Experiment Number: S0541
Route: Intravenous, Gavage, Dosed Feed
Species/Strain: Hamster/Syrian

Toxicokinetics Data Summary
Compound: Gemfibrozil/ **Analyte:** Gemfibrozil
CAS Number: 25812-30-0

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

Male

	Treatment Group (mg/kg)			
	15 IV Plasma[a,d]	**15 IV Plasma[b]**	**8 Gavage Plasma[a]**	**15 Gavage Plasma[a,e]**
Cmax_obs (ug/mL)	238		0.874	2.16
Tmax_obs (minute)			15	10
Beta Half-life (minute)	56.9		41.3	61.4
k01 (min^{-1})		0.0145 ± 0.0013		
k10 (min^{-1})		0.161 ± 0.011		
k12 (min^{-1})		0.0261 ± 0.0051		
k21 (min^{-1})		0.0164 ± 0.0031		
Cl (mL/min/kg)	17.4			
Cl1_F (mL/min/kg)			143	123
V1 (L/kg)		0.241 ± 0.012		
Vss (L/kg)				
MRT (minute)	10.5		73.4	88.3
AUCinf_pred (ug/mL*min)	862		56	122
F (percent)		0.252 ± 0.022	0.12	0.14

Male

Treatment Group (mg/kg)

	30 Gavage Plasma[a,e]	8 Gavage Plasma[b]
Cmax_obs (ug/mL)	6.95	
Tmax_obs (minute)	10	
Beta Half-life (minute)	46.0	
k01 (min^{-1})		0.0145 ± 0.0013
k10 (min^{-1})		0.161 ± 0.011
k12 (min^{-1})		0.0261 ± 0.0051
k21 (min^{-1})		0.0164 ± 0.0031
Cl (mL/min/kg)		
Cl1_F (mL/min/kg)	103	
V1 (L/kg)		0.241 ± 0.012
Vss (L/kg)		
MRT (minute)	74.9	
AUCinf_pred (ug/mL*min)	292	
F (percent)	0.17	0.252 ± 0.022

Male

Treatment Group (ppm)	
1500 Dosed Feed Plasma[c,f]	12000 Dosed Feed Plasma[c]

NO DATA RECORDED

LEGEND

MODELING SOFTWARE

PCNONLIN, Models 200 and 201, PCNONLIN

MODELING METHOD & BEST FIT MODEL

[a]Models 200 and 201, PCNONLIN software, SCI Software, Lexington, KY, Non-compartmental analysis

[b]Compartmental modeling techniques with established models or models written to simultaneously solve iv and oral data sets (SimuSolv, Version 3.0, The Dow Chemical Company, Midland, MI). 2-compartment model without the delay term

[c]Plasma concentrations attained after approximately 1 week of dosing with 1500 or 12000 ppm GEM in the feed were simulated using the 2-compartment equation derived from fitting the iv and low oral data (Studies or Supergroups T and V).

EXCEPTIONS

[d]Cmax equals C0 calculated by back extrapolation, For MRT parameter Estimate(0-T) divided by Estimate(inf) is less than 0.90.

[e]For MRT parameter Estimate(0-T) divided by Estimate(inf) is less than 0.90.

[f]No plasma samples were above the LOQ

ANALYTE

Gemfibrozil

TK PARAMETERS

Cmax_obs = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax_obs = Time at which Cmax predicted or observed occurs
Beta Half-life = Half-life for the beta phase
k01 = Absorption rate constant, ka
k12 = Distribution rate constant from first to second 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
Vss = Volume of distribution at steady state
MRT = Mean residence time
AUCinf_pred = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity
F = Bioavailability, absolute bioavailability

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Blood was collected post-dosing at 13 time points, 3 animals per time point. Analysis by HPLC. The limit of detection, LOD, is 0.031 ug/mL and the limit of quantitation, LOQ is 0.1 ug/mL.

TK_INTRAVENOUS PLASMA

15 mg/kg Male

Hamsters were administered a single intravenous dose of gemfibrozil (GEM) in the cephalic vein.

TK PARAMETERS PROTOCOL (cont'd)

ANALYSIS METHOD

Simulations of plasma concentrations after repeated dietary exposure were made using compartmental models of the single dose toxicokinetic data, anticipated feed consumption values, and 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.

TK_INTRAVENOUS PLASMA

15 mg/kg Male

Hamsters were administered a single intravenous dose of gemfibrozil (GEM) in the cephalic vein.

TK_GAVAGE PLASMA

8 mg/kg Male

Hamsters were administered a single oral gavage dose of gemfibrozil (GEM).

ANALYSIS METHOD

Blood was collected post-dosing at 11 time points, 3 animals per time point. Analysis by HPLC. The limit of detection, LOD, is 0.031 ug/mL and the limit of quantitation, LOQ is 0.1 ug/mL.

TK_GAVAGE PLASMA

8 mg/kg, 30 mg/kg Male

Hamsters were administered a single oral gavage dose of gemfibrozil (GEM).

TK PARAMETERS PROTOCOL (cont'd)

ANALYSIS METHOD

Blood was collected post-dosing at 10 time points, 3 animals per time point. Analysis by HPLC. The limit of detection, LOD, is 0.031 ug/mL and the limit of quantitation, LOQ is 0.1 ug/mL.

TK_GAVAGE PLASMA

15 mg/kg Male

Hamsters were administered a single oral gavage dose of gemfibrozil (GEM).

ANALYSIS METHOD

Blood was collected at 10 time points from one animal per time point on Study Day 7 beginning at 2 pm until the final time point at 10 am on Study Day 8. Analysis by HPLC. The limit of detection, LOD, is 0.031 ug/mL and the limit of quantitation, LOQ is 1.0 ug/mL.

TK_DOSED FEED PLASMA

1500 mg/kg Male

Hamsters were administered gemfibrozil (GEM) in dosed feed for 8 days. Analyzed feed concentration 1347 ppm. Calculated Study day 2-6 mean daily dose is 84.58 mg GEM/kg body weight/day. Each animal had free access to feed until time of sacrifice.

TK PARAMETERS PROTOCOL (cont'd)

ANALYSIS METHOD

Blood was collected at 11 time points from one animal per time point on Study Day 7 beginning at 2 pm until the final time point at noon on Study Day 8. Analysis by HPLC. The limit of detection, LOD, is 0.031 ug/mL and the limit of quantitation, LOQ is 1.0 ug/mL.

12000 mg/kg Male

Hamsters were administered gemfibrozil (GEM) in dosed feed for 8 days. Analyzed feed concentration 12600 ppm. Calculated Study day 2-6 mean daily dose is 748.62 mg GEM/kg body weight/day. Each animal had free access to feed until time of sacrifice.