

Experiment Number: S0541

Route: Intravenous, Gavage, Dosed Feed

Species/Strain: Rats/Sprague Dawley

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)

4.29 IV Plasma<sup>a,d</sup> 4.29 IV Plasma<sup>b,e</sup> 4.29 Gavage Plasma<sup>a,f</sup> 50 Gavage Plasma<sup>a,f</sup>

	4.29 IV Plasma <sup>a,d</sup>	4.29 IV Plasma <sup>b,e</sup>	4.29 Gavage Plasma <sup>a,f</sup>	50 Gavage Plasma <sup>a,f</sup>
Cmax_obs (ug/mL)	30.9		1.17	64.6
Tmax_obs (minute)			10	10
Beta Half-life (minute)	597		532	354
k01 (minute <sup>-1</sup> )		0.00468 ± 0.0012		
k12 (min <sup>-1</sup> )		0.112 ± 0.012		
Cl (mL/min/kg)	7.1			
Cl1_F (mL/min/kg)			9.1	8.9
V1 (L/kg)		0.529 ± 0.060		
Vss (L/kg)				
MRT (minute)	607		855	528
AUCinf_pred (ug/mL*min)	603		470	5621
F (percent)		1.09 ± 0.17	0.78	0.80

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Treatment Group (ppm)

100 Gavage Plasma<sup>a,f</sup> 4.29 Gavage Plasma<sup>b,e</sup>

Cmax_obs (ug/mL)	73.5	
Tmax_obs (minute)	10	
Beta Half-life (minute)	331	
k01 (min <sup>-1</sup> )		0.00468 ± 0.0012
k12 (min <sup>-1</sup> )		0.112 ± 0.012
Cl (mL/min/kg)		
Cl1_F (mL/min/kg)	7.8	
V1 (L/kg)		0.529 ± 0.060
Vss (L/kg)		
MRT (minute)	463	
AUCinf_pred (ug/mL*min)	12776	
F (percent)	0.91	1.09 ± 0.17

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**Male**

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**Treatment Group (mg/kg)**

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**100 Dosed Feed Plasma<sup>c,g</sup>    16000 Dosed Feed Plasma<sup>c</sup>**

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**NO DATA RECORDED**

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LEGEND

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MODELING SOFTWARE

PCNONLIN, Models 200 and 201, PCNONLIN

MODELING METHOD & BEST FIT MODEL

<sup>d</sup>Models 200 and 201, PCNONLIN software, SCI Software, Lexington, KY, Non-compartmental analysis

<sup>b</sup>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 employing a delay term in order to simulate the effect of enterohepatic recirculation

<sup>c</sup>Plasma concentrations attained after approximately 1 week of dosing with 100 or 16000 ppm GEM in the feed were simulated using the 2-compartment equation derived from fitting the iv and low oral data (Studies or Supergroups X and Y).

EXCEPTIONS

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

<sup>e</sup>km0, kmv, kvm values were 0.00297 SE 0.0028, 0.0125 SE -0.011, 0.00691 SE 0.0017 min<sup>-1</sup> respectively where SE means standard error

<sup>f</sup>For MRT parameter Estimate(0-T) divided by Estimate(inf) is less than 0.90.

<sup>g</sup>No plasma samples were above the LOQ

ANALYTE

Gemfibrozil

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TK PARAMETERS

C<sub>max\_obs</sub> = Observed or Predicted Maximum plasma (or tissue) concentration

T<sub>max\_obs</sub> = Time at which C<sub>max</sub> predicted or observed occurs

Beta Half-life = Half-life for the beta phase

k<sub>01</sub> = Absorption rate constant, k<sub>a</sub>

k<sub>12</sub> = Distribution rate constant from first to second compartment

Cl = Clearance, includes total clearance

Cl<sub>1\_F</sub> = Apparent clearance of the central compartment, also Cl<sub>1\_F</sub> for gavage groups in non-compartmental model

V<sub>1</sub> = Volume of distribution of the central compartment, includes V<sub>d</sub> and V volume of distribution, V<sub>z</sub> apparent volume of distribution NCA,  
V<sub>app</sub> apparent volume of distribution for intravenous studies

V<sub>ss</sub> = Volume of distribution at steady state

MRT = Mean residence time

AUC<sub>inf\_pred</sub> = 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

4.29 mg/kg Male

Rats were administered a single intravenous dose of gemfibrozil (GEM) in the tail vein.

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## 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\_INTRAVENTOUS PLASMA

#### 4.29 mg/kg Male

Two compartment model with delay absorption-ka to Central compartment-k12 to Metabolism-kpm to Re-absorption with km0 to excretion and kmp return to central compartment

### TK\_GAVAGE PLASMA

#### 4.29 mg/kg Male

Two compartment model with delay absorption-ka to Central compartment-k12 to Metabolism-kpm to Re-absorption with km0 to excretion and kmp return to central compartment

### ANALYSIS METHOD

Blood was collected post-dosing at 12 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.

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TK PARAMETERS PROTOCOL (cont'd)

TK\_GAVAGE PLASMA

4.29 mg/kg, 50 mg/kg, 100 mg/kg Male

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

ANALYSIS METHOD

Blood was collected at 9 time points from one animal per time point on Study Day 7 beginning at 6 am until the final time point at 1 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

100 mg/kg Male

Rats were administered gemfibrozil (GEM) in dosed feed for 7 days. Analyzed feed concentration 81.0 ppm. Calculated Study day 2-5 mean daily dose is 5.63 mg GEM/kg body weight/day. Each animal had free access to feed until time of sacrifice.

ANALYSIS METHOD

Blood was collected at 10 time points from one animal per time point on Study Day 7 beginning at 6 am until the final time point at 1 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

16000 mg/kg Male

Rats were administered gemfibrozil (GEM) in dosed feed for 7 days. Analyzed feed concentration 81.0 ppm. Calculated Study day 2-5 mean daily dose is 5.63 mg GEM/kg body weight/day. Each animal had free access to feed until time of sacrifice.