Experiment Number: K12011 | **Toxicokinetics Data Summary** | **Request Date:** 3/12/2021

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

Species/Strain: Rat/Harlan Sprague-Dawley | **CAS Number:** 3896-11-5 | **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)	22400 ± 4700		
Cmax_pred (ng/mL)		2020 ± 490	2450 ± 710
Tmax_pred (hour)		3.08 ± 0.77	5.06 ± 1.24
Cmax_obs (ng/mL)	18100	3290	2840
Tmax_obs (hour)		2.00	4.00
Alpha_Half-life (hour)	0.0673 ± 0.0137	3.22 ± 1.71	6.39 ± 7.01
Beta_Half-life (hour)	1.85 ± 0.12	48.4 ± 116	37.5 ± 401
Gamma_Half-life (hour)	31.7 ± 7.3		
k01 ($hour^{-1}$)		0.473 ± 0.368	0.330 ± 0.315
k01_Half-life (hour)		1.47 ± 1.14	2.10 ± 2.01
k10 ($hour^{-1}$)	2.20 ± 0.42	0.185 ± 0.107	0.101 ± 0.097
k10_Half-life (hour)	0.315 ± 0.060	3.74 ± 2.17	6.84 ± 6.55
k12 ($hour^{-1}$)	6.68 ± 1.64	0.0276 ± 0.0193	0.00588 ± 0.00837
k21 ($hour^{-1}$)	1.60 ± 0.27	0.0166 ± 0.0387	0.0198 ± 0. 215
k13 ($hour^{-1}$)	0.199 ± 0.044		
k31 ($hour^{-1}$)	0.0239 ± 0.0055		
Cl1 (mL/hr/kg)	221 ± 13		
Cl2 (mL/hr/kg)	671 ± 110		
Cl3 (mL/hr/kg)	20.0 ± 3.2		
Cl1_F (mL/hr/kg)		1430 ± 360	7220 ± 2020
Cl2_F (mL/hr/kg)		213 ± 175	419 ± 414
V1 (mL/kg)	101 ± 21		
V2 (mL/kg)	420 ± 37		
V3 (mL/kg)	835 ± 234		
V1_F (mL/kg)		7720 ± 5070	71200 ± 60500
V2_F (mL/kg)		12800 ± 37600	21200 ± 228000

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	Treatment Group (mg/kg)		
	2.25 IV[a] Blood	**30 Gav[b] Blood**	**300 Gav[b] Blood**
MRT (hour)	6.13 ± 1.08		
AUC_0-T (ng/mL·hr)	10000	25600	40000
AUC_inf (ng/mL·hr)	10200 ± 600	21000 ± 5300	41600 ± 11600

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

Bumetrizole

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 Bumetrizole. 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 2.0 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 Bumetrizole. 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 2.0 ng/mL. Parameter estimates are reported to three significant figures with standard error (SE). Observed values do not have a reported SE.