Experiment Number: K12010 | **Toxicokinetics Data Summary** | **Request Date:** 3/12/2021

Route: Intravenous, Oral Gavage | **Compound & Analyte:** Drometrizole | **Request Time:** 2:30:16

Species/Strain: Rat/Harlan Sprague-Dawley | **CAS Number:** 2440-22-4 | **Lab:** BAT

Male

Treatment Group (mg/kg)

	2.25 IV[a] Blood	30 Gav[b] Blood	300 Gav[b] Blood
C_0min_pred (ng/mL)	4510 ± 116000		
Cmax_pred (ng/mL)		138 ± 1900	358 ± 26
Tmax_pred (hour)		0.0196 ± 24.6	0.266 ± 0.053
Cmax_obs (ng/mL)	1440	165	446
Tmax_obs (hour)		0.0333	0.500
Alpha_Half-life (hour)	0.00836 ± 0.114	0.583 ± 0.498	3.58 ± 2.72
Beta_Half-life (hour)	0.187 ± 0.020	1120 ± 5780	103 ± 72
Gamma_Half-life (hour)	84.8 ± 20.5		
k01 ($hour^{-1}$)		335 ± 494000	20.3 ± 5.3
k01_Half-life (hour)		0.00207 ± 3.05	0.0341 ± 0.0089
k10 ($hour^{-1}$)	0.430 ± 11.1	0.00105 ± 0.00565	0.0123 ± 0.0064
k10_Half-life (hour)	1.61 ± 41.5	660 ± 3550	56.2 ± 29.2
k12 ($hour^{-1}$)	48.0 ± 1160	0.485 ± 1.34	0.0819 ± 0.0553
k21 ($hour^{-1}$)	27.8 ± 278	0.703 ± 1.78	0.106 ± 0.0096
k13 ($hour^{-1}$)	10.1 ± 240		
k31 ($hour^{-1}$)	0.210 ± 0.422		
Cl1 (mL/hr/kg)	215 ± 45		
Cl2 (mL/hr/kg)	24000 ± 41400		
Cl3 (mL/hr/kg)	5020 ± 9860		
Cl1_F (mL/hr/kg)		226 ± 1150	10100 ± 5000
Cl2_F (mL/hr/kg)		105000 ± 99000	67000 ± 41700
V1 (mL/kg)	499 ± 12900		
V2 (mL/kg)	861 ± 7170		
V3 (mL/kg)	24000 ± 2200		
V1_F (mL/kg)		216000 ± 445000	818000 ± 68000
V2_F (mL/kg)		149000 ± 448000	632000 ± 301000

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	Treatment Group (mg/kg)		
	2.25 IV[a] Blood	**30 Gav[b] Blood**	**300 Gav[b] Blood**
MRT (hour)	118 ± 32		
AUC_0-T (ng/mL·hr)	4700	6020	11900
AUC_inf (ng/mL·hr)	10500 ± 2200	132000 ± 675000	29800 ± 14700

LEGEND

MODELING METHOD & BEST FIT MODEL

[a] WinNonlin three-compartment model with bolus input, first order output, and 1/Yhat^2 weighting (model #18); Cmax_pred based on the model prediction at 0 minutes.

[b] WinNonlin two-compartment model with first order input, first order output, and 1/Yhat^2 weighting (model #13).

ANALYTE

Drometrizole

TK PARAMETERS

C_0min_pred = Fitted plasma concentration at time zero (IV only)
Cmax_obs = Observed maximum plasma concentration
Cmax_pred = Predicted maximum plasma concentration
Tmax_obs = Time at which observed Cmax occurs
Tmax_pred = Time at which predicted Cmax occurs
Alpha_Half-life = Half-life for the alpha phase
Beta_Half- life = Half-life for the beta phase
Gamma Half-life = Half-life for the gamma phase
k01 = Absorption rate constant, ka
k01_Half-life = Half-life of the absorption process to the central compartment
k10 = Elimination rate constant from the central compartment also ke or kelim
k10_Half_life = Half-life for the elimination process from the central compartment
k12 = Distribution rate constant from first to second compartment
k21 = Distribution rate constant from second to first compartment
k13 = Distribution rate constant from first to third compartment
k31 = Distribution rate constant from third to first compartment

TK PARAMETERS (cont'd)

Cl1 = Clearance of central compartment
Cl2 = Clearance of the secondary compartment
Cl3 = Clearance of the tertiary compartment
Cl1_F = Apparent clearance of the central compartment, also Cl_F for gavage groups in non-compartmental model
Cl2_F = Apparent clearance of the secondary compartment
V1 = Volume of distribution of the central compartment, includes Vd and V volume of distribution
V2 = Volume of distribution for the peripheral compartment
V3 = Volume of distribution for the peripheral compartment
V1_F = Apparent volume of distribution for the central compartment includes Vd_F, V_F for oral groups, and Vc_F
V2_F = Apparent volume of distribution for the peripheral compartment
MRT = Mean residence time
AUC_0-T = Area under the plasma concentration versus time curve, AUC, from time ti (initial) to tf (final), AUClast
AUC_inf = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

TK PARAMETERS PROTOCOL

BLOOD

IV 2.25 Rat Male

Harlan Sprague Dawley male rats were intravenously administered a single 2.25 mg/kg dose of Drometrizole. An automated blood sampling system (Culex) was used for this study. Whole blood samples were taken from n=3 animals/timepoint/per group at pre-dose and 16 timepoints at 0.0333, 0.0833, 0.167, 0.25, 0.333, 0.5, 0.75, 1, 2, 4, 8, 12, 18, 24, 48, and 72 hrs. Parent (free) was analyzed by LC-MS/MS with a lower limit of quantitation (LLOQ) of 1.0 ng/mL. Parameter estimates are reported to three significant figures with standard error (SE). Observed values do not have a reported SE.

BLOOD

Gavage 30 Rat Male, 300 Rat Male

Harlan Sprague Dawley male rats were administered a single gavage dose of 30 or 300 mg/kg Drometrizole. An automated blood sampling system (Culex) was used for this study. Whole blood samples were taken from n=3 animals/timepoint/per group at pre-dose and 16 timepoints at 0.0333, 0.0833, 0.167, 0.25, 0.333, 0.5, 0.75, 1, 2, 4, 8, 12, 18, 24, 48, and 72 hrs. Parent (free) was analyzed by LC-MS/MS with a lower limit of quantitation (LLOQ) of 1.0 ng/mL. Parameter estimates are reported to three significant figures with standard error (SE). Observed values do not have a reported SE.