2. Distribution:

Mice

1. Distribution of radioactivity after intravenous and oral administration of the sodium salt of ursodeoxycholic acid (UDCA)-24-[redacted]C.

Animals: Male ddY mice (mean body weight of 20 g; ages were not provided).

Methods: Two groups of 60 mice each were intravenously (via caudal vein) or orally administered (via gastric tube) 1.25 mg/kg of the sodium salt of UDCA-24-[redacted]C (80 μCi/mg), respectively. Dosing concentration and volume were not provided. Subgroups of 6 mice each were sacrificed at 0.083 (i.v. only), 0.25 (p.o. only), 0.50, 1, 2, 4, 8, 12, 24, 48 and 72 h after dosing, respectively. Radioactivity in blood and bile and tissues from stomach, liver, small intestine and large intestine was determined with a liquid scintillation counter.

Results: As shown in the following table (from Vol. 7/page 231 of sponsor's submission); after oral administration, radioactivity was detected in stomach, bile, liver and small intestine tissues at 15 min after dosing. At 1 h after oral dosing, radioactivity was decreasing in stomach tissue and rising in small intestine tissue. On the other hand, radioactivity remained relatively constant in bile, liver and large intestine over 3 days after oral dosing. In the case of i.v. administration, there was no radioactivity in stomach tissue. Otherwise, distributions of radioactivity were similar after oral and i.v. administration. Finally, radioactivity levels in heart, lung, kidney, brain, spleen, muscle and fat tissues were below 0.01 μg/g wet tissue.

TABLE I. Tissue Distribution of Radioactivity in the Mice after Oral or Intravenous Administration of Ursodeoxycholic Acid-24-[redacted]C (1.25 mg/kg)

	μg/g wet tissue or ml blood									
	5 min	15 min	30 min	1 hr.	2 hr	4 hr	8 hr	12 hr	1 day	2 day	3 day
Blood		0.02	0.02	0.01	0.02	0.02	0.02	0.01	0.02	0.01	0.01
	0.41		0.03	0.02	0.01	0.02	0.02	0.02	0.01	0.02	0.01
Stomach		23.70	20.15	16.75	4.70	4.10	0.25	0.15	0.10	0.01	<0.01
	<0.01		<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Bile		6.50	9.03	6.60	4.17	5.83	4.75	5.00	5.02	7.51	6.63
	7.49		5.66	9.16	4.16	3.46	5.21	5.19	9.16	7.50	8.33
Liver		0.48	0.36	0.33	0.35	0.45	0.29	0.21	0.19	0.18	0.21
	3.31		1.64	0.35	0.33	0.30	0.24	0.31	0.26	0.16	0.20
Small intestine		5.43	5.93	6.88	9.36	9.31	8.59	7.89	7.64	5.38	3.13
	5.11		9.00	10.15	9.98	10.05	9.14	8.63	8.11	6.66	5.01
Large intestine		<0.01	0.03	0.07	0.80	0.92	2.68	2.19	1.78	1.51	1.43
	<0.01		<0.01	0.03	0.84	1.02	1.46	2.16	1.59	1.70	1.68

The data after (*p.o.*) administration is shown in upper line in each column, and after (*i.v.*) in lower line. Each value represents the mean of 6 animals. Radioactivity was converted to μg equivalents of ursodeoxycholic acid.

Rats

1. Distribution of radioactivity of orally administered ursodeoxycholic acid (UDCA)-24-[redacted]C (Hiroshima J. Med. Sci. 26, 1977; reprint provided by sponsor).

Animals: Male Wistar rats (180-220 g; ages were not provided).

Methods: Twenty-four rats were orally administered 30 mg/kg of UDCA-24-[redacted]C (26.6 μCi/μmol). Dosing concentration was 150 mg%. Subgroups of 3 rats each were sacrificed at 0.25, 0.5, 1, 2, 3, 4, 8, 24, 72 and 148 h after dosing, respectively. Radioactivity of blood, contents of stomach, small intestine and large intestine, and tissues from stomach, small intestine, large intestine, liver, kidney, lung, brain, adipose tissue, heart, spleen, muscle and skin was measured with a [redacted].

Results: As shown in the following table, highest concentrations of radioactivity were found in the contents of stomach and small intestine. There were no detectable levels of radioactivity in lung, brain, adipose tissue, heart, spleen, muscle and skin.

Tissue Distribution of Radioactivity* in Rats After Single Oral Administration of Ursodeoxycholic Acid (30 mg/kg).

Tissue	Time After Administration (h)						
	0.25	0.5	1	2	4	8	24
Blood	0.6	0.3	0.4	0.4	0.5	0.2	0.3
Stomach	93.9	236.9	51.4	25.4	23.4	2.5	5.0
---contents	7,293.4	2,329.3	926.9	644.6	375.2	3.76	10.4
Small intestine	7.4	17.9	24.4	23.2	97.3	43.4	31.0
---contents	87.8	721.0	270.1	202.8	1,294.2	785.3	553.6
Large intestine	---	0.6	1.7	1.1	9.4	4.7	6.7
---contents	1.5	0.5	33.0	17.3	142.6	83.3	120.2
Liver	13.2	7.1	8.0	14.2	21.3	12.9	12.9
Kidney	1.0	0.7	---	---	---	---	---

*Each value represents the mean of 3 males and is expressed as μg/g wet tissue or μg/ml blood.

When rats were orally administered 30 mg/kg/day of ursodeoxycholic acid-24-[redacted]C for up to 21 days, there was no accumulation of distributed radioactivity.

3. Metabolism:

Mice

1. Metabolism of the sodium salt of ursodeoxycholic acid (UDCA)-24-[redacted]C after intravenous and oral administration.

Animals: Male ddY mice (mean body weight of 20 g; ages were not provided).

Methods: Two groups of mice (number of animals per group was not provided) were intravenously (via caudal vein) or orally administered (via gastric tube) 1.25 mg/kg of the sodium salt of UDCA-24-[redacted]C (80 μCi/mg), respectively. Dosing concentration and volume were not provided. Parent compound and metabolites in bile, feces, tissues from liver and extracts from stomach, small intestine, and large intestine were separated by [redacted] and identified by comparison with reference standards.

Results: The metabolism of intravenously and orally administered ursodeoxycholic acid in mice is summarized in the following figure (from Vol. 7/page 236 of sponsor's submission). After oral administration, UDCA is readily absorbed, primarily by passive diffusion. First-pass metabolism of UDCA in the liver is almost entirely by conjugation with taurine to form tauroursodeoxycholate. During repetitive enterohepatic cycling, some of the UDCA and tauroursodeoxycholate is 6ß-hydroxylated to ß-muricholate and tauro-ß-muricholate in the liver. In the intestine, tauroursodeoxycholate is deconjugated by bacteria to UDCA, which is 7ß-dehydroxylated to form lithocholic acid. Lithocholic acid is not absorbed from the colon in mice. Thus, UDCA and its metabolites are excreted primarily in the feces.

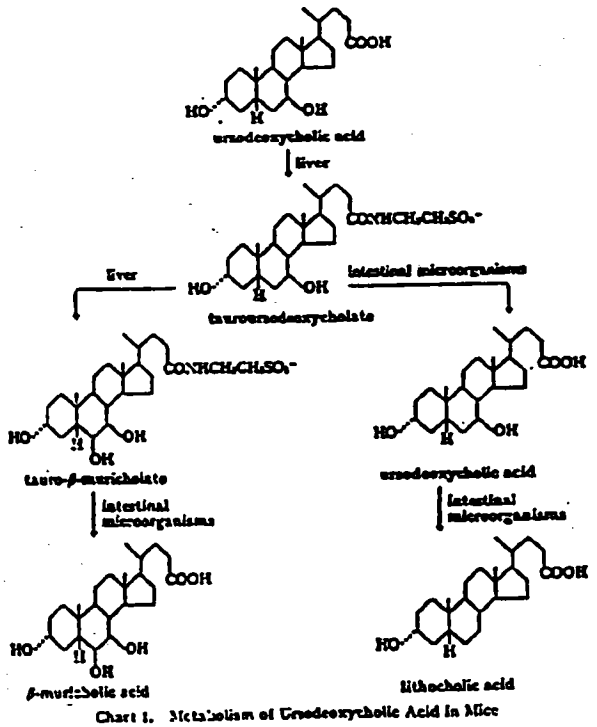

Chart 1. Metabolism of Ursodeoxycholic Acid in Mice

Rats

1. Metabolism of ursodeoxycholic acid (UDCA)-24-[redacted]C after oral and intravenous administration (Hiroshima J. Med. Sci. 26, 1977; reprint provided by sponsor).

Animals: Male Wistar rats (180-220 g; ages were not provided).

Methods: Two groups of rats (number of animals per group was not provided) were intravenously and orally administered 30 mg/kg of UDCA-24-[redacted]C (26.6 μCi/μmol), respectively. Dosing concentration was 150 mg%. Parent compound and metabolites in liver, small and large intestine contents and feces were separated by [redacted] and identified by comparison with reference standards.

Results: As shown in the following figure (from Vol. 7/page 262 of sponsor's submission), after oral administration, UDCA is readily absorbed, primarily by passive diffusion. First-pass metabolism of UDCA in the liver is almost entirely by conjugation with taurine to form tauroursodeoxycholate. During repetitive enterohepatic cycling, some of the UDCA and tauroursodeoxycholate is 6ß-hydroxylated to ß-muricholate and tauro-ß-muricholate in the liver. ß-muricholate in the rat is converted by 7ß-dehydroxylation to hyodeoxycholic acid. In the intestine, tauroursodeoxycholate is deconjugated by bacteria to UDCA, which is 7ß-dehydroxylated to form lithocholic acid. Lithocholic acid is not absorbed from the colon in rats. Thus, UDCA and its metabolites are excreted primarily in the feces.

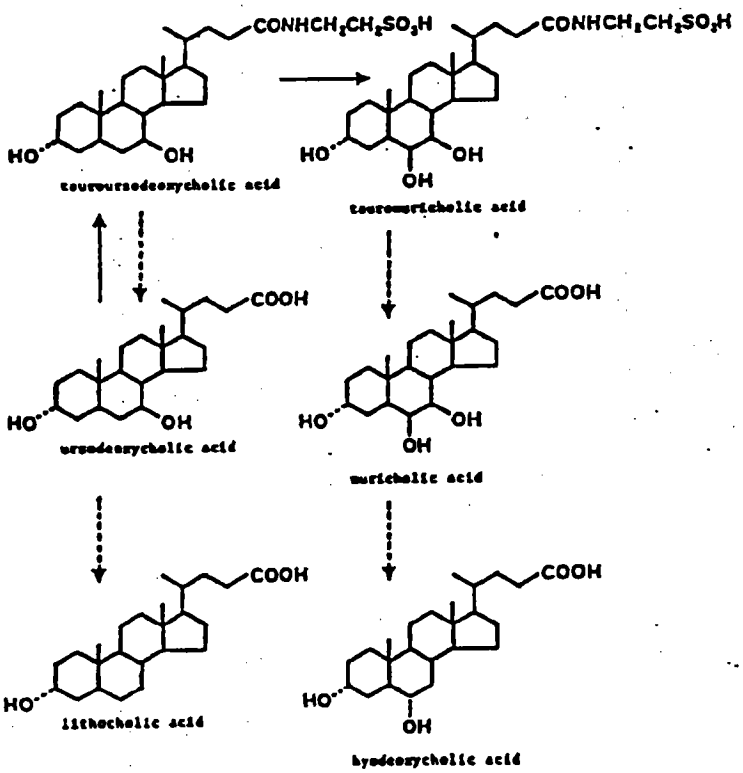

Fig. 12. Metabolism of ursodeoxycholic acid in the rats.

← by the liver enzyme
<-- by the intestinal microorganisms

2. Metabolism of [■C]ursodeoxycholic acid (UDCA) after intravenous and intraduodenal administration (Biochimica et Biophysica Acta 665:299-305, 1981; reprint provided by sponsor).

Animals: Male Sprague-Dawley rats (mean body weight of 175 g; ages were not provided).

Methods: Three groups of rats were fed standard diet (Group A, n=20), standard diet containing 5 mg/kg/day of UDCA (Group B, n=16) and standard diet containing 20 mg/kg/day of UDCA (Group C, n=16) for 3 weeks. After 3 weeks on the diets, one-half of the animals in each group were anesthetized with pentobarbital (5 mg/kg). Catheters were inserted into the bile duct and a carotid artery. Rats were intravenously administered [■C]UDCA (2 μCi, 20 μg) via a saphenous vein in 500 μl of 0.1M NaOH. Blood samples were obtained via the carotid artery at 0, 2, 5, 10, 15, 20, 60, 90 and 120 min after drug administration. Simultaneously, bile samples were obtained every 5 min for the first 30 min after drug administration and at 40, 50, 60, 90 and 120 min after drug administration. Radioactivity was measured in a [■]. After 3 weeks on the diets, the other one-half of the animals in each group were anesthetized and cannulas were placed in the duodenum and bile duct. Rats were intraduodenally administered [■C]UDCA (2 μCi, 20 μg) in 500 μl of 0.1M NaOH. The injection was followed by continuous perfusion of the duodenum with 5% glucose (1.2 ml/h). Bile samples were obtained every 10 min for 1 h and every 30 min for an additional 4 h. Parent compound and metabolites in bile samples were separated by [■] and identified by comparison with reference standards.

Results: As shown in the following table (from Vol. 7/page 269 of sponsor's submission), after both intravenous and intraduodenal administration of UDCA, approximately 50% (% of total bile acids) of the radioactivity in the bile was identified as cholic and ß-muricholic acid. Deoxycholic acid, chenodeoxycholic acid, hyodeoxycholic acid and UDCA each accounted for approximately 10% of the radioactivity. Lithocholic acid accounted for only approximately 1% of the radioactivity [■]

MODIFICATION OF RAT BILE COMPOSITION AFTER URSODEOXYCHOLIC ACID TREATMENT

Individual bile acids values are expressed as percentage of total bile acids. Each value represents the mean ±S.E. of five control and eight treated rats.

	Bile composition (% of total)		
	Control	Group A (5 mg/kg per day)	Group B (20 mg/kg per day)
Cholesterol	6.5 ± 2.4	4.3 ± 0.5	3.1 ± 0.3
Phospholipids	17.5 ± 1.3	11.8 ± 1.2 [a]	14.2 ± 0.8
Bile acids	76.0 ± 1.5	83.8 ± 1.5 [a]	82.7 ± 0.9 [a]
Lithocholic acid	0.7	1.2	1.2
Deoxycholic acid	4.1	6.2	11.8
Chenodeoxycholic acid	5.1	8.3	8.3
Hyodeoxycholic acid	8	9	7
Ursodeoxycholic acid	traces	2.5	7
Cholic and β-muricholic acid	56	52.7	45
Others, mostly keto derivatives	26	20	19

[a] Significantly different from control ($P < 0.01$)

4. Excretion:

Mice

1. Excretion of radioactivity after intravenous and oral administration of the sodium salt of ursodeoxycholic acid (UDCA)-24-[redacted]C.

Animals: Male ddY mice (mean body weight of 20 g; ages were not provided).

Methods: Two groups of 6 mice each were intravenously (via caudal vein) or orally administered (via gastric tube) 1.25 mg/kg of the sodium salt of UDCA-24-[redacted]C (80 μCi/mg), respectively. Dosing concentration and volume were not provided. CO_2 in expired air was trapped in ethanolamine-ethyleneglycol monomethyl ester (2:1, v/v) for 12 h after dosing. Urine and feces were collected for 3 days after dosing. Radioactivity was determined with a [redacted].

As shown in the following table (from Vol. 7/page 231 of sponsor's submission), the major route of elimination was via the feces after both intravenous and oral administration.

TABLE II. Excretion of Radioactivity in the Mice after Oral or Intravenous Administration of Ursodeoxycholic Acid-24-[redacted]C (1.25 mg/kg)

Sample	% of dose			
	Oral administration		i.v. injection	
	0—12 hr	0—3 day	0—12 hr	0—3 day
Respiratory CO_2	<0.01		<0.01	
Urine	0.02	0.03	0.02	0.03
Feces	15.11	55.12	3.21	40.98

Each value represents the mean of 6 animals.

Rat

1. Biliary excretion of [[redacted]C]ursodeoxycholic acid (UDCA) after intravenous and intraduodenal administration (Biochimica et Biophysica Acta 665:299-305, 1981; reprint provided by sponsor).

Animals: Male Sprague-Dawley rats (mean body weight of 175 g; ages were not provided).

Methods: Three groups of rats were fed standard diet (Group A, n=20), standard diet containing 5 mg/kg/day of UDCA (Group B, n=16) and standard diet containing 20 mg/kg/day of UDCA (Group C, n=16) for 3 weeks. After 3 weeks on the diets, one-half of the animals in each group were anesthetized with pentobarbital (5 mg/kg). Catheters were inserted into the bile duct and a carotid artery. Rats were intravenously administered [[redacted]C]UDCA (2 μCi, 20 μg) via a saphenous vein in 500 μl of 0.1M NaOH. Blood samples were obtained via the carotid artery at 0, 2, 5, 10, 15, 20, 60, 90 and 120 min after injection. Simultaneously, bile samples were obtained every 5 min for the first 30 min after injection and at 40, 50, 60, 90 and 120 min after injection. Radioactivity was measured in a [redacted]. After 3 weeks on the diets, the other one-half of the animals in each group were anesthetized and cannulas were placed in the duodenum and bile duct. Rats were intraduodenally administered [[redacted]C]UDCA (2 μCi, 20 μg) in 500 μl of 0.1M NaOH. The injection was followed by continuous perfusion of the duodenum with 5% glucose (1.2 ml/h). Bile samples were obtained every 10 min for 1 h and every 30 min for an additional 4 h.

Results: As shown in the following figure (from Vol. 7/page 269 of sponsor's submission); after intravenous administration of [[redacted]C]UDCA, rate of bile secretion of radioactivity was 9.5 to 12.6 μl/min in the 3 groups. The percent of total administered dose recovered in bile was over 80% at 120 min after dosing.

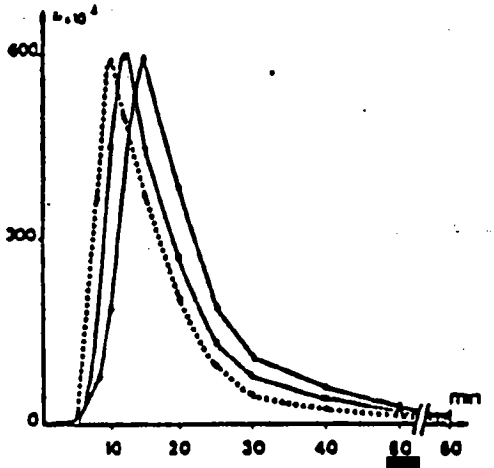

Fig. 2. Kinetics of biliary secretion of [[redacted]C]UDCA after intravenous injection in controls (———) and in UDCA-treated animals: group A, 5 mg/kg per day (·····) and group B, 20 mg/kg per day (.....). Results were expressed as the fraction of dose: R = dpm/10 μl bile/dpm dose. Each point represents the mean value in controls (ten animals) and in treated rats (eight animals).

As shown in the following figure (from Vol. 7/page 269 of sponsor's submission); after intraduodenal administration of [14C]UDCA, rate of bile secretion of radioactivity was 11.1 to 12.5 µl/min in the 3 groups. Declines of radioactivity in bile samples began later and were more prolonged after intraduodenal administration compared to intravenous administration. According to the authors, these findings suggest that when UDCA was administered into the duodenum, it was absorbed without any bacterial metabolism.

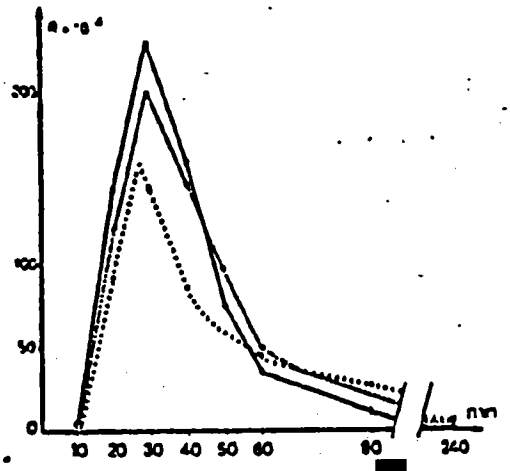

Fig. 3. Kinetics of biliary secretion of [14C]UDCA after a single intraduodenal administration in control (———) and in UDCA-treated rats (group A, 5 mg/kg per day (- - - -) and group B, 20 mg/kg per day (.....)). Results were expressed as the fraction of the administered dose: R = dpm/10 µl bile/dpm dose. Each point represents the mean value in controls (ten animals) and in treated rats (eight animals).

2. Biliary excretion of radioactivity after oral administration of the sodium salt of ursodeoxycholic acid (UDCA)-24-14C.

Animals: Male Wistar rats (mean body weight of 300 g; ages were not provided).

Methods: Two bile duct fistulated rats each were orally administered 5, 50 and 500 mg/kg of the sodium salt of UDCA-24-14C (2 µCi/mg), respectively. Bile samples were obtained at 2, 4, 6, 8, 10, 12, 14, 20, 24, 30, 36, and 48 h after dosing. Radioactivity was determined with a [redacted].

Results: As shown in the following figure (from Vol. 7/page 233 of sponsor's submission), 80-90% of the administered dose was accounted for in the bile over 48 h after dosing. The labeled compound was identified as being primarily tauroursodeoxycholate. Thus, the first-pass metabolism of UDCA is primarily to tauroursodeoxycholic acid.

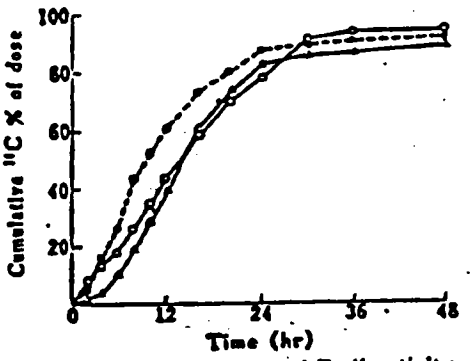

Fig. 2. Biliary Excretion of Radioactivity in Bile Fistula Rats after Oral Administration of Ursodeoxycholic Acid-24-[redacted]C

Each value represents the mean of 3 animals.
○—○: 5 mg/kg
●—●: 50 mg/kg
△—△: 500 mg/kg

3. Biliary excretion of radioactivity after oral administration of ursodeoxycholic acid (UDCA)-24-^{14}C (Hiroshima J. Med. Sci. 26, 1977; reprint provided by sponsor).

Animals: Male Wistar rats (180-220 g; ages were not provided).

Methods: Three bile duct fistulated rats were orally administered 30 mg/kg of UDCA-24-[redacted]C (26.6 μCi/μmol). Dosing concentration was 150 mg%. Bile samples were collected at 1, 2, 3, 4, 6, 8, 12, 24 and 48 h after dosing. Radioactivity of bile samples was measured with a [redacted]. Three other bile duct fistulated rats were orally administered 30 mg/kg/day of UDCA-24 for 20 days. On the 21st day, these rats were orally administered 30 mg/kg of UDCA-24-[redacted]C. Bile sample collection and analysis was accomplished as described above.

Results: As shown in the following figure (from Vol. 7/page 251 of sponsor's submission), nearly all of the orally administered UDCA was excreted into the bile within 24 h after dosing. Rate of excretion was not altered after multiple dosing.

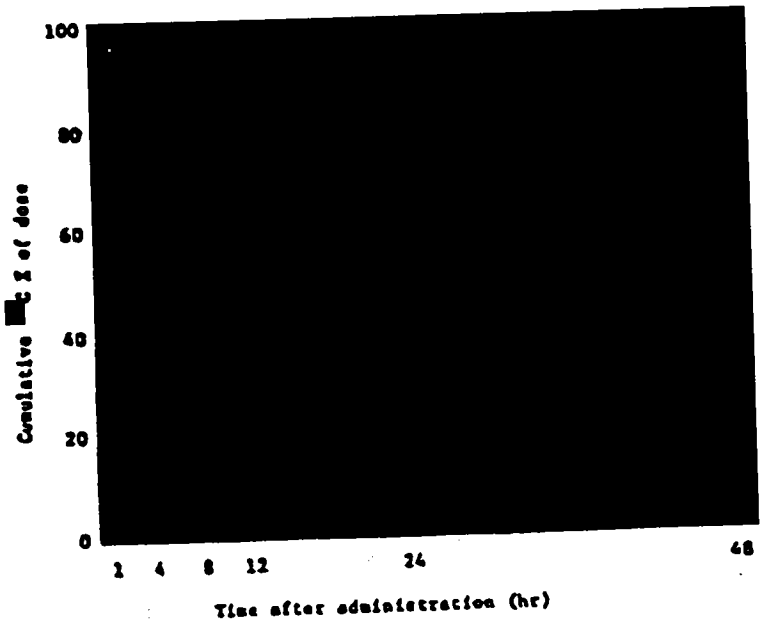

Fig. 8. Biliary excretion of radioactivity in bile fistula rats after oral administration of ursodeoxycholic acid-24-[redacted]C (30 mg/kg)

—•— Rat was given a single dose of ursodeoxycholic acid-24-[redacted]C.

—•— Rat was given ursodeoxycholic acid repeatedly once daily for 20 days followed by a single dose of ursodeoxycholic acid-24-[redacted]C at the 21st day.

4. Reabsorption of biliary excretes after oral administration of ursodeoxycholic acid (UDCA)-24-[redacted]C (Hiroshima J. Med. Sci. 26, 1977; reprint provided by sponsor).

Animals: Male Wistar rat (body weights and ages were not provided).

Methods: Two bile duct cannulated rats were prepared. The cannula of one of the rats was inserted into the proximal end of the duodenum of another bile duct cannulated rat. UDCA-24-[redacted]C (30 mg/kg) was orally administered to the former rat, and the bile excreted from the latter rat was collected. The percent of reabsorption of biliary excretes was calculated.

Results: As shown in the following figure (from Vol. 7/page 252 of sponsor's submission), approximately 90% of the biliary excretes was reabsorbed. These data suggest that UDCA and its metabolites undergo extensive enterohepatic recirculation.

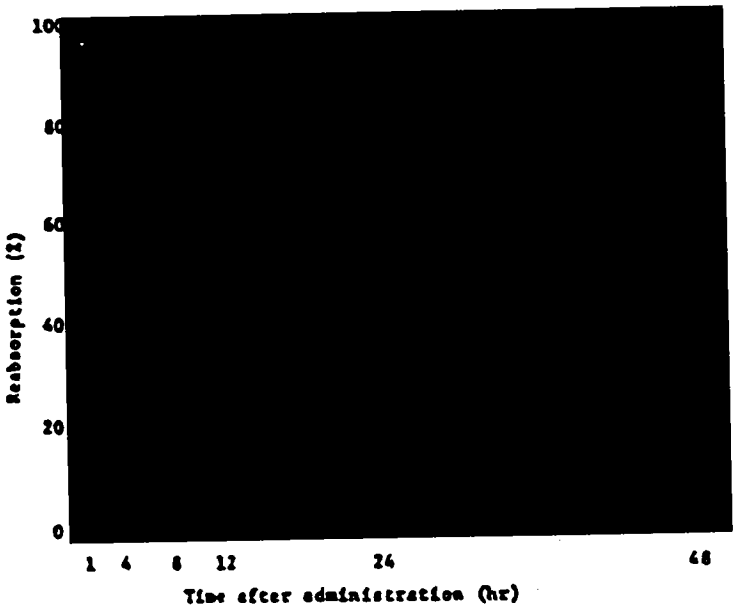

Fig. 9. Reabsorption of biliary excretes after oral administration of ursodeoxycholic acid-24-[redacted]C (30 mg/kg)

5. Biliary excretion of ursodeoxycholic acid (UDCA)-24-[redacted]C after oral administration in females (Hiroshima J. Med. Sci. 27, 1978; reprint provided by sponsor).

Animals: Female Wistar rats (160-200 g; ages were not provided).

Methods: Three bile duct fistulated females were orally administered 30 mg/kg of the sodium salt of UDCA-24-^{14}C (1.0 μCi/mg); vehicle was water; dosing volume was not provided. Bile samples were collected at 1, 2, 4, 6, 8, 12, 24 and 48 h after dosing. Radioactivity was determined in a [redacted]

Results: As shown in the following figure (from Vol. 7/page 280 of sponsor's submission), approximately 85% of the administered dose was excreted in the bile at 24 h after dosing; approximately 99% at 48 h after dosing.

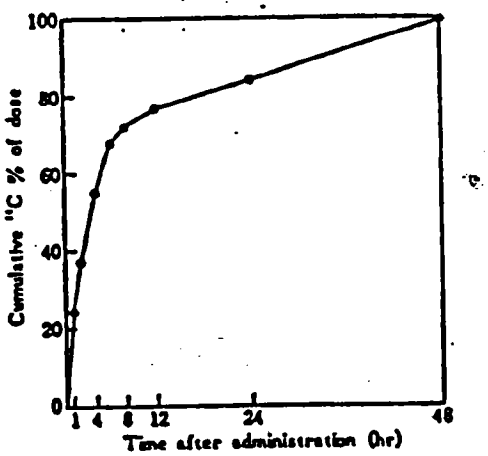

Fig. 2. Biliary excretion of radioactivity in bile fistula female rats after a single oral administration of ursodeoxycholic acid-24-[redacted]C (30 mg/kg).
Each point represents the mean of 3 animals.

6. Excretion of radioactivity after oral administration of ursodeoxycholic acid (UDCA)-24-[redacted]C (Hiroshima J. Med. Sci. 26, 1977; reprint provided by sponsor).

Animals: Male Wistar rats (180-220 g; ages were not provided).

Methods: Three rats were orally administered 30 mg/kg of UDCA-24-[redacted]C (26.6 μCi/μmol). Dosing concentration was 150 mg%. Urine and feces were collected for 7 days after dosing. Radioactivity of urine and feces samples was measured with a liquid scintillation counter. Three other rats were orally administered 30 mg/kg/day of UDCA-24 for 20 days. On the 21st day, these rats were orally administered 30 mg/kg of UDCA-24-[redacted]C. Urine and feces sample collection and analysis was accomplished as described above.

Results: As shown in the following table (from Vol. 7/page 253 of sponsor's submission), over 90% of radioactivity was accounted for in the feces over 7 days after both single oral administration and multiple oral administration of UDCA-24-[redacted]C.

Table VI. Excretion of radioactivity in the rats after a single oral administration of ursodeoxycholic acid-24-[redacted]C (30 mg/kg) and in the rats after repeated oral administration of ursodeoxycholic acid (30 mg/kg) once daily for 20 days followed by a single oral administration of ursodeoxycholic acid-24-[redacted]C (30mg/kg) at the 21st day.

	Cumulative [redacted]C % Of dose		
Time (day)	0-1	0-3	0-7
Feces	20.0 ± 3.61	65.3 ± 8.01	96.3 ± 1.76
	35.0 ± 7.57	85.0 ± 2.08	99.5 ± 0.27
Urine	0.05 ± 0.00	0.13 ± 0.02	
	0.05 ± 0.02	0.11 ± 0.03	
Respiratory CO_2	N D	N D	
	N D	N D	

In upper line in each column is shown the data after a single oral administration of ursodeoxycholic acid-24-[redacted]C and in lower line is shown the data after repeated oral administration of ursodeoxycholic acid [illegible]

7. Excretion of ursodeoxycholic acid (UDCA)-24-[redacted]C after oral administration in females (Hiroshima J. Med. Sci. 27, 1978; reprint provided by sponsor).

Animals: Female Wistar rats (160-200 g; ages were not provided).

Methods: Three females were orally administered 30 mg/kg of the sodium salt of UDCA-24-[redacted]C (1.0 μCi/mg); vehicle was water; dosing volume was not provided. Respiratory CO_2 was collected for 3 h after dosing. Urine and feces were collected for 7 days after dosing. Radioactivity was determined in a [redacted]

Results: As shown in the following table (from Vol. 7/page 281 of sponsor's submission), approximately 95% of the administered dose was excreted in the feces over 7 days after dosing; a minimal amount was excreted in urine (approximately 0.5%; none was detected in respiratory CO_2.

Table II. Excretion of radioactivity in the female rats after a single oral administration of ursodeoxycholic acid-24-[redacted]C (30 mg/kg).

	Cumulative [redacted]% of dose		
Time (day)	0—1	0—3	0—7
Feces	23.3 ±3.79*	68.2 ±5.56	94.7 ±3.23
Urine	0.11±0.04	0.28±0.07	0.42±0.12
Respiratory CO_2	ND**	ND	

*Each value represents the mean and standard error of 3 animals.
**ND : not detected.

In summary, after oral administration of UDCA-24-[redacted]C (4, 10, 30, 60 and 200 mg/kg) in male rats, 70%-90% of total radioactivity was absorbed over 120 min after dosing. After single oral administration of UDCA-24-[redacted]C (30 mg/kg) in non-lactating and lactating female rats, peak blood levels of radioactivity occurred within 30 min after dosing (0.93 and 1.45 μEq of UDCA/ml, respectively). Thus, orally administered UDCA is readily absorbed and bioavailability is high. After 3 weeks of dietary administration of UDCA (5 and 20 mg/kg/day) in male rats, plasma clearance of radioactivity after acute intravenous administration of [[redacted]C]UDCA (20 μg) was biphasic with approximate half-lives of 2 and 30 min, respectively. These relatively short half-lives reflect the extensive first-pass metabolism of UDCA in the liver and secretion in the bile. In male monkeys, after oral administration of UDCA-24-[redacted]C (30 mg/kg), peak blood whole blood (9.56 μg equivalents/ml) and plasma (17.89 equivalents/ml) levels occurred at 30 min and slowly declined. Plasma clearance or radioactivity was biphasic with approximate half-lives of 6.3 and 64.2 h, respectively. The half-life of orally administered UDCA in man is estimated to be 3.5 to 5.8 days.

When the sodium salt of UDCA-24-[redacted]C (1.25 mg/kg) was orally administered to male mice, radioactivity was distributed to stomach, bile, liver and small intestine (peaks of 23.70, [redacted]03, 0.48 and 9.36 μg/g or μg/ml, respectively). When UDCA-24-[redacted]C (30 mg/kg) was orally administered to male rats, highest concentrations of radioactivity were in the contents of stomach and small intestine (peaks of 7,933 and 1,294 μg/ml, respectively). Blood levels of UDCA were relatively low. The extensive enterohepatic recirculation of UDCA and its metabolites suggest that bile levels of UDCA and its metabolites are more reflective of therapeutic efficacy than blood levels.

Orally administered UDCA in mice and rats was metabolized in the liver to tauroursodeoxycholic acid (TUDCA). TUDCA was, in turn, metabolized in the liver to tauromuricholic acid and muricholic acid; muricholic acid being the major metabolite. Relatively small amounts of TUDCA were also metabolized to ursodeoxycholic acid and lithocholic acid by intestinal microorganisms. Lithocholic acid is not absorbed from the colon of rodents.

When the sodium salt of UDCA-24-[redacted]C (1.25 mg/kg) was orally administered to male mice, 55% of total radioactivity was excreted in feces over 3 days. When the sodium salt of UDCA-24-[redacted]C (30 mg/kg) was orally administered to female rats, approximately 95% of the administered dose was excreted in the feces over 7 days after dosing. When UDCA-24-[redacted]C (30 mg/kg) was orally administered to one male rat, and bile was collected and intraduodenally administered to a second rat, approximately 90% of the biliary excretes from the first rat were reabsorbed by the second rat. These data suggest that there is extensive enterohepatic recirculation of UDCA and its metabolites.

TOXICOLOGY:

ACUTE TOXICITY:

Male (M) and Female (F) dd mice (body weights of about 20 g; ages were not provided) were administered ursodeoxycholic acid (males: 180, 235, 265, 300 and 330 mg/kg, i.v.; females: 150, 180, 235, 265 and 300 mg/kg, i.v.); vehicle was purified water; dosing solution was 3% ursodeoxycholic acid. There were 20 mice per group (10 males and 10 females); observation period was 7 days.

M and F dd mice (body weights of about 20 g; ages were not provided) were administered ursodeoxycholic acid (500, 750, 1000, 1500, 2000 and 2500 mg/kg, i.p.); vehicle was 0.5% carboxymethylcellulose (CMC) solution; dosing solution was 20% suspension of ursodeoxycholic acid. There were 20 mice per group (10 males and 10 females); observation period was 7 days.

M and F dd mice (body weights of about 20 g; ages were not provided) were administered ursodeoxycholic acid (1, 4, 6, 8, 10 and 12 mg/kg, s.c.); vehicle was 0.5% carboxymethylcellulose (CMC) solution; dosing solution was 20% suspension of ursodeoxycholic acid. There were 20 mice per group (10 males and 10 females); observation period was 7 days.

M and F dd mice (body weights of about 20 g; ages were not provided) were administered ursodeoxycholic acid (5 and 10 g/kg, p.o.); vehicle was 0.5% carboxymethylcellulose (CMC) solution; dosing solution was 20% suspension of ursodeoxycholic acid. There were 20 mice per group (10 males and 10 females); observation period was 7 days.

M and F Wistar rats (body weights of about 200 g; ages were not provided) were administered ursodeoxycholic acid (200, 250, 300, 350 and 400 mg/kg, i.v.); vehicle was purified water; dosing solution was 3% ursodeoxycholic acid. There were 20 rats per group (10 males and 10 females); observation period was 7 days.

M and F Wistar rats (body weights of about 200 g; ages were not provided) were administered ursodeoxycholic acid (500, 750, 1000, 1500, 2000 and 2500 mg/kg, i.p.); vehicle was 0.5% carboxy-methylcellulose (CMC) solution; dosing solution was 20% suspension of ursodeoxycholic acid. There were 20 rats per group (10 males and 10 females); observation period was 7 days.

M and F Wistar rats (body weights of about 200 g; ages were not provided) were administered ursodeoxycholic acid (1 and 2 g/kg, s.c.); vehicle was 0.5% carboxymethylcellulose (CMC) solution; dosing solution was 20% suspension of ursodeoxycholic acid. There were 20 rats per group (10 males and 10 females); observation period was 7 days.

M and F Wistar rats (body weights of about 200 g; ages were not provided) were administered ursodeoxycholic acid (2 and 5 g/kg, p.o.); vehicle was 0.5% carboxymethylcellulose (CMC) solution; dosing solution was 20% suspension of ursodeoxycholic acid. There were 20 rats per group (10 males and 10 females); observation period was 7 days.

M and F Syrian hamsters (body weight range of 90 to 100 g; approximately 3 months of age) were administered ursodeoxycholic acid (1.21, 1.47, 1.78, 2.15, 2.61 and 3.16 g/kg, p.o.); vehicle was 0.8% aqueous hydroxypropyl-methylcellulose gel (Type E4M); dosing volume was 25 ml/kg. There were 20 hamsters per group (10 males and 10 females), except for the 3.16 g/kg group in which only 10 females were used. Observation period was 14 days.

M (6.8 to 8.2 kg; ages were not provided) and F (7.0 7.5 kg; ages were not provided) mongrel dogs were administered ursodeoxycholic acid (4.00, 5.04, 7.90 and 10.0 g/kg, p.o.); vehicle was 0.8% aqueous hydroxypropyl-methylcellulose gel E 4 M; dosing volume was 5 ml/kg. There were 2 dogs per group (1 male and 1 female); observation period was 14 days.

Results: The results of the acute toxicity studies are summarized in the following table. In mice and rats, intravenously administered UDCA produced convulsions and transitory inhibition of autonomous movement. Intraperitoneal, subcutaneously and orally administered UDCA were immediately followed by slight sedation. The highest nonlethal oral doses of UDCA in mice (10 g/kg) and rats (5 g/kg) did not produce any clinical signs of toxicity.

In hamsters, oral doses produced ataxia, inhibition of motility, dyspnoea, ptosis, decreased food consumption and body weight loss. Death occurred in a comatose state; slight agonal convulsions were often observed.

In dogs, oral doses of 5.04 g/kg and greater produced salivation and vomiting. Thus, in these cases, dogs most likely did not receive full intended doses.

Summary of acute toxicity for UDCA in mice, rats, hamsters and dogs

Species	Route of Adm.	LD_{50} (mg/kg)	Time until death	Minimum lethal dose (mg/kg)
Mice	I.v.	M: 285 mg/kg F: 240 mg/kg	Within 2 days	M: 235 mg/kg F: 180 mg/kg
Mice	I.p.	M: 1.20 g/kg F: 1.25 g/kg	Within 4 days	M: 0.75 g/kg F: 0.75 g/kg
Mice	S.c.	M: 5.8 g/kg F: 6.2 g/kg	Within 3 days	M: 4 g/kg F: 4 g/kg
Mice	Oral	Not determined; >10 g/kg	Not applicable	Not determined; >10 g/kg
Rats	I.v.	M: 310 mg/kg F: 320 mg/kg	Within 1 day	M: 250 mg/kg F: 250 mg/kg
Rats	I.p.	M: 1.08 g/kg F: 0.89 g/kg	Within 3 days	M: 0.75 g/kg F: 0.75 g/kg
Rats	S.c.	Not determined; >2 g/kg	Not applicable	Not determined; >2 g/kg
Rats	Oral	Not determined; >5 g/kg	Not applicable	Not determined; >5 g/kg
Hamsters	Oral	M: 1.8 g/kg F: 2.0 g/kg	Within 18 to 50 h	1.470 g/kg
Dogs	Oral	Not determined; >10 g/kg	Not applicable	Not determined; >10 g/kg

SUBACUTE/SUBCHRONIC/CHRONIC TOXICITY:

Rats

1. 5-Week I.P. Toxicity Study of Ursodiol.

Testing Laboratory: [redacted]

Compliance with Good Laboratory Practices and Quality Assurance Requirements: Statements of compliance were not provided.

Study Started: Not provided.

Study Completed: Not provided.

Animals: Male (180-250 g; ages were not provided) and female (170-230 g; ages were not provided) Wistar rats.

Methods: In a 2-week i.p. dose-ranging study of UDCA (200, 400 and 600 mg/kg/day), UDCA produced death in 1/5 females at the 400 mg/kg/day dose and in 2/5 males and 3/5 females at the 600 mg/kg/day dose. Thus, 5 groups of 20 rats each (10 males and 10 females) were intraperitoneally administered 0, 62.5, 125, 250 and 500 g/kg/day of UDCA, respectively, for 6 days/week for 5 weeks. Vehicle was 1% carboxymethylcellulose; dosing volume was 0.5 ml/kg. Another group of untreated controls (10 males and 10 females) were also studied.

Rats were observed daily for clinical signs of toxicity and mortality. Body weights and food consumption were measured twice a week.

Blood samples for hematological and biochemical examination were collected under ether anesthesia via the left ventricle at the end of the experiment for 3 males and 3 females in each group.

Urine was collected for 20 h at 4 weeks after initiation of drug treatment. Urinalysis was conducted for 3 males and 3 females from each group.

Rats were sacrificed by exsanguination under ether anesthesia. Gross pathological examinations were conducted on all animals. Organ weights were determined for brain, hypophysis, thyroids, heart, thymus, lungs, liver, spleen, kidneys, adrenals and testes/ovaries in all animals. Histopathological examinations were conducted on these organs for 5 males and 5 females from each group.

Data were not subjected to statistical analyses.

Results:

1. Observed Effects: There were no treatment-related clinical signs of toxicity.

2. Mortality: UDCA produced deaths in 1/10 males and 1/10 females at the 250 mg/kg/day dose and in 5/10 males and 4/10 females at the 500 mg/kg/day dose. Autopsies of these animals delineated adhesion of the intestine, abscess formation in kidneys and ascites in abdominal cavity. Cause of death is not clear.

3. Body Weight: Mean body weights were estimated from a figure provided by the sponsor. As shown in the following table, there were dose-related decreases in mean body weight in males and females.

Estimated mean body weights (g)

Group*	Males		Females	
	Week 0	Week 5	Week 0	Week 5
1	220	310	202	250
2	228	315	202	253
3	215	300 (-4.8%)**	202	249 (-1.6%)
4	215	275 (-12.7%)	202	240 (-5.1%)
5	215	272 (-13.7%)	202	225 (-11.1%)
6	215	253 (-19.7%)	202	227 (-10.3%)

*Group 1=untreated controls; 2=vehicle controls; 3=62.5 mg/kg/day UDCA; 4=125 mg/kg/day UDCA; 5=250 mg/kg/day UDCA; 6=500 mg/kg/day UDCA.
**(% of difference from Group 2)

4. Food Consumption: There were no treatment-related effects. Food consumption was variable among groups before any drug treatments.

5. Hematology: There were no treatment-related effects.

6. Blood Chemistry: There were no treatment-related effects.

7. Urinalysis: There were no treatment-related effects.

8. Organ Weights: Mean spleen weights of vehicle control males and females were 493.1 and 459.9 mg/100 g body weight, respectively. Mean spleen weights of males were increased by 45.5%, 47.3% and 69.2% (% of difference from vehicle control) at

the 125, 250 and 500 mg/kg/day doses, respectively. Mean spleen weights of females were increased by 38.0%, 90.5% and 129.3% (% of difference from vehicle control) at the 125, 250 and 500 mg/kg/day doses, respectively.

9. Gross Pathology: As shown in the following table, there were dose-related increases in incidence of adhesion of intestines and treatment-related incidences of ascites in abdominal cavity.

Incidence of gross pathological lesions

Group*	Adhesion of intestines			Ascites in abdominal cavity		
	Males	Females	Total	Males	Females	Total
1	0/10	0/10	0/20	0/10	0/10	0/20
2	0/10	0/10	0/20	0/10	0/10	0/20
3	0/10	0/10	0/20	0/10	0/10	0/20
4	3/10	5/10	8/20	2/10	0/10	2/20
5	8/10	7/10	15/20	2/10	1/10	3/20
6	5/9	6/9	11/18	1/9	2/9	3/18

*Group 1=untreated controls; 2=vehicle controls; 3=62.5 mg/kg/day UDCA; 4=125 mg/kg/day UDCA; 5=250 mg/kg/day UDCA; 6=500 mg/kg/day UDCA.

10. Histopathology: As shown in the following table, there were dose-related increases in incidence of liver histopathological lesions in males and females.

Incidence of histopathological lesions

Group*	Scattered, small necrotic foci		Bile duct proliferation		Cellular infiltration around bile duct	
	Males	Females	Males	Females	Males	Females
1	0/5	0/5	0/5	0/5	0/5	0/5
2	0/5	0/5	0/5	0/5	0/5	1/5
3	0/5	0/5	0/5	0/5	0/5	1/5
4	0/5	0/5	0/5	1/5	1/5	3/5
5	1/5	1/5	1/5	2/5	2/5	3/5
6	5/5	5/5	5/5	3/5	4/5	5/5

*Group 1=untreated controls; 2=vehicle controls; 3=62.5 mg/kg/day UDCA; 4=125 mg/kg/day UDCA; 5=250 mg/kg/day UDCA; 6=500 mg/kg/day UDCA.

Thus, the no effect i.p. dose of UDCA in the rat in a 5-week toxicity study was 62.5 mg/kg/day. Higher doses of UDCA (125 to 500 mg/kg/day) produced deaths, decreases in body weight, increased spleen weights, adhesion of intestines, ascites in abdominal cavity, and increases in incidence of liver histopathological lesions. The liver was a target organ for toxicity.

2. 5-Week Oral Toxicity Study of UDCA (Report No. was not provided).

Testing Laboratory: [redacted]

Compliance with Good Laboratory Practices and Quality Assurance Requirements: Statements of compliance were not provided.

Study Started: Not provided.

Study Completed: Not provided.

Animals: Male (160-220 g; ages were not provided) and female (150-200 g; ages were not provided) Wistar rats.

Methods: In a 2-week oral dose-ranging study of UDCA, it was determined that not only was a dose of 4 g/kg an MTD, but that the dosing concentration for the 4 g/kg dose was the maximum amount that could be physically suspended. Thus, 5 groups of 20 rats each (10 males and 10 females) were orally administered 0, 0.5, 1.0, 2.0 and 4.0 g/kg/day of UDCA, respectively, by intubation for 6 days/week for 5 weeks. Vehicle was 1% carboxymethylcellulose; dosing volume varied from 0.5 to 4 ml/kg. Another group of untreated controls (10 males and 10 females) were also studied.

Rats were observed daily for clinical signs of toxicity and mortality. Body weights and food consumption were measured twice a week.

Blood samples for hematological and biochemical examination were collected under ether anesthesia via the left ventricle at the end of the experiment for 3 males and 3 females in each group.

Urine was collected for 20 h at 4 weeks after initiation of drug treatment. Urinalysis was conducted for 3 males and 3 females from each group.

Rats were sacrificed by exsanguination under ether anesthesia. Gross pathological examinations were conducted on all animals. Organ weights were determined for brain, hypophysis, thyroids, heart, thymus, lungs, liver, spleen, kidneys, adrenals and testes/ovaries in all animals. Histopathological examinations were conducted on these organs for 5 males and 5 females from each group.

Data were not subjected to statistical analyses.

Results:

1. Observed Effects: There were no treatment-related clinical signs of toxicity.

2. Mortality: There were no deaths.

3. Body Weight: Initial body weights were not provided. Mean body weights at the end of the experiment for untreated control males and females were 277.9 and 237.9, respectively, and for vehicle treated control males and females were 275.7 and 239.8 g, respectively. There were not treatment-related effects on body weight.

4. Food Consumption: Food consumption was estimated from a figure provided by the sponsor. Food consumption of vehicle treated control males and females during Week 1 was approximately 10.7 and 10.0 g/100 g body weight, respectively. Food consumption of vehicle treated control males and females during Week 5 was approximately 8.7 and 9.2 g/100 g body weight, respectively. There were no treatment-related effects on food consumption.

5. Hematology: There were no treatment-related effects.

6. Blood Chemistry: There were no treatment-related effects.

7. Urinalysis: There were no treatment-related effects.

8. Organ Weights: There were no treatment-related effects.

9. Gross Pathology: There were no treatment-related effects.

10. Histopathology: There were no treatment-related effects.

Thus, the no effect oral dose of UDCA in the rat in a 5-week study was 4 g/kg/day. Target organs of toxicity were not delineated; higher doses of UDCA would need to be studied in order to delineate target organs of toxicity.

3. 6-Month Oral Toxicity Study of Ursodiol (Study No. was not provided).

Testing Laboratory: [redacted]

Compliance with Good Laboratory Practices and Quality Assurance Requirements: Sponsor provided a letter from [redacted] dated May 7, 1996, stating that studies performed at the above laboratory were conducted according to FDA requirements at that time.

Study Started: Not provided

Study Completed: January 15, 1979

Animals: Male (100-105 g; 38 days of age) and female (100-105 g; 42 days of age) Sprague-Dawley rats.

Methods: Selection of doses was based upon results from a preliminary study; details of the preliminary study were not provided. Thus, 4 groups of 50 rats each (25 males and 25 females) were orally administered 0, 100, 500 and 2500 mg/kg/day of UDCA, respectively, by intubation for 6 months. Vehicle was 0.8% aqueous hydroxypropylmethylcellulose gel (Type E4M); dosing volume was 10 ml/kg.

Animals were observed for clinical signs of toxicity on a daily basis. Food consumption was measured daily. Body weights were measured once weekly.

Blood samples were collected under ether anesthesia via the retrobulbar venous plexus for hematological examination during weeks 6, 13 and 26 for all animals and for biochemical examination during weeks 13 and 26 for all animals.

Urine was collected following administration of 40 ml of 0.3% saline solution/kg during weeks 6, 13 and 26. Urinalysis was conducted for all animals.

Prior to sacrifice during Week 26, all animals received eye, hearing and teeth examinations.

Rats were sacrificed by decapitation and exsanguination. Gross pathological examinations were conducted on all animals. Organ weights were determined for brain, hypophysis, thyroids, heart, thymus, lungs, liver, spleen, kidneys, adrenals and testes/ovaries in all animals. Histopathological examinations were conducted on tissues from heart, lungs, liver, spleen, kidneys, adrenals, thymus, hypophysis, gonads, thyroid, brain, prostate/uterus, stomach, duodenum, jejunum, ileum, colon,

rectum, salivary glands, eye/optic nerve, bladder, bone marrow, trachea, esophagus, pancreas, lymph nodes, peripheral nerve, skeletal muscle, bones and mammary gland in all animals from control and high dosage groups.

Data were analyzed with analyses of variance and student t-tests.

Results:

1. Observed Effects: There were no treatment-related clinical signs of toxicity.

2. Mortality: There were no deaths.

3. Body Weight: Mean body weights of control males and females at the start of the experiment were 102.5 and 102.7 g, respectively. Mean body weights of control males and females at the end of the experiment were 454.0 and 285.7 g, respectively. Mean body weights of males and females in the 2500 mg/kg/day group at the end of the experiment were decreased by -7.5% (% of difference from control) and -6.3%, respectively. There were no other treatment-related effects.

4. Food Consumption: Mean food consumption of control males and females at the start of the experiment were 13.7 and 14.6 g/day, respectively. Mean food consumption of control males and females at the end of the experiment were 24.5 and 16.0 g/day, respectively. There were no treatment-related effects.

5. Hematology: There were no treatment-related effects.

6. Blood Chemistry: There were no treatment-related effects.

7. Urinalysis: There were no treatment-related effects.

8. Eye Examination/Hearing Test/Dental Examination: There were no treatment-related effects.

9. Organ Weights: Mean lung weight was decreased (-23.2%; % of difference from control) in females at the 2500 mg/kg/day dose. There were no other treatment-related effects.

10. Gross Pathology: There were no treatment-related effects.

11. Histopathology: As shown in the following table, there were treatment-related incidences of basophilic deposits in the convoluted tubules of the outer cortex of the kidney. There were no other treatment-related effects.

Incidences of histopathological lesions

Basophilic deposits in kidneys	Males (mg/kg/day)				Females (mg/kg/day)			
	0	100	500	2500	0	100	500	2500
	0/25	7/25	5/25	4/25	0/25	6/25	3/25	9/25

Thus, oral UDCA doses of 500 mg/kg/day and less were well-tolerated in the rat in a 6-month toxicity study. The 2500 mg/kg/day dose produced body weight loss in males and females, and decreased lung weight in females. There were also treatment-related basophilic deposits in kidneys of males and females. Target organs of toxicity may include kidneys; higher doses of UDCA would need to be studied in order to delineate target organs of toxicity.

4. 6-Month Oral Toxicity Study of Ursodiol (Study No. was not provided).

Testing Laboratory: [redacted]

Compliance with Good Laboratory Practices and Quality Assurance Requirements: Statements of compliance were not provided.

Study Started: Not provided

Study Completed: Not provided

Animals: Male (130-160 g; ages were not provided by the sponsor) Wistar rats.

Methods: Since the no effect oral dose of UDCA in a previous 5-week toxicity study in the same laboratory was 4 g/kg/day, the 4 g/kg/day dose was selected as the highest dose for the present study. Thus, 5 groups of 15 males each were orally administered 0, 0.5, 1.0, 2.0 and 4.0 g/kg/day of UDCA, respectively, by intubation for 6 days/week for 26 weeks. Vehicle was 1% carboxymethylcellulose; dosing volume varied from 0.5 to 4 ml/kg. Another group of untreated controls (20 males) were also studied.

Rats were observed daily for clinical signs of toxicity and mortality. Body weights and food consumption were measured twice a week.

Blood samples for hematological examination were collected under ether anesthesia via the coccygeal vein before initiation of treatment and at the end of the experiment for 5 rats in each group. Blood samples for blood chemistry examination were collected under ether anesthesia via the left ventricle at the end of the experiment for 5 rats in each group.

Urine was collected for 20 h at 25 weeks after initiation of drug treatment. Urinalysis was conducted for 5 rats from each group.

Rats were sacrificed by exsanguination under ether anesthesia. Gross pathological examinations were conducted on all animals. Organ weights were determined for brain, hypophysis, thyroids, heart, thymus, lungs, liver, spleen, kidneys, adrenals and testes/ovaries in all animals. Histopathological examinations were conducted on these organs for 10 rats from each group.

Data were not subjected to statistical analyses.

Results:

1. Observed Effects: There were no treatment-related effects.

2. Mortality: As shown in the following table, there appeared to be treatment-related deaths in the 4 g/kg/day dosage group. All deaths in all groups occurred from Week 20 onward.

Incidence of Mortality

Group*	Week					
	18	20	22	24	26	Total
1	0/15	1/15	0/14	0/14	0/14	1/15
2	0/15	0/15	0/15	0/15	1/15	1/15
3	0/15	0/15	0/15	1/15	0/14	1/15
4	0/15	0/15	0/15	1/15	1/14	2/15
5	0/15	0/15	0/15	0/15	1/15	1/15
6	0/15	1/15	0/14	0/14	3/14	4/15

*Group 1=untreated controls; 2=vehicle controls; 3=0.5 g/kg/day UDCA; 4=1.0 g/kg/day UDCA; 5=2.0 g/kg/day UDCA; 6=4.0 g/kg/day UDCA.

3. Body Weight: Mean body weights were estimated from a figure provided by the sponsor. As shown in the following table; mean body weight of the vehicle control group was 5.4% less than the mean body weight of the untreated control group, suggesting that 1% carboxymethylcellulose solution decreased body weight.

Furthermore, the mean body weight in the 4 g/kg/day group was 14.5% less than the mean body weight of the vehicle control group, suggesting that UDCA also decreased body weight.

Estimated Mean Body Weights (g)

Group*	Body Weight (g)	
	Week 0	Week 25
1	~175	460
2	~175	435 (-5.4%)**
3	~175	425
4	~175	415
5	~175	425
6	~175	380 (-14.5%)***

*Group 1=untreated controls; 2=vehicle controls; 3=0.5 g/kg/day UDCA; 4=1.0 g/kg/day UDCA; 5=2.0 g/kg/day UDCA; 6=4.0 g/kg/day UDCA.
**(% of difference from Group 1)
***(% of difference from Group 2)

4. Food consumption: There were no treatment-related effects.

5. Hematology: There were no treatment-related effects.

6. Blood Chemistry: There were no treatment-related effects.

7. Urinalysis: There were no treatment-related effects.

8. Organ Weights: Mean organ weights of brain, thyroid gland and adrenal glands were increased by 12.1%, 26.0% and 23.0% (% of difference from control) in the 4 g/kg/day dosage group.

9. Gross Pathology: There were no treatment-related gross pathological lesions.

10. Histopathology: Although the sponsor did not provide incidence data for histopathological lesions, sponsor stated that intrahepatic cholangitis, hyperplasia of the bile ducts and multiple focal necrosis were noted in about 4 of 10 cases examined in each of the 1.0, 2.0 and 4.0 g/kg/day groups.

Thus, the no effect oral dose of UDCA was 0.5 g/kg/day in the rat in a 6-month toxicity study. There were treatment-related incidences of hepatic lesions in the 1.0, 2.0 and 4.0 g/kg/day groups. Furthermore, the 4.0 mg/kg/day dose also produced lethality, reduced body weight and increased organ weights of brain, thyroid glands and adrenal glands. The liver was a target organ of toxicity.