ADME NTP Study S0637 Gemfibrozil

The contract laboratory abbreviation for the test article is GEM.
Radiolabeled Phenolphthalein (PTH) was also tested for comparison.

Species: adult male and female Sprague Dawley rats and Syrian Golden hamsters (Lak:LVG(SYR)BR).
Vehicles: intravenous (GEM and PTH), Emulphor:ethanol:water 1:1:8; oral (GEM), 0.5% aqueous methylcellulose (Studies A-G) or feed slurry (Studies H-I); oral (PTH), Emulphor:ethanol:water 1:1:8.

CASRN 25812-30-0
Gemfibrozil was radiolabeled with carbon-14 in the ring methyl groups; Gemfibrozil, [ring methyl-UL-^{14}C]-.
Phenolphthalein was radiolabeled with carbon-14 in the hydroxyphenyl rings; [^{14}C]Phenolphthalein

Gemfibrozil Studies Performed:

Study A – Single 30 mg/kg oral administration to male and female rats with sacrifice 72 hours postdose.

Study B – Single 30 mg/kg oral administration to male and female hamsters with sacrifice 72 hours postdose.

Study C – Single 3 mg/kg intravenous administration to male and female rats with bile collected to 4 hours postdose.

Study D – Single 3 mg/kg intravenous administration to male and female hamsters with bile collected to 4 hours postdose.

Study E – Single 2000 mg/kg oral administration to male and female rats with sacrifice 72 hours postdose.

Study F – Single 2000 mg/kg oral administration to male and female hamsters with sacrifice 72 hours postdose.

Study G – 11-day repeat 30 mg/kg/day oral administration to male rats with radiolabeled GEM administered on days 1, 5, and 9 and sacrifice on day 12.

Study H – 50 mg/kg dosed feed study in male rats with sacrifice at 24 hours.

Study I – 50 mg/kg dosed feed study in male hamsters with sacrifice at 24 hours.

Determination of tissue partition coefficients for GEM in rat and hamster tissues.

Phenolphthalein Studies Performed:

Study 1 – Single 25 mg PTH/kg intravenous administration to female rats with bile collection to 4 hours postdose.

Study 2 – Single 25 mg PTH/kg intravenous administration to female hamsters with bile collection to 4 hours postdose.

Study 3 – Single 800 mg PTH/kg oral administration (feed slurry) to female hamsters with sacrifice 72 hours postdose.

Study 4 – Single 800 mg PTH/kg oral administration (feed slurry) to female rats with sacrifice 72 hours postdose.

In Study G, male rats received 11 daily oral doses of 30 mg GEM per kg body weight (N = 4). Non-radiolabeled GEM was administered on days 2-4, 6-8, 10 and 11. On days 1, 5, and 9, radiolabeled GEM was added to the non-radiolabeled GEM dose solution for the same 4 rats. Excreta was collected for time intervals following radiolabeled dosing on days 1, 5, or 9 (maximum 96, 96, and 72 hours, respectively, following radiolabel administration) and tissues were collected at terminal sacrifice on day 12.

Study H (rats) and Study I (hamsters) are oral absorption studies using feed slurry (NTP2000 meal milled to 80 mesh, water and radiolabel). An indwelling jugular cannula was surgically implanted into animals used in these absorption studies (GEM) to facilitate serial collection of blood samples.

Toxicokinetics:
Standard noncompartmental models (WinNonlin Version 1.5, Scientific Consulting, Inc., Cary, NC) were used to analyze plasma GEM concentration versus time data from the oral feed study and from a previous gemfibrozil toxicokinetic study (Grizzle TB, Buckley LA, and Handy RW. 1995. Toxicokinetics of Gemfibrozil. Research Triangle Institute, Research Triangle Park). Data from each of the four cannulated animals per species were analyzed separately and the pharmacokinetic parameters were then averaged for the four animals. In the previous study, male Sprague-Dawley rats and male Syrian Golden hamsters were administered a single oral (aqueous methylcellulose vehicle) or intravenous (1:1:8, ethanol:Emulphor:water vehicle) dose of GEM and plasma was obtained from three animals per time point. A single mean plasma GEM concentration versus time curve was available for analysis.

All data were weighted as 1/Y, and the following pharmacokinetic parameters were determined: maximum observed concentration (C_{max}) and time that C_{max} was observed T_{min}, elimination rate constant (ß), elimination half-life ($t_{1/2}$), area under the plasma concentration versus time curve (AUC), apparent volume of distribution (V), clearance (CI), mean residence time (MRT), and bioavailability (F).

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Table 1

Cumulative Excretion of Radioactivity by Rats Following Oral Administration of 30 mg/kg [^{14}C]Gemfibrozil[a] - Study A

(Percent of Administered Dose; Mean ± SD; N = 4)

End of Collection Period (h)	Urine	Feces	Volatile Organics[b]	CO_2[b]	Total
		Males			
6	2.9 ± 0.7	c	d	d	2.9 ± 0.7
12	6.7 ± 1.5	d	d	d	6.7 ± 1.5
24	15.4 ± 3.4	37.2 ± 11.9	d	d	52.6 ± 9.1
48	24.1 ± 6.5	54.4 ± 12.3	d	d	78.5 ± 6.6
72	29.9 ± 9.0[e]	58.5 ± 11.8	d	d	88.4 ± 4.0
		Females			
6	4.4 ± 1.4	c	d	d	4.4 ± 1.4
12	8.8 ± 2.2	2.6 ± 4.8	d	d	11.5 ± 4.0
24	19.8 ± 2.5	27.5 ± 7.1	d	d	47.3 ± 5.1
48	28.0 ± 3.3	51.2 ± 3.9	d	d	79.2 ± 3.1
72	32.7 ± 3.8[e]	56.1 ± 3.7	d	d	88.7 ± 1.8

a The target dose was 30 mg GEM/kg. The actual doses delivered were 30 and 29 mg GEM/kg to male and female rats, respectively.

b Volatile organics and CO_2 in exhaled breath.

c The first feces collection was 0-12 h.

d Values are less than 0.05%.

e Includes results from bladder, urine, and final cage rinse.

Table 2

Cumulative Excretion of Radioactivity by Male Rats Following Repeated Oral Administration of 30 mg/kg [^{14}C]Gemfibrozil[a] - Study G (Percent of Administered Dose[b]; Mean ± SD; N = 4)

Day #1 Results

End of Collection Period (h)	Urine	Feces	Total
4	3.0 ± 1.6	c	3.0 ± 1.6
8	5.8 ± 1.9	c	5.8 ± 1.9
24	15.8 ± 2.0[d]	24.8 ± 8.0	40.5 ± 8.8
48	24.1 ± 2.5	44.2 ± 5.7	68.2 ± 6.6
72	28.2 ± 3.2[d]	49.6 ± 5.1	77.7 ± 3.1
96	29.4 ± 3.4	51.2 ± 5.3	80.6 ± 3.1

Day #5 Results

End of Collection Period (h)	Urine	Feces	Total
4	3.6 ± 2.7	c	3.6 ± 2.7
8	8.2 ± 1.9	c	8.2 ± 1.9
24	18.1 ± 2.9[d]	31.5 ± 2.9	49.6 ± 4.8
48	22.4 ± 3.1	43.8 ± 4.6	66.2 ± 6.6
72	25.0 ± 2.5[d]	49.4 ± 4.2	74.4 ± 5.2
96	26.1 ± 2.3	51.0 ± 4.3	77.1 ± 4.8

Day #9 Results

End of Collection Period (h)	Urine	Feces	Total
4	3.5 ± 1.8	c	3.5 ± 1.8
8	6.7 ± 1.9	c	6.7 ± 1.9
24	15.5 ± 2.1[d]	39.4 ± 6.5	54.8 ± 4.8
48	19.9 ± 3.1	54.1 ± 7.6	73.9 ± 5.2
72	22.6 ± 3.7[e]	59.6 ± 8.0	82.2 ± 4.9

Summary of Excretion Results[f]

Overall Percent of Dose Recovered in :		Overall Percent Dose Excreted
Urine	Feces	
26.0 ± 2.5	54.1 ± 5.4	80.1 ± 3.6

a The target dose was 30 mg GEM/kg. The actual radiolabeled doses were 29.6, 29.6, and 30.1 mg GEM/kg delivered on days # 1, 5, and 9, respectively.

b Results are based on the percent of administered dose excreted after each of the three radiolabeled doses. (Note, the excretion results of each of the radiolabeled doses are independent of the radiolabeled doses previously delivered.)

c The first feces collection was 0-24 h.

d Includes results from cage rinse.

e Includes results from bladder urine and final cage rinse.

f Results are based on the sum of the three radiolabeled doses delivered.

Table 3

Cumulative Excretion of Radioactivity by Rats Following Oral Administration of 2000 mg/kg [^{14}C]Gemfibrozil[a] - Study E

(Percent of Administered Dose; Mean ± SD; N = 4)

End of Collection Period (h)	Urine	Feces	Volatile Organics[b]	CO_2[b]	Total
		Males			
6	3.7 ± 1.2	c	d	d	3.7 ± 1.2
12	7.9 ± 1.2	1.2 ± 1.1	d	d	9.1 ± 0.9
24[e]	15.7 ± 1.5	12.9 ± 5.8	d	0.1 ± d	28.6 ± 5.2
48[ef]	38.4 ± 11.2	26.1 ± 16.0	d	0.1 ± d	64.6 ± 8.0
72[ef]	55.1 ± 15.8[g]	33.9 ± 19.5	d	0.1 ± d	89.1 ± 3.8
		Females			
6	4.0 ± 1.3	c	d	d	4.1 ± 1.3
12	8.1 ± 1.7	0.8 ± 0.5	d	0.1 ± d	8.9 ± 1.3
24	16.1 ± 3.0	5.8 ± 0.9	d	0.1 ± d	22.0 ± 2.6
48	42.1 ± 6.0	12.0 ± 1.4	d	0.1 ± d	54.2 ± 4.9
72	70.1 ± 1.9[g]	17.1 ± 2.0	d	0.1 ± d	87.3 ± 1.5

a The target dose was 2000 mg GEM/kg. The actual doses delivered were 1840 and 1745 mg GEM/kg to male and female rats, respectively.

b Volatile organics and CO_2 in exhaled breath.

c The first feces collection was 0-12 h.

d Values are less than 0.05%.

e Starting at 24 h and continuing through 72 h following dosing, there was a disparity in the percent dose recovered in feces of male rats as shown by the large standard deviations. The percent dose recovered for each individual animal at each timepoint is as follows : E.M1 – 24 h = 6.3%, 48 h = 3.1%, 72 h = 6.8%, Total = 16.2%; E.M3 – 24 h = 18.9%, 48 h = 19.0%, 72 h = 12.8%, Total = 50.7%; E.M4 – 24 h = 14.9%, 48 h = 25.3%, 72 h = 9.2%,
Total = 49.4%; E.M5 - 24h = 6.5%, 48h = 5.7%, 72h = 2.4%, Total = 14.6%.

f As with feces, the percent dose recovered in urine of male rats varied beginning at 48 h and continuing through 72 h following dosing. The percent dose recovered for each individual animal at the two timepoints is as follows : E.M1 – 48 h = 25.2%, 72 h = 25.5%, Total = 50.7%; E.M3 – 48 h = 12.9%, 72 h = 12.9%, Total = 25.8%; E.M4 – 48 h = 15.4%, 72 h = 11.6%, Total = 27.0%; E.M5 – 48 h = 37.4%, 72 h = 16.9%, Total = 54.3%.

g Includes results from bladder urine and final cage rinse.

Table 4

Cumulative Excretion of Radioactivity by Hamsters Following Oral Administration of 30 mg/kg [^{14}C]Gemfibrozil[a] - Study B

(Percent of Administered Dose; Mean ± SD; N = 4)

End of Collection Period (h)	Urine	Feces	Volatile Organics[b]	CO_2[b]	Total
		Males			
6	48.8 ± 5.1	c	d	d	48.8 ± 5.1
12	69.3 ± 0.6	2.2 ± 0.3	d	d	71.5 ± 0.7
24	78.6 ± 0.4	3.1 ± 0.4	d	d	81.7 ± 0.6
48	83.8 ± 1.2	3.6 ± 0.5	d	d	87.4 ± 1.4
72	90.1 ± 1.1[e]	3.7 ± 0.5	d	d	93.8 ± 1.0
		Females			
6	51.6 ± 4.4	c	d	d	51.6 ± 4.4
12	66.6 ± 4.2	1.3 ± 0.6	d	d	67.9 ± 4.2
24	77.6 ± 5.5	1.8 ± 0.6	d	d	79.4 ± 6.0
48	85.0 ± 3.7	2.7 ± 1.5	d	d	87.7 ± 4.7
72	90.5 ± 2.5[e]	3.0 ± 1.7	d	d	93.5 ± 3.5

a The target dose was 30 mg GEM/kg. The actual dose delivered was also 30 mg GEM/kg to both male and female hamsters.
b Volatile organics and CO_2 in exhaled breath.
c The first feces collection was 0-12 h.
d Values are less than 0.05%.
e Includes results from bladder urine and final cage rinse.

Table 5

Cumulative Excretion of Radioactivity by Hamsters Following Oral Administration of 2000 mg/kg [^{14}C]Gemfibrozil[a] - Study F (Percent of Administered Dose; Mean ± SD; N = 4)

End of Collection Period (h)	Urine	Feces	Volatile Organics[b]	CO_2[b]	Total
		Males			
6	6.0 ± 2.3	c	d	d	6.0 ± 2.3
12	19.1 ± 2.1	0.3 ± 0.5	d	d	19.4 ± 2.1
24	41.5 ± 5.8	0.7 ± 0.4	d	d	42.1 ± 5.8
48	71.7 ± 6.5	2.8 ± 0.6	d	d	74.5 ± 7.0
72	90.6 ± 2.4[e]	3.6 ± 0.3	d	d	94.1 ± 2.5
		Females			
6	4.6 ± 1.0	c	d	d	4.5 ± 1.4
12	15.4 ± 2.4	0.2 ± 0.3	d	d	15.5 ± 2.6
24	44.3 ± 6.4	0.5 ± 0.3	d	d	44.7 ± 6.2
48	75.7 ± 7.4	2.6 ± 0.7	d	d	78.4 ± 7.2
72	89.7 ± 3.7[e]	3.6 ± 0.7	d	d	93.3 ± 3.4

a The target dose was 2000 mg GEM/kg. The actual doses delivered were 1873 and 1886 mg GEM/kg to male and female hamsters, respectively.
b Volatile organics and CO_2 in exhaled breath.
c The first feces collection was 0-12 h.
d Values are less than 0.05%.
e Includes results from bladder urine and final cage rinse.

Table 6

Concentration of Radioactivity in Tissue Following Oral Administration of [^{14}C]GEM to Rats and Hamsters

Study ID	Species / Sex	Dose Level mg/kg[a]	Tissue Name[b]	µg-eq /g Tissue	% Administered Dose in Tissue
Study A	Rat / Male	30	Blood[c]	0.359 ± 0.111	0.06 ± 0.02
			Testes[d]	0.372	e
	Rat / Female	30	Blood	0.236 ± 0.0193	0.04 ± e
Study B	Hamster / Male	30	Blood	0.0242 ± 0.00354	e
			Testes	0.0228	e
	Hamster / Female	30	Blood	0.0120 ± 0.00183	e
Study E	Rat / Male	2000	Blood	38.9 ± 2.38	0.10 ± 0.06
			Kidney	105 ± 48.6	0.04 ± 0.02
			Liver	95.6 ± 23.8	0.23 ± 0.12
			Testes	29.7	0.01
	Rat / Female	2000	Blood	53.1 ± 25.0	0.15 ± 0.07
			Kidney	76.9 ± 25.9	0.03 ± 0.01
			Liver	93.7 ± 25.3	0.24 ± 0.06
Study F	Hamster / Male	2000	Blood	3.96 ± 1.06	0.01 ± e
			Kidney	6.63 ± 1.92	e
			Liver	24.5 ± 2.40	0.06 ± 0.01
			Testes	2.74	e
	Hamster / Female	2000	Blood	7.55 ± 3.82	0.02 ± 0.01
			Kidney	27.7 ± 30.7	0.01 ± 0.02
			Liver	25.4 ± 3.41	0.06 ± 0.01
Study G[f]	Rat / Male	30 x 11 days	Blood	0.383 ± 0.179	0.02 ± 0.01
			Kidney	0.948 ± 0.304	0.01 ± e
			Liver	1.55 ± 0.210	0.08 ± 0.02
			Sm. Intestine	2.74 ± 1.56	0.33 ± 0.17
			Sm. Int. Contents	266 ± 63.7	1.49 ± 0.20
			Cecum	1.08 ± .577	0.11 ± 0.06
			Cecum Contents	49.7 ± 12.5	0.68 ± 0.27
			Lg. Intestine	0.116 ± 0.108	0.01 ± 0.01
			Lg. Int. Contents	25.4 ± 9.95	0.16 ± 0.10
			Bile	g	0.03 ± 0.02
			Testes	0.265	e

a The dose (mg GEM/kg) values listed are the target values. The actual doses delivered were: Study A - 30 and 29 mg GEM/kg to male and female rats, respectively; Study B - 30 mg GEM/kg to both male and female rats; Study E - 1840 and 1745 mg GEM/kg to male and female hamsters, respectively; Study F - 1873 and 1886 mg GEM/kg to male and female hamsters, respectively; Study G - a daily average for 11 days of 29 mg GEM/kg.

b The tissues analyzed differed depending on the study.

c Blood represents 5.2% of total body weight.

d The testes from only two male animals per study were examined; therefore, there is no standard deviation.

e Value(s) less than 0.005%.

f Study G was a repeated-dose oral study. Radiolabeled GEM was administered to rats on Days #1, 5, and 9. The milligrams of GEM and the microcuries of radiolabeled GEM delivered to each rat from the three radiolabeled doses were summed and used for these calculations.

g At the time of sacrifice the bile duct of each rat was cannulated in order to account for any radioactivity in the duct between the liver and the small intestine. The weight of the bile collected was not measured. The bile was analyzed directly. Therefore, only the percent dose recovered in the bile that was collected was determined.

Table 7

Cumulative Excretion of Radioactivity by Female Rats Following Oral Administration of 800 mg/kg [^{14}C]PTH[a] - Study 4

(Percent of Administered Dose; Mean ± SD; N = 5)

End of Collection Period (h)	Urine	Feces	Total
6	0.9 ± 1.0	[b]	0.9 ± 1.0
12	2.4 ± 0.8	4.3 ± 9.6	6.7 ± 9.7
24	3.0 ± 0.9	74.2 ± 19.3	77.2 ± 20.1
48	3.2 ± 0.8	80.9 ± 18.3	84.2 ± 19.0
72	3.5 ± 0.7[c]	82.2 ± 18.2	85.7 ± 18.9

a The target dose was 800 mg PTH/kg. The actual dose delivered was 719 mg PTH/kg.

b The first feces collection was 0-12 h.

c Includes results from cage rinse.

Table 8

Cumulative Excretion of Radioactivity by Female Hamsters Following Oral Administration of 800 mg/kg [^{14}C]PTH[a] - Study 3

(Percent of Administered Dose; Mean ± SD; N = 5)

End of Collection Period (h)	Urine	Feces	Total
6	14.3 ± 3.6	b	14.3 ± 3.6
12	21.0 ± 5.2	36.6 ± 11.1	57.6 ± 9.6
24	26.1 ± 6.0	42.2 ± 10.4	68.3 ± 8.0
48	29.7 ± 5.7	45.3 ± 10.5	75.0 ± 7.8
72	35.0 ± 3.9[c]	46.2 ± 10.6	81.2 ± 7.7

a The target dose was 800 mg PTH/kg. The actual dose delivered was 715 mg PTH/kg.

b The first feces collection was 0-12 h.

c Includes results from cage rinse.

Table 9

Cumulative Excretion of Radioactivity in Bile by Rats Following Intravenous Administration of [^{14}C]GEM (3 mg/kg)[a] - Study C (Percent of Administered Dose)

Males

End of Collection Period (h)	C.M1	C.M3	C.M4	C.M5	Mean ± SD
0.5	17.9	78.6	64.6	73.3	58.6 ± 27.8
1	63.7	92.9	87.3	88.4	83.1 ± 13.1
1.5	93.4	95.7	93.9	93.6	94.1 ± 1.05
2	100	96.4	95.4	95.0	96.7 ± 2.34
2.5	102	96.8	96.0	95.5	97.7 ± 3.25
3	103	97.0	96.3	95.7	98.1 ± 3.56
3.5	104	97.1	96.5	95.8	98.3 ± 3.71
4	104	97.2	96.6	95.9	98.5 ± 3.83

Females

End of Collection Period (h)	C.F1	C.F2	C.F4	C.F5	Mean ± SD
0.5	52.3	62.3	66.4	52.2	58.3 ± 7.17
1	82.2	82.6	91.1	84.7	85.1 ± 4.11
1.5	95.0	90.9	97.7	93.1	94.1 ± 2.89
2	101	95.3	99.5	96.7	98.0 ± 2.42
2.5	103	96.8	100	98.0	99.6 ± 2.84
3	105	97.5	101	98.5	100 ± 3.28
3.5	105[b]	97.8	101	98.7[c]	101 ± 3.28
4	105[b]	98.0	101	98.7[c]	101 ± 3.22

a The target dose was 3 mg GEM/kg. The actual dose delivered was also 3 mg GEM/kg to both male and female rats.

b C.F1 died between 3 and 3.5 h following dosing.

c C.F5 died at 3.5 h following dosing.

Table 10

Rate of Excretion of Bile by Rats Following Intravenous Administration of [^{14}C]GEM (3 mg/kg)[a] - Study C

(mg Bile Excreted/min/kg)

Males

End of Collection Period (h)	C.M1	C.M3	C.M4	C.M5	Mean ± SD
0.5	26	103	73	99	75 ± 36
1	61	89	73	93	79 ± 15
1.5	74	84	68	87	78 ± 9
2	71	77	66	78	73 ± 6
2.5	69	70	61	73	68 ± 5
3	62	68	60	66	64 ± 4
3.5	62	65	81	63	68 ± 9
4	60	64	41	64	57 ± 11

Females

End of Collection Period (h)	C.F1	C.F2	C.F4	C.F5	Mean ± SD
0.5	62	108	103	62	84 ± 25
1	58	98	120	65	85 ± 29
1.5	63	83	116	50	78 ± 29
2	64	104	87	63	80 ± 20
2.5	65	91	83	73	78 ± 12
3	65	86	75	70	74 ± 9
3.5	30[b]	76	63	42[c]	53 ± 21
4	b	73	74	c	74[d]

a The target dose was 3 mg GEM/kg. The actual dose delivered was also 3 mg GEM/kg to both male and female rats.

b C.F1 died between 3 and 3.5 h following dosing.

c C.F5 died at 3.5 h following dosing.

d N = 2.

Table 11

Cumulative Excretion of Radioactivity in Bile by Hamsters Following Intravenous Administration of [^{14}C]GEM (3 mg/kg)[a] - Study D

(Percent of Administered Dose)

Males

End of Collection Period (h)	D.M1	D.M2	D.M3	D.M4	Mean ± SD
1	9.47	23.2	8.96	11.5	13.3 ± 6.7
2	15.4	27.1	11.8	15.7	17.5 ± 6.6
3	18.1	29.0	12.9	17.4	19.4 ± 6.8
4	19.4	29.7	13.6	18.5	20.3 ± 6.8

Females[b]

End of Collection Period (h)	D.F1	D.F6	D.F7	Mean ± SD
1	4.80	5.14	5.98	5.31 ± 0.61
2	6.71	7.07	7.18	6.99 ± 0.25
3	7.31	7.73	7.54	7.53 ± 0.21
4	7.49	8.10	7.69	7.76 ± 0.31

a The target dose was 3 mg GEM/kg. The actual dose delivered was also 3 mg GEM/kg to both male and female hamsters.

b D.F5 died shortly after the 3-h timepoint. As shown in footnote b of Table 16, D.F5 bile flow was diminished throughout the collection period as compared to the other female hamsters. The cumulative excretion of radioactivity in bile by D.F5 was as follows: 1 h = 2.03; 2 h = 3.52; 3 h = 3.85; 4 h = 3.89. If the data from D.F5 are included with the data from the other female hamsters, the following cumulative excretion results are obtained (N=4): 1 h = 4.49 ± 1.71; 2 h = 6.12 ± 1.75; 3h = 6.61 ± 1.85; 4 h = 6.79 ± 1.95.

Table 12

Rate of Excretion of Bile by Hamsters Following Intravenous Administration of [^{14}C]GEM (3 mg/kg)[a] - Study D

(mg Bile Excreted/min/kg)

Males

End of Collection Period (h)	D.M1	D.M2	D.M3	D.M4	Mean ± SD
1	41	64	42	51	50 ± 10
2	46	71	49	56	56 ± 11
3	45	69	46	63	55 ± 12
4	47	37	44	68	49 ± 13

Females[b]

End of Collection Period (h)	D.F1	D.F6	D.F7	Mean ± SD
1	44	39	55	46 ± 8
2	61	55	56	57 ± 3
3	66	43	54	54 ± 12
4	64	42	49	52 ± 11

a The target dose was 3 mg GEM/kg. The actual dose delivered was also 3 mg GEM/kg to both male and female hamsters.

b D.F5 died shortly after the 3-h timepoint and had diminished bile flow throughout the collection period. The rate of excretion of bile for D.F5 was as follows: 1 h = 32; 2 h = 31; 3 h = 9; 4 h = 10. If the data from D.F5 are included with the data from the other female hamsters, the following average rate of excretion results are obtained (N=4) : 1 h = 42 ± 10; 2 h = 51 ± 14; 3 h = 43 ± 25; 4 h = 41 ± 23.

Table 13

Cumulative Excretion of Radioactivity in Bile by Female Rats Following Intravenous Administration of [^{14}C]PTH (25 mg/kg)[a] - Study 1 (Percent of Administered Dose)

End of Collection Period (h)	R-F1	R-F2	R-F3	R-F4	R-F6	Mean ± SD
0.5	33.4	49.7	37.7	30.5	42.5	38.8 ± 7.6
1	54.9	71.6	66.2	57.9	68.3	63.8 ± 7.1
1.5	66.1	81.5	79.0	72.1	79.3	75.6 ± 6.4
2	73.5	86.6	84.9	79.0	85.4	81.9 ± 5.5
2.5	79.0	89.5	88.4	82.8	89.0	85.8 ± 4.6
3	83.4	91.3	90.3	85.0	90.9	88.2 ± 3.7
3.5	86.0	92.3	91.6	86.7	92.1	89.7 ± 3.2
4	88.4	93.1	92.7	88.4	92.9	91.1 ± 2.5

[a] The target dose was 25 mg PTH/kg. The actual dose delivered was 25 mg PTH/kg.

Table 14

Rate of Excretion of Bile by Female Rats Following Intravenous Administration of [^{14}C]PTH (25 mg/kg)[a] - Study 1

(mg Bile Excreted/min/kg)

End of Collection Period (h)	R-F1	R-F2	R-F3	R-F4	R-F6	Mean ± SD
0.5	73.3	117	78.0	81.8	96.9	89.3 ± 17.6
1	81.0	120	92.2	83.2	108	96.8 ± 16.6
1.5	75.8	114	101	87.1	99.0	95.3 ± 14.4
2	70.4	108	87.6	85.3	94.4	89.2 ± 13.8
2.5	67.4	93.4	93.6	82.4	92.4	85.8 ± 11.3
3	71.7	82.9	97.0	80.5	77.7	82.0 ± 9.4
3.5	63.8	90.2	89.9	79.6	74.9	79.7 ± 11.1
4	73.7	94.8	96.0	125	79.8	93.9 ± 20.0

[a] The target dose was 25 mg PTH/kg. The actual dose delivered was 25 mg PTH/kg.

Table 15

Cumulative Excretion of Radioactivity in Bile by Female Hamsters Following Intravenous Administration of [^{14}C]PTH (25.8 mg/kg)[a] - Study 2 (Percent of Administered Dose)

End of Collection Period (h)	H-F1	H-F2	H-F3	H-F4	H-F6	Mean ± SD
1	40.7	51.3	23.6	34.9	46.4	39.4 ± 10.8
2	52.9	62.8	37.3	48.9	57.2	51.8 ± 9.6
3	58.5	66.0	45.5	52.6	61.4	56.8 ± 8.0
4	61.8	68.6	50.5	54.7	64.1	60.0 ± 7.3

[a] The target dose was 25 mg PTH/kg. The actual dose delivered was 25.8 mg PTH/kg.

Table 16

Rate of Excretion of Bile by Female Hamsters Following Intravenous Administration of [^{14}C]PTH (25.8 mg/kg)[a] - Study 2

(mg Bile Excreted/min/kg)

End of Collection Period (h)	H-F1	H-F2	H-F3	H-F4	H-F6	Mean ± SD
1	83.4	106	41.7	47.5	72.3	70.2 ± 26.4
2	51.4	81.2	44.0	44.2	56.4	55.4 ± 15.3
3	57.7	68.4	46.2	37.1	46.8	51.2 ± 12.1
4	70.4	83.9	53.3	40.0	52.4	60.0 ± 17.2

[a] The target dose was 25 mg PTH/kg. The actual dose delivered was 25.8 mg PTH/kg.

Table 17

GEM Tissue Partition Coefficients for Male Rats and Hamsters
(Mean ± SD; N = 6)

Tissues	Rat Samples		Hamster Samples	
	Tissue : Saline	Tissue : Blood	Tissue : Saline	Tissue : Blood
Blood	34 ± 9	unity	46 ± 10	unity
Liver	633 ± 247	19 ± 7	267 ± 195	5.8 ± 4.2
Adipose	268 ± 81	7.9 ± 2.4	88 ± 55	1.9 ± 1.2
Muscle	19 ± 3	0.57 ± 0.08	43 ± 16	0.94 ± 0.36
Testes	25 ± 6	0.73 ± 0.17	11 ± 4	0.23 ± 0.08

Table 18

GEM and Acyl-Glucuronide Concentration in Plasma following a Single Oral Dose of [^{14}C]GEM in a Feed Slurry[a]

	Male Sprague-Dawley Rats				Male Syrian Golden Hamsters							
Time after Dosing	GEM (μg/mL)				GEM (μg/mL)				Acyl-Glucuronide (μg-eq[d]/mL)			
	H.R2[b]	H.R4	H.R5	H.R6	I.M3	I.M4	I.M6	I.M7	I.M3	I.M4	I.M6	I.M7
5 min	11.3	4.8	7.7	7.9	6.1	0.3	7.4	5.4	16.0	0.6	38.4	32.5
10 min	8.8	7.6	8.7	10.7	5.0	0.7	4.4	1.0	24.4	2.3	34.5	13.6
15 min	7.0	SL[c]	8.3	9.9	2.9	0.8	2.6	2.1	22.9	4.6	31.4	26.0
30 min	6.7	6.5	9.4	12.0	3.9	4.2	2.1	1.0	32.7	28.8	29.7	20.3
45 min	—	—	—	—	2.8	3.1	2.0	0.9	27.5	31.4	26.3	17.3
1 h	10.5	9.8	14.6	13.0	2.5	3.4	1.6	0.9	26.3	37.7	21.3	17.0
1.5 h	—	—	—	—	3.0	4.0	1.4	1.4	34.7	39.8	23.7	21.1
2 h	7.7	9.0	SL	7.3	2.1	3.0	1.3	1.3	29.3	46.1	21.6	22.4
3 h	8.9	11.1	6.9	5.5	2.0	1.2	1.2	2.1	26.8	21.4	20.6	24.8
4 h	8.3	8.7	SL	5.6	0.6	0.4	0.4	1.4	12.6	8.9	8.2	25.6
5 h	6.6	7.6	7.8	3.2	0.4	0.2	0.3	0.5	7.6	4.9	6.2	12.7
6 h	5.3	7.8	2.2	2.6	—	—	—	—	—	—	—	—
8 h	5.1	6.0	1.6	4.9	—	—	—	—	—	—	—	—
24 h	1.2	1.4	0.7	1.2	—	—	—	—	—	—	—	—

a The target dose was 50 mg GEM/kg. For delivered dose, see Table 1.

b H.R2, H.R4, H.R5, H.R6 = Individual animal codes; I.M3, I.M4, I.M6, I.M7 = Individual animal codes.

c SL = Sample Lost during HPLC analysis.

d μg-eq calculations based on specific activity = 4.7619 μCi/mg GEM in the dose solution.

Table 19

Noncompartmental Pharmacokinetic Analysis of Data from Male Sprague-Dawley Rats and Male Syrian Golden Hamsters Administered a Single Oral or IV dose of GEM[a]

Parameter	Male Sprague-Dawley Rat			Male Syrian Golden Hamster		
	Oral, FS[b]	Oral, MC[c]	IV[c]	Oral, FS[b]	Oral MC[c]	IV[c]
Dose (mg/kg)	47.7 ± 1.8	50	4.29	51.0 ± 1.2	30	15
T_{max} (h)	1.27 ± 1.23	0.17	0	0.19 ± 0.21	0.17	0
C_{max} (mg/L)	12.5 ± 1.6	64.6	51.2	5.8 ± 1.3	6.95	238
β (h^{-1})	0.083 ± 0.01	0.088	0.062	0.65 ± 0.20	0.60	0.69
$t_{½}$ (h)	8.5 ± 0.8	7.9	11.1	1.2 ± 0.4	1.2	1.0
AUC (h mg/L)	114 ± 24	96.1	10.8	8.8 ± 1.6	4.9	14.1
V (L/kg)[d]	5.3 ± 1.6	5.9	6.4	10.0 ± 4.2	10.2	1.5
Cl (L/h/kg)[d]	0.43 ± 0.09	0.52	0.40	6.0 ± 1.2	6.1	1.1
MRT (h)	10.1 ± 0.9	9.5	9.3	2.2 ± 0.4	1.3	0.18
F	0.95 ± 0.18	0.76	NA[e]	0.18 ± 0.04	0.17	NA

a In the oral administration studies, GEM was administered in either a feed slurry (FS) or aqueous methyl cellulose (MC) vehicle.

b Data from current oral administration studies (rats, Study H; hamsters, Study I). Complete concentration-time course for four jugular-vein cannulated animals were analyzed for each dose group. Reported values are mean ± standard deviation from four animals per species.

c Data from previously reported oral and IV administration studies (Grizzle et al., 1995). A single mean concentration-time course was analyzed for each dose group (i.e., n = 1)

d V and Cl are V/F and Cl/F for oral dose studies.

e NA = not applicable.