Experiment Number: K12007 **Toxicokinetics Data Summary** **Request Date:** 3/12/2021

Route: Intravenous, Oral Gavage **Compound & Analyte:** 2-(2H-Benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol **Request Time:** 2:30:16

Species/Strain: Rat/Harlan Sprague-Dawley **CAS Number:** 70321-86-7 **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)	45900 ± 1700		
Cmax_pred (ng/mL)		386 ± 194	697 ± 305
Tmax_pred (hour)		5.18 ± 2.04	7.80 ± 2.34
Cmax_obs (ng/mL)	52400	642	787
Tmax_obs (hour)		2.00	4.00
Alpha_Half-life (hour)	0.759 ± 0.085	3.39 ± 44.5	8.26 ± 51.3
Beta_Half-life (hour)	2.10 ± 0.36	19.8 ± 26.3	42.7 ± 1170
Gamma_Half-life (hour)	25.1 ± 2.0		
k01 ($hour^{-1}$)		0.269 ± 2.83	0.197 ± 0.641
k01_Half-life (hour)		2.57 ± 27.0	3.51 ± 11.4
k10 ($hour^{-1}$)	0.646 ± 0.025	0.0856 ± 0.877	0.0657 ± 0.334
k10_Half-life (hour)	1.07 ± 0.04	8.10 ± 82.9	10.6 ± 53.6
k12 ($hour^{-1}$)	0.103 ± 0.034	0.0703 ± 1.51	0.0137 ± 0.0564
k21 ($hour^{-1}$)	0.414 ± 0.102	0.0834 ± 0.367	0.0207 ± 0.589
k13 ($hour^{-1}$)	0.0752 ± 0.0061		
k31 ($hour^{-1}$)	0.0310 ± 0.0026		
Cl1 (mL/hr/kg)	31.6 ± 0.7		
Cl2 (mL/hr/kg)	5.05 ± 1.58		
Cl3 (mL/hr/kg)	3.69 ± 0.27		
Cl1_F (mL/hr/kg)		3240 ± 890	15400 ± 33200
Cl2_F (mL/hr/kg)		2660 ± 30300	3210 ± 7270
V1 (mL/kg)	49.0 ± 1.8		
V2 (mL/kg)	12.2 ± 2.1		
V3 (mL/kg)	119 ± 10		
V1_F (mL/kg)		37800 ± 388000	23400 ± 717000
V2_F (mL/kg)		31800 ± 238000	155000 ± 4430000

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	Treatment Group (mg/kg)		
	2.25 IV[a] Blood	**30 Gav[b] Blood**	**300 Gav[b] Blood**
MRT (hour)	5.69 ± 0.30		
AUC_0-T (ng/mL·hr)	74300	8430	15300
AUC_inf (ng/mL·hr)	71100 ± 1700	9270 ± 2580	19500 ± 41800

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

2-(2H-Benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol

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 2-(2H-benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol (DiMeEtPh-BZT). 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 2-(2H-benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol (DiMeEtPh-BZT). 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.