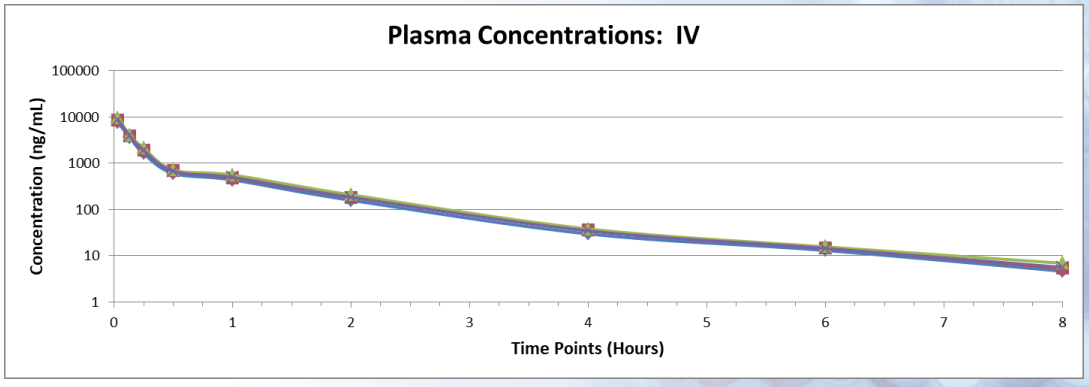
Bioanalytical & Biomarker Services

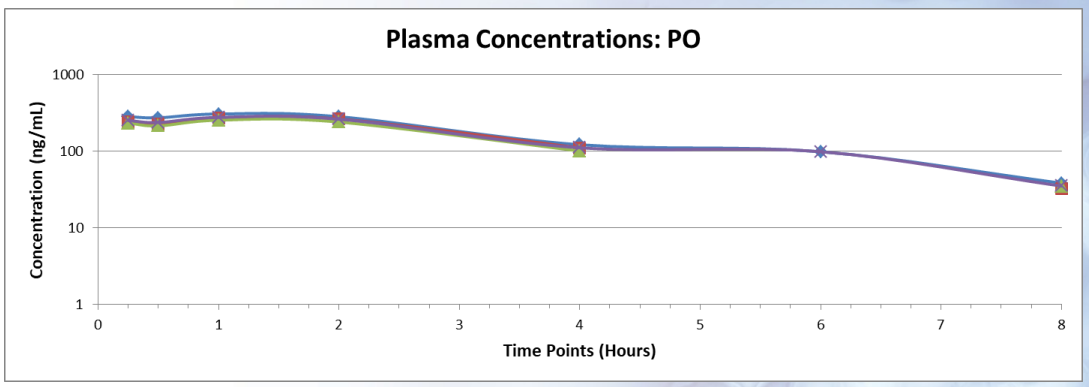
Pharma Discovery:

Pharmacokinetics of a model compound

Pharmacokinetics of Diclofenac as a Model Compound, following Intravenous and Oral Gavage Single Dose Administration

Sprague Dawley (age appropriate weight, minimum 225 g) were utilized to administer Diclofenac as a model compound by intravenous (bolus intravenous into tail vein) and oral (oral gavage) routes. The dosing amounts were adjusted according to actual body weight with the following parameters: Test article 2.0 mg/kg, 1 mg/mL concentration, 2.0 mL/kg, and 0.9% sterile saline vehicle. Diclofenac was administered following a 14 to 16 hours of fasting. The time points for whole blood collection were 2, 8, 15, 30 minutes, and 1, 2, 4, 6, 8, and 24 hours post IV dose and 15, 30 minutes, 1, 2, 4, 6, 8, and 24 hours post PO dose. Approximately 300 uL of whole blood in K2EDTA anti-coagulant was drawn at each time point.





Pharmacokinetics parameters were estimated using Watson LIMS 7.5 SP1 (Thermo Fisher Scientific Inc.) using a non-compartmental approach consistent with the various routes of administration. All parameters were generated from serial animal concentrations in plasma. Parameters were estimated using nominal sampling times to be relative to the start of each dose administration (within an acceptable tolerance limit). The nominal calculated dose for active ingredient were determined based on actual body weight using the following parameters: Dose 2 mg/kg, Concentration 1.0 mg/mL, Dose Volume 2.0 mg/mL, Vehicle 0.9% Sterile Saline.

The area under the analyte concentration versus time curve (AUC) was calculated using the linear-log linear trapezoidal method. AUC was not calculated for PK profiles with less than 3 consecutive quantifiable concentrations of test article at separate time points. When practical, the terminal elimination phase of each concentration versus time curve was identified using at least the final three observed concentration values. The slope of the terminal elimination phase was determined using linear regression on the unweighted concentration data. Parameters relying on the determination of the terminal elimination phase were excluded from the summary statistics where the extrapolation of the AUC to infinity represented more than 30% of the total area and/or if the number of regression points were less than three. The parameters described below were reported to 3 significant figures.

Plasma Diclofenac Concentration (ng/mL)
Treatment: IV

Parameter	Units	Subject 01	Subject 02	Subject 03	Mean	S.D.	%CV	n
AUC	ng*Hours/mL	2110	2400	2630	2380	261	10.9	3
AUC Extrap	ng*Hours/mL	2120	2410	2650	2393	265	11.1	3
% AUC Extrap	%	0.648	0.455	0.725	0.609	0.139	22.8	3
CL (0-t)	mL/kg/Hours	950	834	760	848	95.8	11.3	3
CL	mL/kg/Hours	943	830	755	843	94.6	11.2	3
Vdss (0-t)	mL/kg	673	599	551	608	61.5	10.1	3
Vdss	mL/kg	708	634	590	644	59.6	9.30	3
MRT (0-t)	Hours	0.709	0.719	0.725	0.718	0.00808	1.10	3
MRT	Hours	0.750	0.763	0.781	0.765	0.0156	2.00	3
T1/2	Hours	1.49	1.45	1.62	1.52	0.0889	5.80	3
RegressionPoints	Hours	4, 6, 8	4, 6, 8	4, 6, 8				

Plasma Diclofenac Concentration (ng/mL)
Treatment: PO

Parameter	Units	Subject 01	Subject 02	Subject 03	Mean	S.D.	%CV	n
AUC	ng*Hours/mL	1240	1060	993	1098	128	11.6	3
AUC Extrap	ng*Hours/mL	1370	1150	1100	1207	144	11.9	3
% AUC Extrap	%	9.45	8.08	9.76	9.10	0.894	9.80	3
Tmax	Hours	1.00	1.00	1.00	1.00	0.00	0.00	3
Cmax	ng/mL	307	270	255	277	27	9.70	3
T1/2	Hours	2.40	2.01	2.21	2.21	0.195	8.80	3
RegressionPoints	Hours	4, 6, 8	2, 4, 8	2, 4, 8				
Cmin	ng/mL	38.4	32.3	35.0	35.2	3.06	8.70	3
R-Squared		0.881	0.992	0.982	0.95	0.0614	6.50	3