

Experiment Number: S0541
Route: Intravenous, Gavage, Dosed Feed
Species/Strain: Mouse/B6C3F1

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)

8.4 IV Plasma^{a,d} 8.4 IV Plasma^{b,e} 8.4 Gavage Plasma^{a,f} 16.6 Gavage Plasma^a

	8.4 IV Plasma ^{a,d}	8.4 IV Plasma ^{b,e}	8.4 Gavage Plasma ^{a,f}	16.6 Gavage Plasma ^a
Cmax_obs (ug/mL)	36.9		12.3	24.8
Tmax_obs (minute)			15	15
Beta Half-life (minute)	208		166	122
k01 (minute ⁻¹)		0.0730 ± 0.010		
k12 (min ⁻¹)		0.0854 ± 0.0078		
Cl (mL/min/kg)	8.5			
Cl1_F (mL/min/kg)			9.1	7.4
V1 (L/kg)		0.333 ± 0.039		
Vss (L/kg)				
MRT (minute)	180		205	193
AUCinf_pred (ug/mL*min)	987		927	2231
F (percent)		1.11 ± 0.097	0.94	1.14

Experiment Number: S0541
Route: Intravenous, Gavage, Dosed Feed
Species/Strain: Mouse/B6C3F1

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)

49.8 Gavage Plasma^a 8.4 Gavage Plasma^{b,e} 200 Dosed Feed Plasma^{c,g} 16000 Dosed Feed Plasma^c

Cmax_obs (ug/mL)	73.1			
Tmax_obs (minute)	15			
Beta Half-life (minute)	57.9			
k01 (min ⁻¹)		0.0730 ± 0.010		
k12 (min ⁻¹)		0.0854 ± 0.0078		
Cl (mL/min/kg)				
Cl1_F (mL/min/kg)	9.5			
V1 (L/kg)		0.333 ± 0.039		
Vss (L/kg)				
MRT (minute)	197			
AUCinf_pred (ug/mL*min)	5237			
F (percent)	0.89	1.11 ± 0.097		

Experiment Number: S0541

Route: Intravenous, Gavage, Dosed Feed

Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary

Compound: Gemfibrozil/ **Analyte:** Gemfibrozil

CAS Number: 25812-30-0

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: RTI

LEGEND

MODELING SOFTWARE

Models 200 and 201, PCNONLIN

MODELING METHOD & BEST FIT MODEL

^aModels 200 and 201, PCNONLIN software, SCI Software, Lexington, KY, Non-compartmental analysis

^bCompartmental 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

^cPlasma concentrations attained after approximately 1 week of dosing with 200 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 P and Q).

EXCEPTIONS

^dC_{max} equals C₀ calculated by back extrapolation, For MRT parameter Estimate(0-T) divided by Estimate(inf) is less than 0.90.

^ekm₀, km_v, km_w values were 0.0110 SE 0.0036, 0.150 SE 0.0047, and 0.0112 SE 0.0020 min⁻¹ respectively where SE means standard error

^fFor MRT parameter Estimate(0-T) divided by Estimate(inf) is less than 0.90.

^g3 out of 9 plasma samples below the LOQ

ANALYTE

Gemfibrozil

Experiment Number: S0541

Route: Intravenous, Gavage, Dosed Feed

Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary

Compound: Gemfibrozil/ **Analyte:** Gemfibrozil

CAS Number: 25812-30-0

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: RTI

TK PARAMETERS

C_{max_obs} = Observed or Predicted Maximum plasma (or tissue) concentration

T_{max_obs} = Time at which C_{max} predicted or observed occurs

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

k₀₁ = Absorption rate constant, k_a

k₁₂ = Distribution rate constant from first to second compartment

Cl = Clearance, includes total clearance

Cl_{1_F} = Apparent clearance of the central compartment, also Cl_{1_F} for gavage groups in non-compartmental model

V₁ = Volume of distribution of the central compartment, includes V_d and V volume of distribution, V_z apparent volume of distribution NCA,
V_{app} apparent volume of distribution for intravenous studies

V_{ss} = Volume of distribution at steady state

MRT = Mean residence time

AUC_{inf_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_INTRAVENTOUS PLASMA

8.4 mg/kg Male

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

Experiment Number: S0541

Route: Intravenous, Gavage, Dosed Feed

Species/Strain: Mouse/B6C3F1

Toxicokinetics Data Summary

Compound: Gemfibrozil/ **Analyte:** Gemfibrozil

CAS Number: 25812-30-0

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: RTI

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

8.4 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

8.4 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.

TK_GAVAGE PLASMA

8.4 mg/kg, 16.6 mg/kg Male

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

Experiment Number: S0541
Route: Intravenous, Gavage, Dosed Feed
Species/Strain: Mouse/B6C3F1

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

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

TK PARAMETERS PROTOCOL (cont'd)

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

49.8 mg/kg Male

Mice 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

200 mg/kg Male

Mice were administered gemfibrozil (GEM) in dosed feed for 7 days. Analyzed feed concentration 174 ppm. Calculated Study day 2-5 mean daily dose is 32.82 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.

Experiment Number: S0541
Route: Intravenous, Gavage, Dosed Feed
Species/Strain: Mouse/B6C3F1

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

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

TK PARAMETERS PROTOCOL (cont'd)

TK_DOSED FEED PLASMA

16000 mg/kg Male

Mice were administered gemfibrozil (GEM) in dosed feed for 7 days. Analyzed feed concentration 20069 ppm. Calculated Study day 2-5 mean daily dose is 3014.78 mg GEM/kg body weight/day. Each animal had free access to feed until time of sacrifice.