with dosing, such as a delay in drug administration.

Because of the relatively long $t_{\frac{1}{2}}$ of mavacoxib, a regimen with a nonconstant dosing interval (i.e. 2 weeks between the first two doses but with a maintenance 4 week interval) was used for rapid attainment of steady-state concentrations. With this regimen, trough plasma mavacoxib concentrations were relatively constant. Mavacoxib's dosage regimen was determined in a number of induced model studies in laboratory dogs following procedures similar to those used previously (Brandt *et al.*, 1991; Hauge *et al.*, 1995; Li *et al.*, 2004). The correlation in these studies of *in vivo* effects (e.g. reduction of lameness) and mavacoxib plasma concentrations revealed that about 0.4 μ g mavacoxib per mL are needed for a statistically significant reduction of pain in comparison to a control group (EMEA, 2008b; Lees *et al.*, 2009). At a dosage of 4 or 5 mg/kg bw, 16 of 17 dogs in multi-dose studies 3 and 4 had trough mavacoxib concentrations that met or exceeded this target concentration of 0.4 μ g/mL at all time points, and a nominal dosage of 4 mg/kg bw was selected for the first field trial with mavacoxib in osteoarthritic patients.

The bioavailability of mayacoxib is increased when the drug is given with food. An increase in F following administration with food was also noted in dogs with celecoxib and deracoxib (Paulson et al., 2001; EMEA, 2006; Novartis Animal Health, 2007). When mavacoxib is administered with food, the absolute bioavailability is approximately 90%, indicating that the drug has good permeability. The aqueous solubility of mavacoxib is relatively low (0.006 mg/mL, Pfizer internal data), and the increase in bioavailability by food could be consistent with mavacoxib being a poorly soluble, highly permeable drug (i.e. class 2 of the Biopharmaceutics Class System). Food could increase the bioavailability, for example, by increasing gastric residence time to allow more time for tablet dispersion and drug dissolution, or by facilitating dissolution and increasing solubility via meal-stimulated secretion of bile salts. The relatively broad 90% CI for the effect of the meal to increase F (38.3-159.8% increase) illustrates the difficulty in performing wellcontrolled studies with this long $t_{\frac{1}{2}}$ drug. Crossover studies were not considered to be feasible because of the necessarily long washout period, and parallel group studies were performed instead. With the relatively broad inter-individual variability in mavacoxib pharmacokinetics, the estimate for the effect of food on bioavailability is relatively imprecise with a group size of 10 dogs. Due to the pronounced food-effect, the label for Trocoxil recommends that the drug be administered with the dog's main meal (EMEA, 2008b). Absorption occurs soon after administration of mavacoxib, and plasma mavacoxib concentrations associated with efficacy were achieved in all dogs in study 1 at 1 h after administration of drug with food.

Mavacoxib was found to exhibit dose-proportional PK in laboratory beagles over the dosage range of 2–12 mg/kg. The test for dose-proportionality was based on the confidence intervals for the slopes of regressions of log-transformed parameters against log-dose, with dose-proportionality declared because the 90% *CIs* for the slopes included 1. Although doseproportionality was concluded, modest nonproportionality could not be ruled out from the confidence intervals; based on the upper confidence bound for the slope in the regression with AUC_{∞} ; a halving of dose from 4 to 2 mg/kg could result in a mean AUC_{∞} that is approximately 20% lower than the prediction based on dose-proportionality. The data from the safety study are also consistent with dose-proportionality in laboratory Mongrel dogs over a somewhat higher dose range, 5-25 mg/kg bw.

The t_{max} values for orally administered mavacoxib spanned a large range, from 1 h to more than 120 h. Such long t_{max} values were unexpected, as gastrointestinal (GI) transit time in the dog is typically less than 24 h (Davies & Morris, 1993). It is possible that these prolonged t_{max} values arose in some dogs because of the relatively flat concentration-time profile for mavacoxib for approximately a week after dosing. The relatively flat profile, along with variability in the measurement of plasma mavacoxib concentrations, could contribute to t_{max} values for some dogs exceeding GI transit times. Mavacoxib may undergo enterohepatic recycling (Hummel et al., 2010), and this could contribute to prolonged t_{max} and the secondary peaks apparent in the plasma concentration-time profiles of some dogs. The appearance of a second peak at about 5-days postdose in study 1, the absolute bioavailability study, is longer than what might be expected for enterohepatic recycling, but it is possible that the reduced frequency of blood sampling at more than 24 h postdose could have contributed to a diminished ability to detect secondary peaks between 1 and 5-days postdose. The prolonged $t_{\frac{1}{2}}$ of mavacoxib could also be related, in part, to enterohepatic recirculation.

Target animal safety studies are necessarily performed with healthy animals (VICH, 2007), and the safety study with mavacoxib was performed with young adult Mongrel dogs with body weights and ages that were similar to those of the laboratory Beagle dogs in the pharmacokinetic studies. To maximize systemic exposure to mavacoxib in the safety study, the drug was administered after the dogs were presented with their daily food ration. The dose-normalized steady-state AUC_{τ} values from the safety study were similar to the single-dose AUC_{∞} from the fed-oral treatment in the absolute bioavailability study (study 1), indicating that the pharmacokinetics of mavacoxib may be similar in young adult dogs that are either Beagles or Beagle-sized Mongrels. The two dogs with intestinal perforations in the safety study had mavacoxib plasma concentrations intermediate to those of all the dogs in the same dose group (25 mg/kg) at all time points evaluated, indicating that their pharmacokinetics did not diverge from those of the group. One can speculate that at a high dose of 25 mg/kg bw plasma concentrations are achieved that correspond to >20% inhibition of COX-1 (Lees et al., 2009), and the intestinal perforations could have arisen, in part, as a consequence of COX-1 inhibition.

Mavacoxib exhibits relatively large between-subject variability in pharmacokinetics in laboratory dogs. In the relatively small dog studies with 8–10 dogs per treatment group, mavacoxib pharmacokinetic variables typically spanned a 2–4 fold range of values. When $t_{\frac{1}{2}}$ data were pooled from the three Beagle dog studies, the $t_{\frac{1}{2}}$ values from the 63 dogs had almost a 5-fold range of values. It is not possible to understand, based on these limited data, the factors that contribute to the large variability in clearance or $t_{\frac{1}{2}}$. The long $t_{\frac{1}{2}}$, and relatively large between-subject variability in pharmacokinetics emphasized the need for a robust assessment of the risk: benefit ratio of the drug. Osteoarthritic patients are typically geriatric large breed dogs, and the population pharmacokinetics of mavacoxib were evaluated as a component of field trials with the drug (Cox *et al.*, 2010). The pharmacokinetic data from the laboratory dog studies provided information about mavacoxib regarding posology and basic pharmacokinetics, and also served as a bridge to better understand the risk:benefit ratio.

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