Experiment Number: S0629
Route: IV, Gavage, Dosed Feed
Species/Strain: Hamster/Syrian Golden

Toxicokinetics Data Summary
Compound: Wyeth-14643/ **Analyte:** Wyeth-14643
CAS Number: 50892-23-4

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: TI

Male

Treatment Group (mg/kg)

3.0 IV Plasma[a,d]

Cmax_pred (ug/mL)	62.4
Beta Half-life (minute)	108
Cl (mL/min/kg)	3.72
MRT (minute)	38.1
AUCinf_pred (ug/mL*min)	806

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	Treatment Group (mg/kg)			
	1.0 Gavage Plasma[a,e]	**1.0 Gavage Plasma[b]**	**3.0 Gavage Plasma[a,f]**	**10 Gavage Plasma[a,c]**
Cmax_obs (ug/mL)	0.485		2.88	6.04
Tmax_obs (minute)	10		15	15
Alpha (minute^{-1})		0.1494 ± 0.0115		
Beta (minute^{-1})		0.0244 ± 0.0021		
Beta Half-Life (minute)	51.7		78.6	51.1
k01 (minute^{-1})		0.0139		
k10 (minute^{-1})		0.0852 ± 0.0034		
k12 (minute^{-1})		0.0458 ± 0.0063		
k21 (minute^{-1})		0.0428 ± 0.0052		
Cl1_F (mL/min/kg)	20.1		15.8	23.2
V1 (L/kg)		0.0480 ± 0.0019		
MRT (minute)	97.1		102	100
AUCinf_pred (ug/mL*min)	50		190	431
F	0.19		0.24	0.16

Male

	Treatment Group (ppm)	
	100 Dosed Feed Plasma[a,g]	**1000 Dosed Feed Plasma[a,g]**
Cmax_obs (ug/mL)	0.447	4.04
Tmax_obs (hour)	1000	1000
AUCinf_pred (ug/mL*min)	301	3390

LEGEND

MODELING SOFTWARE

PCNONLIN software, Version 4.2

MODELING METHOD & BEST FIT MODEL

[a]Models 200 and 201, PCNONLIN software, Version 4.2, SCI Software, Lexington, KY, Noncompartmental model

[b]PCNONLIN software, Version 4.2, SCI Software, Lexington, KY, Best fit is one compartmental which simultaneously solves iv and mid dose oral data sets. Simultaneous solution of Sprague-Dawley rat intravenous dose (2.0 mg/kg Study X) and mid oral gavage dose (2.0 mg/kg Study Z).

EXCEPTIONS

[c]Terminal elimination Beta range is 180 to 360 minute.

[d]MRT (Estimate(0-T)/ Estimate(inf) is less than 0.90. Terminal elimination Beta range is 150 to 300 minute.

[e]AUC inf and MRT (Estimate(0-T)/ Estimate(inf) is less than 0.90. Terminal elimination Beta range is 90 to 180 minute.

[f]MRT (Estimate(0-T)/ Estimate(inf) is less than 0.90. Terminal elimination Beta range is 180 to 360 minute.

[g]For feed studies, Tmax is reported as 24-hour clock time

ANALYTE

Wyeth-14643

TK PARAMETERS

Cmax = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax_obs = Time at which Cmax predicted or observed occurs
Alpha = Hybrid rate consistent of the alpha phase
Beta = Hybrid rate constant of the beta phase
Beta Half-Life = Half-life for the beta phase
k01 = Absorption rate constant, ka
k10 = Elimination rate constant from the central compartment also ke or kelim
k12 = Distribution rate constant from first to second compartment
k21 = Distribution rate constant from second to first compartment
Cl = Clearance, includes total clearance
Cl1_F = Apparent clearance of the central compartment, also Cl_F for gavage groups in non-compartmental model
V1 = Volume of distribution of the central compartment, includes Vd and V volume of distribution, Vz apparent volume of distribution NCA, Vapp apparent volume of distribution for intravenous studies
MRT = Mean residence time
AUCinf_pred = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity
F = Bioavailability, absolute availability

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Plasma was analyzed for Wyeth 14,643 concentration by high performance liquid chromatography (HPLC) using UV detection at 254 nm and indomethacin as the internal standard.

TK PARAMETERS PROTOCOL (cont'd)

TK_INTRAVENOUS PLASMA

3.0 mg/kg

Mice, Sprague Dawley rats, and Syrian (Golden) hamsters were administered a single intravenous or gavage dose. Blood was collected post-dosing from 3 animals/species/route/dose/timepoint for up to 13 timepoints.

TK_GAVAGE PLASMA

1.0 mg/kg,3.0 mg/kg,10 mg/kg

Mice, Sprague Dawley rats, and Syrian (Golden) hamsters were administered a single intravenous or gavage dose. Blood was collected post-dosing from 3 animals/species/route/dose/timepoint for up to 13 timepoints.

ANALYSIS METHOD

Plasma was analyzed for Wyeth 14,643 concentration by high performance liquid chromatography (HPLC) using UV detection at 254 nm and indomethacin as the internal standard. Not shown here are simulations of plasma concentrations after dietary exposure which were made using the method of superposition Yuan,J. 1993. Modeling blood/plasma concentrations in dosed feed and dosed drinking water toxicology studies. Toxicol.Appl.Pharmacol. 119,131-141. A program at RTI was written to perform the computations which used 24-hour feed consumptions data for the rat and mouse provided by NTP. Feed consumption data for the rat were used in hamster simulations. Observed plasma concentrations were greatly over predicted at both dose levels in mice, under predicted by approximately 2-fold (low dose) and 5- fold (high dose) levels for the Sprague-Dawley rat, and although within the range of observed plasma concentrations in the hamster, the shape of the simulated curves was not in good agreement with the hamster data.

TK_DOSED FEED PLASMA

100 ppm, 1000 ppm

Date given as first exposure is date blood samples taken. Animals were administered Wyeth 14,643 in certified NIH-07 feed (meal for dosed feed) for 9 days and into the 10th day for some. On the 9th day blood was taken from one animal per time point for 10-11 timepoints. Blood samples were collected beginning at noon on the 9th day and ending at 9 am on the 10th day (mice) or ending on 7 am (Wistar Furth rats) or beginning on 2 pm day 9 and ending on 10 am (100 ppm hamster) or noon (1000 ppm hamster).