COVERSHEET FOR CARCINOGENICITY STUDY IN RATS

1. Study No.: 97-134-0
2. Name of Laboratory: Merck Research Laboratories, Merck & Co. Inc., West Point, PA 19486.
3. Strain: Crl:CD (SD) IGS BR rats
4. No./sex/group: 50
5. Doses (0, L, M, and H): 0, 0, 0.10, 0.50 and 2.0 mg/kg/day for both males and females.
6. Basis for dose selection stated: No.
7. Interim sacrifice: No
8. Total duration (weeks): 106
9. Week/site for first tumor:

	Male	**Female**
Control 1	68/pituitary adenoma	50/mammary gland adenocarcinoma
Control 2	56/malignant schwannoma of the heart	34/mammary gland fibroadenoma
Low dose	29/ lymphoma (primary site undetermined)	55/pituitary adenoma
Mid dose	21/mammary gland adenocarcinoma	52/pituitary adenoma
High dose	37/pituitary adenoma	50/mammmary gland adenocarcinoma

10. No. alive at termination:

	Male	**% survival**	**Female**	**% survival**
Control 1	30/50	60%	38/50	76%
Control 2	28/50	56%	33/50	66%
Low dose	27/50	54%	33/50	66%
Mid dose	29/50	58%	33/50	66%
High dose	34/50	68%	36/50	72%

11. Statistical methods used: For evaluation of the carcinogenic potential of the compound, a trend analysis was performed to determine the significant effect on mortality in male and female rats. The incidence of various tumor types was analyzed for statistically significant ($P<0.05$) trend with adjustments made for potentially confounding factors such as, mortality, time-to-tumor onset.

12. Attach tumor and non-tumor data for each tissue: See Appendix 1.

Study title: One-hundred-six (106)-Week Oral Carcinogenicity Study with MK-8069 (L-754030) in Rats.

Key study findings: Treatment with MK-0869 was associated with increased incidences of papilloma of the skin (Control 1, 0/50 [0%], control 2, 1/50 [2%]; low dose, 1/50 [2%]; mid dose, 0/50 [0%]; high dose, 3/50 [6%]; P=0.042, Trend test) in the male animals. However, the incidence of skin papilloma is within the spontaneous incidences reported for this tumor in this strain of rat (0.87% to 6.0%, [redacted]

On the basis of CDER statistical standard, the incidence of this tumor was not significant as the P-value (0.042) exceeded the required P-value of 0.005 for common tumors (incidences >1%). Thus, MK-0869 was not carcinogenic in male and female rats when administered by the oral route for 106 weeks at doses up to 2.0 mg/kg/day.

Study number: 97-134-0

Conducting laboratory and location: Merck Research Laboratories, Merck & Co. Inc., West Point, PA 19486.

Date of study initiation: December 15, 1997

GLP compliance: yes

QA report: yes (x) no ( )

Drug lot #, and % purity: MK-0869 (L-754030); Lot Nos. 004H026 and 004H048; Purity ≥ 99.4% by [redacted]

CAC concurrence: No

Study Type: Long-term rodent carcinogenicity study

Species/strain: CR1:CD (SD) IGS BR rats

Number/sex/group; age at start of study: 50/sex/group; 36 days old at the start of the study.

Animal housing: The animals were housed individually in suspended stainless-steel, wire-bottom cages. The room was environmentally controlled with high efficiency particulate air (HEPA) filters with a 12-hour light cycle.

Drug stability/homogenicity: The drug was suspended in 0.5% methylcellulose/0.02% sodium lauryl sulfate in deionized water. The suspensions were prepared daily. Samples of all dosing formulations were analyzed for stability and homogenicity during weeks 1, 7, 19, 27, 39, 51, 63, 75, 80, 87, 94 and 105. The sponsor stated that the compound was stable in the formulation under the conditions of the study and the results were within the acceptable concentration range except during dosing week 75 at which time the concentration of the low dose formulation was 31% higher than the expected concentration.

Methods:

Doses: 0, 0.05, 0.25 and 1.0 mg/kg b.i.d. (0.10, 0.50 and 2.0 mg/kg/day).

Two control groups received the vehicle only. The treatment groups received the drug at a constant volume (5 ml/kg), administered b.i.d. by oral gavage (at least 4 hours apart for the vehicle and 6 hours apart for the treatment groups).

Basis of dose selection: The basis for dose selection was not stated.

Route of administration: Oral (gavage)

Frequency of drug administration: The drug was administered twice daily. The doses were administered at least 6 hours apart.

Dual controls employed: Yes
Interim sacrifices: No
Satellite PK or special study group(s): None.
Deviations from original study protocol: None
Statistical methods: For evaluation of the carcinogenic potential of the compound, a trend analysis was performed to determine the significant effect on mortality in male and female rats. The incidence of various tumor types was analyzed for statistically significant ($P<0.05$) trend with adjustments made for potentially confounding factors such as, mortality, time-to-tumor onset.

Observations and times:

Clinical signs: The animals were observed once daily for mortality and once weekly for physical signs. Beginning from administration week 26, all rats were examined for palpable masses once every 4 weeks.

Body weights: The body weights were measured once in week-1, twice a week through week-13 and once a week thereafter.

Hematology: Blood samples for hematology examinations were collected from the surviving animals prior to the terminal necropsy.

Ophtahlmologic Examinations: Ophthalmic examinations were conducted of all animals before initiation of dosing and of the control-1 and the high dose animals during dosing weeks 52 and 102.

Gross pathology: All surviving animals were sacrificed at the end of the dosing period and complete necropsies done. Animals died or sacrificed moribund during the dosing period, also underwent complete necropsy examinations.

Histopathology: The following tissues from all animals were histologically examined after fixation and staining.
Salivary gland (submandibular/sublingual), esophagus, stomach, small intestine (duodenum, jejunum, ileum), large intestine (colon), liver, pancreas, adrenals, parathyroid, skin (from mammary region), putuitary, thyroid, kidneys, urinary bladder, ovaries, uterus, testes and epididymides, prostate, skin, mammary gland, lung. heart, spleen, lymph nodes (cervical and mesenteric), thymus, bone marrow, bone (femur, including femorotibial joint), skeletal muscle, brain, spinal cord (cervical), peripheral nerve (sciatic), eyes (with optic nerves). Harder's glands.

Results:

Mortality: No treatment-related effects on mortality were observed in any group. The cumulative mortalities among males and females at weeks 52, 65, 78, 91 and 104 of the treatment period are summarized in the Tables below.

Table: Cumulative mortalities in **male** rats receiving MK-0869 for 106 weeks.

Weeks	Control 1		Control 2		0.10 mg/kg/day		0.50 mg/kg/day		2.0 mg/kg/day	
	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death
52	0/50	0%	0/50	0%	0/50	0%	1/50	2%	0/50	0%
65	0/50	0%	2/50	4%	2/50	4%	3/50	6%	4/50	8%
78	1/50	2%	9/50	18%	5/50	10%	6/50	12%	5/50	10%
91	6/50	12%	13/50	26%	12/50	24%	10/50	20%	10/50	20%
104	20/50	40%	22/50	44%	23/50	46%	21/50	42%	16/50	32%

Table: Cumulative mortalities in **female** rats receiving MK-0869 for 106 weeks.

Weeks	Control 1		Control 2		0.10 mg/kg/day		0.50 mg/kg/day		2.0 mg/kg/day	
	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death
52	2/50	4%	1/50	2%	3/50	6%	2/50	4%	2/50	4%
65	2/50	4%	3/50	6%	4/50	8%	3/50	6%	4/50	8%
78	3/50	6%	4/50	8%	8/50	16%	5/50	10%	7/50	14%
91	9/50	18%	8/50	16%	10/50	20%	12/50	24%	9/50	18%
104	12/50	24%	17/50	34%	17/50	34%	17/50	34%	14/50	28%

[a], One female mouse (#98-0179) escaped during case change in Week 49 and this mouse was not available for necropsy.

Clinical signs: No treatment-related clinical signs were observed in any group.

Body weights: The mean body weights of the control male and female rats at the beginning of dosing (week-1) were 155±13 g and 125±7 g, and at the end of the dosing (week-104) were 422±58 g and 302±32 g, respectively. The body weights of the males and females were not affected by treatment with MK-0869 at any time of the dosing period. The mean body weights and the percent changes in the body weights of the male and female rats receiving different doses of MK-0869 in weeks 13, 26, 54, 78 and 104 are summarized in the Table below.

Table: Body weights and changes in body weights of the male and female rats receiving MK-0869

Weeks	Males					Females				
	Control 1	Control 2	0.10 mg/kg/day	0.50 mg/kg/day	2.0 mg/kg/day	Control 1	Control 2	0.10 mg/kg/day	0.50 mg/kg/day	2.0 mg/kg/day
Week-13										
Body Weight (g)	400	402	398	401	407	233	234	233	239	240
% of Control	100%	100.5%	99.5%	100.3%	101.8%	100%	100.4%	100%	102.6%	103%
Week-26										
Body Weight (g)	474	475	468	466	474	259	259	260	265	263
% of Control	100%	100.2%	98.7%	98.3%	100%	100%	100%	100.4%	102.3%	101.5%
Week-52										
Body Weight (g)	540	542	535	530	538	280	280	282	291	285
% of Control	100%	100.4%	99.1%	98.2%	99.6%	100%	100%	100.7%	103.9%	101.8%
Week-78										
Body Weight (g)	564	567	558	558	561	289	291	296	303	293
% of Control	100%	100.5%	98.9%	98.9%	99.5%	100%	100.7%	102.4%	104.8%	101.4%
Week-104										
Body Weight (g)	559	564	550	562	558	302	296	295	310	296
% of Control	100%	99.1%	98.4%	100.5%	99.8%	100%	98.0%	97.7%	102.6%	98.0%
Body Weight gain(g)	422	424	414	429	423	187	178	183	193	179
% of Control	100%	100.4%	98.1%	101.7%	100.2%	100%	95.2%	97.9%	103.2%	95.7%

The body weights (in g) of the male and female animals of different groups during the dosing period are shown in the sponsor's figure below.

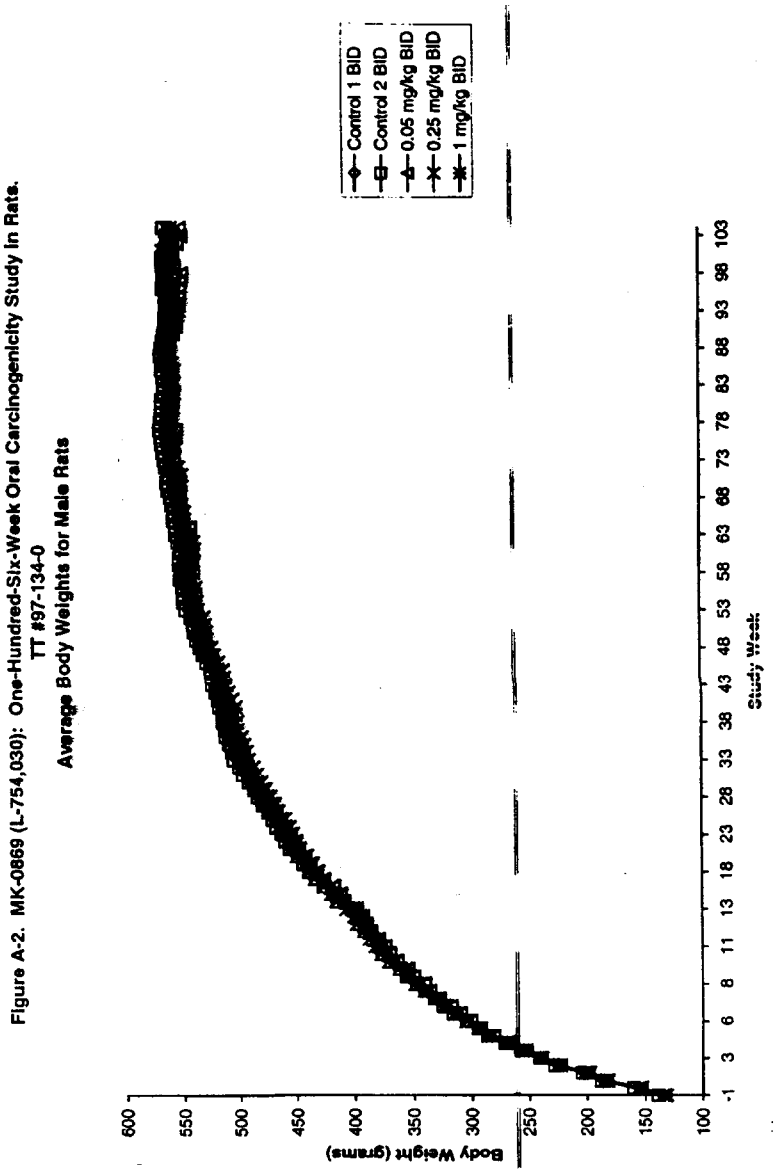
Figure A-2. MK-0869 (L-754,030): One-Hundred-Six-Week Oral Carcinogenicity Study in Rats.
TT #97-134-0
Average Body Weights for Male Rats
Control 1 BID
Control 2 BID
0.05 mg/kg BID
0.25 mg/kg BID
1 mg/kg BID
Body Weight (grams)
Study Week

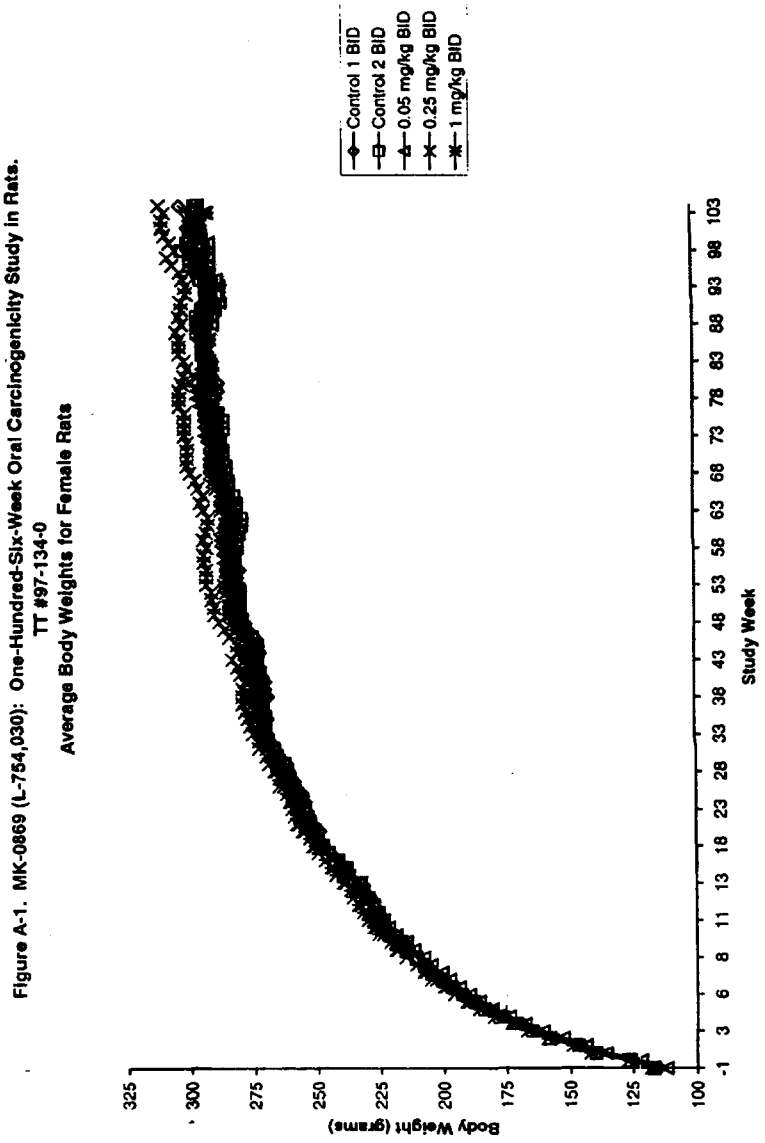
Figure A-1. MK-0869 (L-754,030): One-Hundred-Six-Week Oral Carcinogenicity Study in Rats.
TT #97-134-0
Average Body Weights for Female Rats
Control 1 BID
Control 2 BID
0.05 mg/kg BID
0.25 mg/kg BID
1 mg/kg BID
Body Weight (grams)
325
300
275
250
225
200
175
150
125
100
Study Week
-1
3
6
8
11
13
18
23
28
33
38
43
48
53
58
63
68
73
78
83
88
93
98
103

Ophthalmic Examinations: No treatment related ophthalmic changes were observed in any group.

Hematology: The following hematological parameters were determined: erythrocyte, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, RBC morphology, platelet count, leukocyte count and leukocyte differential count. No treatment-related changes in the hematological parameters were observed in any group.

Gross pathology: No treatment-related gross pathological changes were reported in any group.

Histopathology:

Nonneoplastic: Males receiving the mid and the high dose had slightly higher incidences of bile duct hyperplasia and vacuolation of hepatocytes and females receiving the mid and the high dose had higher incidences of peripheral fibrosis of the liver. The nonneoplastic histopathological findings in the male and female rats are summarized in the Table below.

Table: Histopathological changes in the male and female rats receiving MK-0869 for 106 weeks

Observations	Control 1	Control 2	0.10 mg/kg/day	0.50 mg/kg/day	2.0 mg/kg/day
Males					
Liver-					
Bile duct hyperplasia	27/50 (54%)	25/50 (50%)	25/50 (50%)	31/50 (62%)	32/50 (64%)
Hepatocyte vacuolation	4/50 (8%)	3/50 (6%)	4/50 (8%)	7/50 (14%)	8/50 (16%)
Females					
Liver-					
Peripheral fibrosis	1/50 (2%)	1/50 (2%)	1/50 (2%)	5/50 (10%)	5/50 (10%)

Neoplastic: The high dose males had higher incidences of skin papilloma (Control 1, 0/50 [0%], control 2, 1/50 [2%]; low dose, 1/50 [2%]; mid dose, 0/50 [0%]; high dose, 3/50 [6%]; P=0.042, Trend test). The incidence of papilloma at the high dose is within the spontaneous incidences reported for this strain of rat (0.87% to 6.0%; [redacted] The incidences of skin papilloma in the male rats are summarized in the Table below.

Observation	Control 1	Control 2	0.10 mg/kg/day	0.50 mg/kg/day	2.0 mg/kg/day	P- value (Trend-test)
Males						
Skin-						
Papilloma	0/50 (0%)	1/50 (2%)	1/50 (2%)	0/50 (0%)	3/50 (6%)	0.042

Toxicokinetics: No data provided.

Summary:

In the 106-week oral gavage carcinogenicity study with MK-0869 in Sprague Dawley rats, groups of animals (50/sex/group) received 0, 0.10, 0.50 and 2.0 mg/kg/day (0, 0.05, 0.25 and 1.0 mg/kg b.i.d) of the drug. The basis for dose selection for the carcinogenicity study was not stated and no concurrence for dose selection was sought from the CDER Executive CAC. No treatment-related effects on the body weights or survival were observed in any group. Treatment with MK-0869 was associated with increased incidences of papilloma of the skin (Control 1, 0/50 [0%], control 2, 1/50 [2%]; low dose, 1/50 [2%]; mid dose, 0/50 [0%]; high dose, 3/50 [6%]; P=0.042, Trend test) in the male animals. However, the incidence of skin papilloma is within the spontaneous incidences reported for this tumor in this strain of rat (0.87% to 6.0%, [redacted] On the basis of CDER statistical standard, the incidence for this tumor was not significant as the P-value (0.042) exceeded the required P-value of 0.005 for common tumors (incidences >1%). Thus, MK-0869 was not carcinogenic in male and female rats when administered by the oral route for 106 weeks at doses up to 2.0 mg/kg/day. Plasma exposure levels in the male and female rats at the high dose were approximately .019 and 0.086 times the exposure levels in humans at the recommended clinical dose, respectively.

Analysis of tumor data by the CDER Statistician (Dr Mushfiqur Rashid), did not show any significant trend for any type of tumor in the male and and female rat in this 106 week carcinogenicity study.

Twenty-Seven-Week Oral Toxicokinetic Study with MK-0869 (L-754030) in Rats (Study # 97-134-1):

Methods: The sponsor conducted a 27-week toxicokinetic study to determine the pharmacokinetic parameters of MK-0869 (L-754030) after oral dosing in rats. This is an extension of the 27-week oral carcinogenicity study in rats (Study # 97-134-0) and the doses were the same used for the 106-week oral carcinogenicity study in rats (0.05, 0.25 and 1 mg/kg b.i.d; 0.10, 0.50 and 2 mg/kg/day). Samples of blood were collected in weeks 14 and 27 (from 5 animals/sex/group; approximately 0.5, 2, 8 and 24 hours post-dose) for determination of plasma drug concentrations. Plasma drug concentrations were determined by [redacted] The lower limit of detection for the assay was [redacted]

Results: After oral dosing of MK-0869 (L-754030) to the male and female rats, the C_{max} and AUC values increased with increasing doses, both at week 17 and week 27. The plasma exposure levels in the female rats were 2 to 4 times higher than that in the male animals and the plasma exposure levels did not change significantly from week 14 to week 27. The toxicokinetic parameters for the male and female rats at weeks 14 and 27 are summarized in the sponsor's Tables below.

Plasma MK-0869 (L-754,030) Toxicokinetic Parameters
Drug Week 14 - Mean Values

	Females (L-754,030 mg/kg b.i.d.)		
	0.05	0.25	1
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	0.490	1.65	3.72
C_{max} (µg/mL)[a]	0.0254 ± 0.00105	0.0924 ± 0.00796	0.240 ± 0.0228
C_{min} (µg/mL)[a]	0.0129 ± 0.00113	0.0361 ± 0.00281	0.0391 ± 0.00618
	Males (L-754,030 mg/kg b.i.d.)		
	0.05	0.25	1
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	0.126	0.604	1.68
C_{max} (µg/mL)[a]	0.00835 ± 0.00176	0.0366 ± 0.00250	0.105 ± 0.00998
C_{min} (µg/mL)[a]	0.000336 ± 0.000336	0.00731 ± 0.00152	0.0117 ± 0.00257
a = Mean ± standard error of the mean.			

Plasma MK-0869 (L-754,030) Toxicokinetic Parameters
Drug Week 27 - Mean Values

	Females (L-754,030 mg/kg b.i.d.)		
	0.05	0.25	1
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	0.519	1.88	4.42
C_{max} (µg/mL)[a]	0.0272 ± 0.00119	0.101 ± 0.0148	0.297 ± 0.0249
C_{min} (µg/mL)[a]	0.0134 ± 0.000871	0.0430 ± 0.00393	0.0403 ± 0.0105
	Males (L-754,030 mg/kg b.i.d.)		
	0.05	0.25	1
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	0.164	0.829	1.85
C_{max} (µg/mL)[a]	0.00998 ± 0.00109	0.0482 ± 0.00102	0.123 ± 0.00836
C_{min} (µg/mL)[a]	0.00234 ± 0.000878	0.0132 ± 0.00512	0.0101 ± 0.00160
a = Mean ± standard error of the mean.			

The sponsor conducted a toxicokinetic study to determine the plasma exposure levels of MK-0869 (L-754030) in Sprague Dawley rats during oral administration for 27 weeks. The doses used were the same doses used for the 106-week oral carcinogenicity study in rats (0.05, 0.25 and 1 mg/kg b.i.d, or 0.10, 0.50 and 2 mg/kg/day). Plasma exposure levels of the drug increased with increasing doses, and there was no apparent difference in the exposure levels between week 14 and week 28. There was a sex difference in the plasma exposure levels; females had 2-4 times higher exposure levels than males. Plasma exposure levels in the male and female rats at the high dose were approximately .019 and 0.086 times the exposure levels in humans at the recommended clinical dose, respectively.

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CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT AND FDA CDER RODENT CARCINOGENICITY DATABASE FACT SHEET

P/T REVIEWER: Sushanta Chakder, Ph.D
DATE: March 12, 2003

NDA: 21-549
DRUG CODE #: MK-0869 (L-754030)
CAS #: 170729-80-3
DIVISION: Gastrointestinal and Coagulation Drug Products (HFD-180)
DRUG NAME(s): EMEND (Aprepitant) Capsules

SPONSOR: Merck & Co. Inc.
LABORATORY: Merck Research Laboratories.
CARCINOGENICITY STUDY REPORT DATE: July 30, 2002

THERAPEUTIC CAREGORY: Anti-emetic.
PHARMACOLOGICAL/CHEMICAL CLASSIFICATION: NK1 (Substance P) Receptor Antagonist
MUTAGENIC/GENOTOXIC (y/n/equivocal/na; assay): No

RAT CARCINOGENICITY STUDY (multiple studies? Std1; Std2 etc.):

RAT STUDY DURATION (weeks): 106
STUDY STARTING DATE: April 02, 1998
STUDY ENDING DATE: July 29, 2002
RAT STRAIN: Crl:CD (SD)IGS BR
ROUTE: Oral gavage
DOSING COMMENTS: The doses were administered twice a day at 0, 5, 25 and 125 mg/kg doses (0, 10, 50 and 250 mg/kg/day). The sponsor stated that the daily doses were administered at least 6 hours apart from each other.

NUMBER OF RATS:
- Control 1 (C1): 50/sex
- Control 2 (C2): 50/sex
- Low Dose (LD): 50/sex
- Middle Dose (MD): 50/sex
- High Dose (HD): 50/sex

RAT DOSE LEVELS (mg/kg/day):
- Low Dose: 10 mg/kg/day
- Middle Dose: 50 mg/kg/day
- High Dose: 250 mg/kg/day

(*Dose adjusted during study): Yes

BASIS FOR DOSES SELECTED (MTD; AUC ratio; saturation; maximum feasible): The doses for the carcinogenicity study were selected on the basis of saturation. The toxicology and toxicokinetic profiles of two different formulations of MK-0869 (formulation M, average particle [redacted] and formulation NB, average particle [redacted] were determined during oral administration for 5 weeks. Formulation M was administered at oral doses of 0 and 125 mg/kg B.I.D. (0 and 250 mg/kg/day), and formulation NB was administered at 0, 5, 125, 250, 500 and 750 mg/kg B.I.D. (0, 10, 250, 500, 1000 and 1500 mg/kg/day) doses. A no effect dose was not observed with formulation M or NB. Treatment-related hypertrophy and diffuse vacuolation of hepatocytes were observed in the liver of all groups receiving the M or NB formulation. Treatment-related diffuse thyroid follicular cell hyperplasia was observed in all M or NB formulation treated groups. Benign parafollicular cell adenomas were observed in two animals, one in the M formulation group and one in 250 mg/kg B.I.D. NB formulation group. Toxicokinetic analysis was confined to the parent compound, MK-0869. Plasma AUC values for the female animals receiving both formulations were higher than that of males. The AUC values were similar in male and female animals receiving 125 mg/kg B.I.D. doses of formulation M or NB. The AUC values for males and females receiving the NB formulation increased with dose, but the increases were less than dose-proportional. A plateau in AUC value for MK-0869 in animals receiving the NB formulation was evident at 500 mg/kg B.I.D. in males and at 250 mg/kg B.I.D. in females. The sponsor did not assess systemic exposure of the metabolites as requested in the April 5, 1999 teleconference or the letter from the Division August 20, 1999. However, in a subsequent 5-week oral toxicokinetic study, in which the plasma exposure levels of both the parent compound and the metabolites were determined, it was shown that saturation of absorption was achieved at the high dose (250 mg/kg/day).

RAT CARCINOGENICITY (negative; positive; MF; M; F): positive in M and F

PRIOR FDA DOSE CONCURRENCE (Div./CAC)? (y/n; Date): No. However, as asked by the executive CAC, in a subsequent toxicokinetic study, saturation of absorption was demonstrated.

RAT CARCINOGENICITY (conclusion: negative; positive; MF; M; F): Oral administration of MK-0869 was associated with increased incidences of thyroid follicular cell adenoma and carcinoma in the male rats, and hepatocellular adenoma and thyroid follicular cell adenoma and in the female rats. Thus, MK-0869 was carcinogenic in both male and female rats in the 106-week oral carcinogenicity study.

RAT TUMOR FINDINGS: Treatment with MK-0869 was associated with higher incidences of thyroid follicular cell adenoma (control 1, 0/50 [0%], control 2, 0/50 [0%]; low dose, 1/50 [2%]; mid dose, 1/50 [2%]; high dose, 3/50 [6%]; P=0.014, Trend test) and carcinoma (control 1, 0/50 [0%], control 2, 0/50 [0%]; low dose, 1/50 [2%]; mid dose, 1/50 [2%]; high dose, 2/50 [4%]; P=0.036, Trend test) in the **male** rats. On the basis of CDER statistical standard, the incidences for these tumors were not significant as the P-values (0.014 and 0.036) exceeded the required P-value of 0.005 for common tumors. The incidences for these tumors at the high dose are higher than the historical control incidences from the sponsor's laboratory (follicular cell adenoma, 0%-4%; follicular cell carcinoma, 0%-2%). The incidences of thyroid follicular cell adenoma and carcinoma in males were similar to the spontaneous incidences for these tumors in this strain of rat (follicular cell adenoma, 1.67% to 12%; follicular cell carcinoma, 0.87% to 3.85%; [redacted]. Treatment group **females** had higher incidences of hepatocellular adenoma (control 1, 1/50 [2%], control 2, 1/50 [2%]; low dose, 1/50 [2%]; mid dose, 4/50 [8%]; high dose, 6/50 [12%]; P=0.003, Trend test), thyroid follicular cell adenoma (control 1, 3/50 [6%], control 2, 1/50 [2%]; low dose, 1/50 [2%]; mid dose, 4/50 [8%]; high

dose, 6/50 [12%]; P=0.018, Trend test) and adenocarcinoma of the uterus (control 1, 0/50 [0%], control 2, 0/50 [0%]; low dose, 0/50 [0%]; mid dose, 0/50 [0%]; high dose, 2/50 [4%]; P=0.043, Trend test). On the basis of CDER statistical standard, the incidences of thyroid follicular cell adenoma and uterine adenocarcinoma were not significant as the P-values (0.018 and 0.043) exceeded the required P-value of 0.005 for common tumors. Historical control incidences for thyroid follicular cell adenoma and uterine adenocarcinoma in female rats from the sponsor's laboratory were 0% - 3% and 0% - 3.85%, respectively. The incidences of thyroid follicular cell adenoma and adenocarcinoma of the uterus at the high dose were higher than the spontaneous incidences reported in this strain of rat (thyroid follicular cell adenoma, 1.43% to 6.12%; uterine adenocarcinoma, 1.67%; [redacted]).

RAT STUDY COMMENTS: The dose selection for the 106-week carcinogenicity study was appropriate. The doses were selected on the basis of saturation of absorption. Saturation of absorption at the high dose was shown in a 5-week oral toxicokinetic study in which the plasma levels of the parent compound and its metabolites were measured. The conduct of the study and the methodologies are appropriate.

COVERSHEET FOR CARCINOGENICITY STUDY IN RATS

1. Study No.: 98-047-0
2. Name of Laboratory: Merck Research Laboratories, Merck & Co. Inc., West Point, PA 19486.
3. Strain: Crl:CD (SD) IGS BR rats.
4. No./sex/group: 50
5. Doses (0, L, M, and H): 0, 0, 5, 25 and 125 mg/kg b.i.d (0, 0, 10, 50 and 250 mg/kg/day) for both males and females.
6. Basis for dose selection stated: The doses for the carcinogenicity study were selected on the basis of saturation. The toxicology and toxicokinetic profiles of two different formulations of MK-0869 (formulation M, average particle size —— and formulation NB, average particle size . ——) were determined during oral administration for 5 weeks. Formulation M was administered orally at 0 and 125 mg/kg B.I.D. doses (0 and 250 mg/kg/day), and formulation NB was administered at 0, 5, 125, 250, 500 and 750 mg/kg B.I.D. (0, 10, 250, 500, 1000 and 1500 mg/kg/day) doses. A no effect dose was not observed with formulation M or NB. Treatment-related hypertrophy and diffuse vacuolation of hepatocytes were observed in the liver of all groups receiving the M or NB formulation. Treatment-related diffuse thyroid follicular cell hyperplasia was observed in all M or NB formulation treated groups. Benign parafollicular cell adenomas were observed in two animals, one in the M formulation group and one in 250 mg/kg B.I.D. NB formulation group. Toxicokinetic analysis was confined to the parent compound, MK-0869. Plasma AUC values for the female animals receiving both formulations were higher than that of males. The AUC values were similar in male and female animals receiving 125 mg/kg B.I.D. doses of formulation M or NB. The AUC values for males and females receiving the NB formulation increased with dose, but the increases were less than dose-proportional. A plateau in AUC value for MK-0869 in animals receiving the NB formulation was evident at 500 mg/kg B.I.D. in males and at 250 mg/kg B.I.D. in females. The sponsor did not assess systemic exposure of the metabolites as requested in the April 5, 1999 teleconference or the letter from the Division August 20, 1999. However, in a subsequent 5-week oral toxicokinetic study, in which the plasma exposure levels of both the parent compound and the metabolites were determined, it was shown that saturation of absorption was achieved at the high dose (250 mg/kg/day).
7. Interim sacrifice: No
8. Total duration (weeks): 106
9. Week/site for first tumor:

	Male	**Female**
Control 1	45/malignant schwannoma of the heart	54/pituitary adenoma
Control 2	73/pituitary adenoma	51/pituitary adenoma
Low dose	75/pituitary adenoma	53/colon leiomyosarcoma
Mid dose	38/skin subcutaneous fibrosarcoma	22/skin subcutaneous fibrosarcoma
High dose	89/thyroid follicular cell carcinoma	63/pituitary adenoma/uterus polyp

10. No. alive at termination:

	Male	**% survival**	**Female**	**% survival**
Control 1	34/50	68%	24/50	48%
Control 2	36/50	72%	28/50	56%
Low dose	33/50	66%	29/50	58%

Mid dose	39/50	78%	32/50	64%
High dose	37/50	74%	29/50	58%

11. Statistical methods used: For evaluation of the carcinogenic potential of the compound, a trend analysis was performed to determine the significant effect on mortality in male and female rats. The incidence of various tumor types was analyzed for statistically significant ($P<0.05$) trend with adjustments made for potentially confounding factors such as, mortality, time-to-tumor onset.
12. Attach tumor and non-tumor data for each tissue: See Appendix 2.

Study title: One-hundred-six (106)-Week Oral Carcinogenicity Study with MK-8069 (L-754030) in Rats

Key study findings: Treatment with MK-0869 was associated with higher incidences of thyroid follicular cell adenoma (control 1, 0/50 [0%], control 2, 0/50 [0%]; low dose, 1/50 [2%]; mid dose, 1/50 [2%]; high dose, 3/50 [6%]; P=0.014, Trend test) and carcinoma (control 1, 0/50 [0%], control 2, 0/50 [0%]; low dose, 1/50 [2%]; mid dose, 1/50 [2%]; high dose, 2/50 [4%]; P=0.036, Trend test) in the **male** rats. On the basis of CDER statistical standard, the incidences for these tumors were not significant as the P-values (0.014 and 0.036) exceeded the required P-value of 0.005 for common tumors. The incidences for these tumors are higher than the historical control incidences from the sponsor's laboratory (follicular cell adenoma, 0%-4%; follicular cell carcinoma, 0%-2%).The incidences of thyroid follicular cell adenoma and carcinoma in males were similar to the spontaneous incidences for these tumors in this strain of rat (follicular cell adenoma, 1.67% to 12%; follicular cell carcinoma, 0.87% to 3.85%; [redacted] Treatment group **females** had higher incidences of hepatocellular adenoma (control 1, 1/50 [2%], control 2, 1/50 [2%]; low dose, 1/50 [2%]; mid dose, 4/50 [8%]; high dose, 6/50 [12%]; P=0.003, Trend test), thyroid follicular cell adenoma (control 1, 3/50 [6%], control 2, 1/50 [2%]; low dose, 1/50 [2%]; mid dose, 4/50 [8%]; high dose, 6/50 [12%]; P=0.018, Trend test) and adenocarcinoma of the uterus (control 1, 0/50 [0%], control 2, 0/50 [0%]; low dose, 0/50 [0%]; mid dose, 0/50 [0%]; high dose, 2/50 [4%]; P=0.043, Trend test). On the basis of CDER statistical standard, the incidences of thyroid follicular cell adenoma and uterine adenocarcinoma were not significant as the P-values (0.018 and 0.043) exceeded the required P-value of 0.005 for common tumors. Historical control incidences for thyroid follicular cell adenoma and uterine adenocarcinoma in female rats from the conducting laboratory were 0% - 3% and 0% - 3.85%, respectively. The incidences of thyroid follicular cell adenoma and adenocarcinoma of the uterus at the high dose were higher than the spontaneous incidences reported in this strain of rat (thyroid follicular cell adenoma, 1.43% to 6.12%; uterine adenocarcinoma, 1.67%; [redacted]

Study number: 98-047-0
Conducting laboratory and location: Merck Research Laboratories, Merck & Co. Inc., West Point, PA 19486.

Date of study initiation: April 02, 1998
GLP compliance: yes
QA report: yes (x) no ( )
Drug lot #, and % purity: MK-0869 (L-754030); Lot Nos. 004H030, 004H033 and 004H048; Purity ≥ 99.8% .
CAC concurrence: No.

Study Type: Long-term rodent carcinogenicity study.
Species/strain: CR1:CD (SD) IGS BR rats
Number/sex/group; age at start of study: 50/sex/group; 39 days old at the start of the study.
Animal housing: The animals were housed individually in suspended stainless-steel, wire-bottom cages. The room was environmentally controlled with high efficiency particulate air (HEPA) filters with a 12-hour light cycle.
Drug stability/homogenicity: The drug was suspended in 0.5% (w/v) methylcellulose/0.02% (w/v) sodium lauryl sulfate in deionized water. The suspensions were prepared daily. Samples of all dosing formulations were analyzed for stability and homogenicity during weeks 1, 7, 19, 26, 38, 50, 62, 74, 79, 91, 103 and 105.

The sponsor stated that the compound was stable in the formulation under the conditions of the study and the results were within the acceptable concentration range.

Methods:

Doses: 0, 5, 25 and 125 mg/kg b.i.d. (0, 10, 50 and 250 mg/kg/day).

Two control groups (control 1 and Control 2) received the vehicle only. The treatment groups received the drug at a constant volume (5 ml/kg), administered b.i.d. by oral gavage (at least 4 hours apart for the vehicle and 6 hours apart for the treatment groups).

Basis of dose selection: The doses for the carcinogenicity study were selected on the basis of saturation. The toxicology and toxicokinetic profiles of two different formulations of MK-0869 (formulation M, average particle —— ', and formulation NB, average particle size —— ' were determined during oral administration for 5 weeks. Formulation M was administered orally at 0 and 125 mg/kg B.I.D. doses (0 and 250 mg/kg/day), and formulation NB was administered at 0, 5, 125, 250, 500 and 750 mg/kg B.I.D. (0, 10, 250, 500, 1000 and 1500 mg/kg/day) doses. A no effect dose was not observed with formulation M or NB. Treatment-related hypertrophy and diffuse vacuolation of hepatocytes were observed in the liver of all groups receiving the M or NB formulation. Treatment-related diffuse thyroid follicular cell hyperplasia was observed in all M or NB formulation treated groups. Benign parafollicular cell adenomas were observed in two animals, one in the M formulation group and one in 250 mg/kg B.I.D. NB formulation group. Toxicokinetic analysis was confined to the parent compound, MK-0869. Plasma AUC values for the female animals receiving both formulations were higher than that of males. The AUC values were similar in male and female animals receiving 125 mg/kg B.I.D. doses of formulation M or NB. The AUC values for males and females receiving the NB formulation increased with dose, but the increases were less than dose-proportional. A plateau in AUC value for MK-0869 in animals receiving the NB formulation was evident at 500 mg/kg B.I.D. in males and at 250 mg/kg B.I.D. in females. The sponsor did not assess systemic exposure of the metabolites as requested in the April 5, 1999 teleconference or the letter from the Division August 20, 1999. However, in a subsequent 5-week oral toxicokinetic study, in which the plasma exposure levels of both the parent compound and the metabolites were determined, saturation was demonstrated at the high dose (125 mg/kg b.i.d).

Route of administration: Oral (gavage)

Frequency of drug administration: The drug was administered twice daily. The doses were administered at least 6 hours apart.

Dual controls employed: Yes

Interim sacrifices: No

Satellite PK or special study group(s): None

Deviations from original study protocol: N/A

Statistical methods: For evaluation of the carcinogenic potential of the compound, a trend analysis was performed to determine the significant effect on mortality in male and female rats. The incidence of various tumor types was analyzed for statistically significant ($P<0.05$) trend with adjustments made for potentially confounding factors such as, mortality, time-to-tumor onset.

Observations and times:

Clinical signs: The animals were observed once daily for mortality and once weekly for physical signs. All rats were examined for palpable masses every 4 weeks beginning from administration week 26.

Body weights: The body weights were measured once in week-1, twice a week in weeks 2 through 13 and once a week thereafter.

Hematology: Blood samples for hematology examinations were collected from the surviving animals prior to the terminal necropsy.

Ophtahlmologic Examinations: Ophthalmic examinations were conducted of all animals before initiation of dosing and of the control-1 and the high dose animals during dosing weeks 51 and 101.

Gross pathology: All surviving animals were sacrificed at the end of the dosing period and complete necropsies done. Animals died or sacrificed moribund during the dosing period, also underwent complete necropsy examinations.

Histopathology: The following tissues from all animals were histologically examined after fixation and staining.

Salivary gland (submandibular/sublingual), esophagus, stomach, small intestine (duodenum, jejunum, ileum). large intestine (colon), liver, pancreas, adrenals, parathyroid, skin (from mammary region), putuitary, thyroid. kidneys, urinary bladder, ovaries, uterus, testes and epididymides, prostate, skin, mammary gland. lung, heart. spleen, lymph nodes (cervical and mesenteric), thymus, bone marrow, bone (femur, including femorotibial joint), skeletal muscle, brain, spinal cord (cervical), peripheral nerve (sciatic), eyes (with optic nerves), Harder's glands.

Results:

Mortality: No treatment-related effects on mortality were observed in any group. At the end of the dosing period, the mortalities for females of all groups, including controls, were higher than that of males. The cumulative mortalities among males and females at different times of the treatment period are summarized in the Tables below.

Table: Cumulative mortalities in **male** rats receiving MK-0869 for 106 weeks.

Weeks	Control 1		Control 2		10 mg/kg/day		50 mg/kg/day		250 mg/kg/day	
	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death
52	1/50	2%	0/50	0%	0/50	0%	0/50	0%	1/50	2%
65	2/50	4%	0/50	0%	0/50	0%	3/50	6%	2/50	4%
78	6/50	12%	3/50	6%	1/50	2%	4/50	8%	3/50	6%
91	11/50	22%	7/50	14%	8/50	16%	7/50	14%	6/50	12%
104	16/50	32%	14/50	28%	17/50	34%	11/50	22%	13/50	26%

Table: Cumulative mortalities in **female** rats receiving MK-0869 for 106 weeks.

Weeks	Control 1		Control 2		10 mg/kg/day		50 mg/kg/day		250 mg/kg/day	
	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death
52	0/50	0%	1/50	2%	0/50	0%	1/50	2%	1/50	2%
65	3/50	6%	5/50	10%	2/50	4%	2/50	4%	2/50	4%
78	9/50	18%	5/50	10%	6/50	12%	3/50	6%	5/50	10%
91	16/50	32%	15/50	30%	13/50	26%	8/50	16%	11/50	22%
104	26/50	52%	22/50	44%	21/50	42%	18/50	36%	21/50	42%

Clinical signs: No treatment-related clinical signs were observed in any group.

Body weights: The mean body weights of the control male and female rats at the beginning of dosing (week-1) were 155±12 g and 124±7 g, and at the end of the dosing (week-104) were 543±56 g and 289±33 g, respectively. The body weights of the males and females were not significantly affected by treatment with MK-0869 at any time of the dosing period. The mean body weights of all groups of animals, including controls, were slightly lower during week-104 as compared with that during week-78. The body weight gains of the mid and high dose males (5.4%) and the treated females (4.8% to 10.8%) were slightly lower than those of controls. The mean body weights and the percent changes in the body weights of the male and female rats receiving different doses of MK-0869 in weeks 13, 26, 54, 78 and 104 are summarized in the Table below.

Table: Body weights and changes in body weights of the male and female rats receiving MK-0869 (% of control)

Weeks	Males					Females				
	Control 1	Control 2	10 mg/kg/day	50 mg/kg/day	250 mg/kg/day	Control 1	Control 2	10 mg/kg/day	50 mg/kg/day	250 mg/kg/day
Week-13										
Body Weight (g)	398	397	400	405	404	234	232	231	233	238
% of Control	100%	99.7%	100.5%	101.8%	101.8%	100%	99.2%	98.7%	99.6%	101.7%
Week-26										
Body Weight (g)	465	466	470	472	472	261	262	260	263	262
% of Control	100%	100.2%	101.1%	101.5%	101.5%	100%	100.4%	99.6%	100.8%	100.4%
Week-52										
Body Weight (g)	531	531	532	524	530	278	285	280	281	279
% of Control	100%	100%	100.2%	98.7%	99.8%	100%	102.5%	100.7%	101.1%	100.4%
Week-78										
Body Weight (g)	560	554	556	547	551	287	295	288	288	290
% of Control	100%	98.9%	99.3%	97.7%	98.4%	100%	102.8%	100.3%	100.3%	101.1%
Week-104										
Body Weight (g)	543	531	541	526	525	289	288	279	271	283
% of Control	100%	97.8%	99.6%	96.9%	96.7%	100%	99.7%	96.5%	93.8%	97.9%
Body Weight gain(g)	389	378	385	368	368	166	164	155	148	158
% of Control	100%	97.2%	99%	94.6%	94.6%	100%	98.8%	93.4%	89.2%	95.2%

The body weights (in g) of the male and female animals of different groups during the dosing period are shown in the sponsor's figures below.

Figure A-2. MK-0869: One-Hundred-Six-Week Oral Carcinogenicity Study in Rats
TT #98-047-0
Average Body Weights for Male Rats

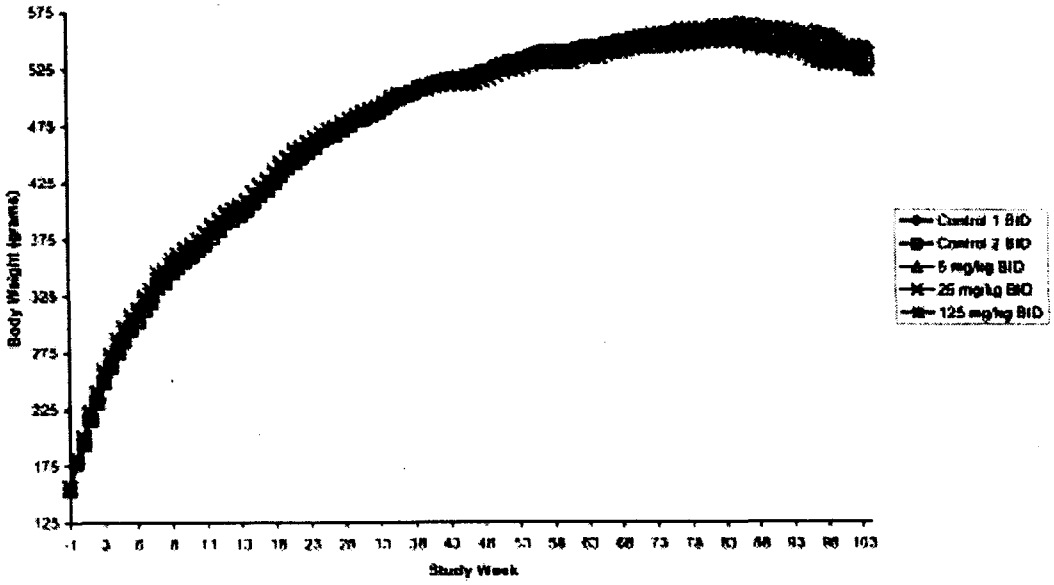
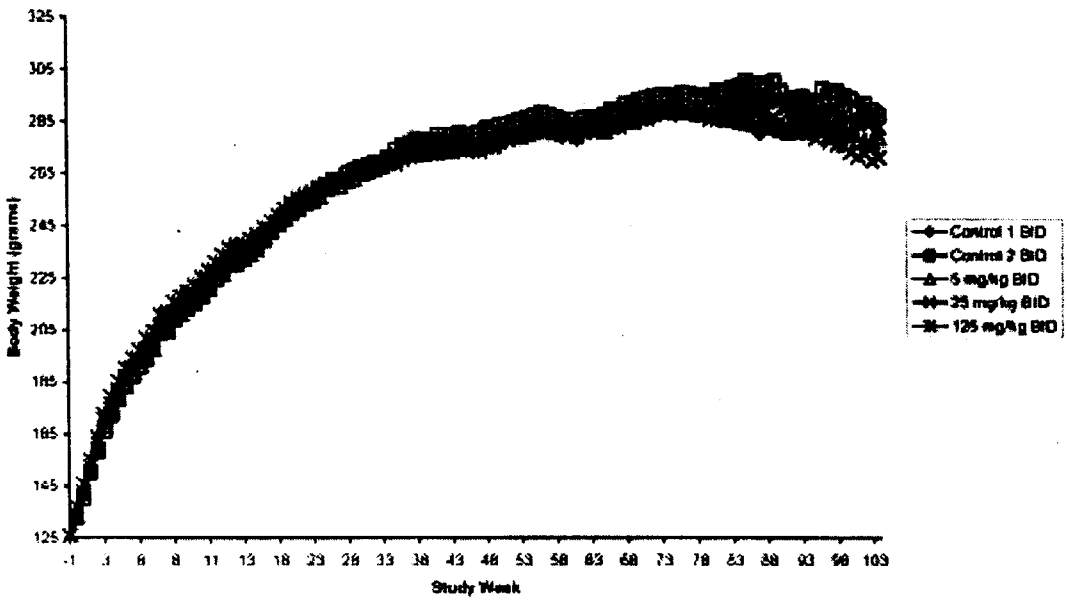


Figure A-1. MK-0869: One-Hundred-Six-Week Oral Carcinogenicity Study in Rats.
TT #98-047-0
Average Body Weights for Female Rats



Ophthalmic Examinations: No treatment related ophthalmic changes were observed in any group.

Hematology: The following hematological parameters were determined: erythrocyte, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, RBC morphology, platelet count, leukocyte count and leukocyte differential count. No treatment-related changes in the hematological parameters were observed in any group.

Gross pathology: No treatment-related gross pathological changes were observed in any group.

Histopathology:

Nonneoplastic: Treatment-related histopathologic changes were observed in the liver and thyroid glands of both males and females. Changes observed in the liver of both sexes included: focal eosinophilic cellular alteration, centrilobular cytoplasmic rarefaction, cystic focal degeneration, cytoplasmic eosinophilic body, peripheral fibrosis, bile duct hyperplasia, centrilobular hypertrophy, multinucleated hepatocytes, single cell necrosis, kupffer cell pigmentation and hepatocyte vacuolation. In addition, the treatment group females had higher incidences of pigmentation of hepatocytes. Thyroid follicular cell diffuse hyperplasia and follicular cell focal cystic hyperplasia were observed in both males and females. Treatment-related chronic nephritis was observed in the high dose males and mid and high dose females. The nonneoplastic histopathological changes in male and female rats are summarized in the sponsor's Table below.

Non-Neoplastic Histomorphologic Changes
(Incidence, n=50)

	MK-0869 (mg/kg b.i.d.)									
	Females					Males				
	C1	C2	5	25	125	C1	C2	5	25	125
Liver										
Hepatocyte, focal eosinophilic cellular alteration	8	15	15	26[a]	24[a]	16	16	27[a]	30[a]	30[a]
Centrilobular cytoplasmic rarefaction	2	1	22[a]	33[a]	35[a]	0	2	14[a]	29[a]	33[a]
Cystic focal degeneration	1	0	1	3	7	2	9	11	15[a]	26[a]
Cytoplasmic eosinophilic body	1	0	0	2	6[a]	1	1	2	3	9[a]
Periportal fibrosis	6	8	18[a]	16[a]	13[a]	8	12	19[a]	23[a]	14[a]
Bile duct, hyperplasia	13	14	30[a]	26[a]	27[a]	18	20	32[a]	39[a]	43[a]
Centrilobular hypertrophy	0	1	26[a]	39[a]	45[a]	0	0	15[a]	41[a]	41[a]
Hepatocellular diffuse hypertrophy	0	0	0	0	1[a]	0	0	0	0	1[a]
Hepatocyte, multinucleated cells	2	4	8[a]	7[a]	11[a]	0	0	0	0	2
Single cell necrosis	2	1	0	4[a]	4[a]	0	0	0	2[a]	2[a]
Kupffer cell, pigmentation	7	7	12[a]	12[a]	14[a]	1	1	1	2	3
Hepatocyte, pigmentation	1	0	3	8[a]	14[a]	0	0	0	0	0
Vacuolation	2	3	8	10[a]	18[a]	4	8	4	15[a]	23[a]

Non-Neoplastic Histomorphologic Changes
(Incidence, n=50) (Cont.)

	MK-0869 (mg/kg b.i.d.)									
	Females					Males				
	C1	C2	5	25	125	C1	C2	5	25	125
Thyroid										
Follicular cell, diffuse hyperplasia	0	0	6[a]	28[a]	38[a]	0	1	13[a]	40[a]	40[a]
Follicular cell, focal cystic hyperplasia	2	0	0	6[a]	6[a]	1	1	7[a]	8[a]	9[a]
Kidney										
Chronic nephritis	2	0	2	7	10[a]	7	7	5	7	15[a]

[a] Treatment-related changes based on incidence and/or severity.
C1 = Control 1.
C2 = Control 2.

Neoplastic: Treatment with MK-0869 was associated with higher incidences of thyroid follicular cell adenoma (control 1, 0/50 [0%], control 2, 0/50 [0%]; low dose, 1/50 [2%]; mid dose, 1/50 [2%]; high

dose, 3/50 [6%]; P=0.014, Trend test) and carcinoma (control 1, 0/50 [0%], control 2, 0/50 [0%]; low dose, 1/50 [2%]; mid dose, 1/50 [2%]; high dose, 2/50 [4%]; P=0.036, Trend test) in the **male** rats. On the basis of CDER statistical standard, the incidences for these tumors were not significant as the P-values (0.014 and 0.036) exceeded the required P-value of 0.005 for common tumors. The incidences for these tumors at the high dose are higher than the historical control incidences from the sponsor's laboratory (follicular cell adenoma, 0%-4%; follicular cell carcinoma, 0%-2%).The incidences of thyroid follicular cell adenoma and carcinoma in males were similar to the spontaneous incidences for these tumors in this strain of rat (follicular cell adenoma, 1.67% to 12%; follicular cell carcinoma, 0.87% to 3.85%; [redacted]. Treatment group **females** had higher incidences of hepatocellular adenoma (control 1, 1/50 [2%], control 2, 1/50 [2%]; low dose, 1/50 [2%]; mid dose, 4/50 [8%]; high dose, 6/50 [12%]; P=0.003, Trend test), thyroid follicular cell adenoma (control 1, 3/50 [6%], control 2, 1/50 [2%]; low dose, 1/50 [2%]; mid dose, 4/50 [8%]; high dose, 6/50 [12%]; P=0.018, Trend test) and adenocarcinoma of the uterus (control 1, 0/50 [0%], control 2, 0/50 [0%]; low dose, 0/50 [0%]; mid dose, 0/50 [0%]; high dose, 2/50 [4%]; P=0.043, Trend test). On the basis of CDER statistical standard, the incidences of thyroid follicular cell adenoma and uterine adenocarcinoma were not significant as the P-values (0.018 and 0.043) exceeded the required P-value of 0.005 for common tumors. Historical control incidences for thyroid follicular cell adenoma and uterine adenocarcinoma from the conducting laboratory in female rats were 0% - 3% and 0% - 3.85%, respectively. The incidences of thyroid follicular cell adenoma and adenocarcinoma of the uterus at the high dose were higher than the spontaneous incidences reported in this strain of rat (thyroid follicular cell adenoma, 1.43% to 6.12%; uterine adenocarcinoma, 1.67%; [redacted].
The incidences of different types of tumors in the male and female rats are **summarized** in the Table below.

Table: Tumor incidences of the male and female rats receiving different doses of MK-0869 for 106 weeks

Observation	Control 1	Control 2	10 mg/kg/day	50 mg/kg/day	250 mg/kg/day	P- value (Trend-test)
Males						
Thyroid-						
Follicular cell adenoma	0/50 (0%)	0/50 (0%)	1/50 (2%)	1/50 (2%)	3/50 (6%)	P=0.014
Follicular cell carcinoma	0/50 (0%)	0/50 (0%)	1/50 (2%)	1/50 (2%)	2/50 (4%)	P=0.036
Adenoma + carcinoma	0/50 (0%)	0/50 (0%)	2/50 (4%)	2/50 (4%)	5/50 (10%)	
Females						
Liver-						
Hepatocellular adenoma	1/50 (2%)	1/50 (2%)	1/50 (2%)	4/50 (8%)	6/50 (12%)	P=0.003
Hepatocellular carcinoma	0/50 (0%)	1/50 (2%)	0/50 (0%)	1/50 (2%)	2/50 (4%)	P=0.110
Adenoma + carcinoma	1/50 (2%)	2/50 (4%)	1/50 (2%)	5/50 (10%)	8/50 (16%)	
Thyroid-						
Follicular cell adenoma	3/50 (6%)	1/50 (2%)	1/50 (2%)	4/50 (8%)	6/50 (12%)	P=0.018
Follicular cell carcinoma	0/50 (0%)	1/50 (2%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	
Adenoma + carcinoma	3/50 (6%)	2/50 (4%)	1/50 (2%)	4/50 (8%)	6/50 (12%)	
Uterus-						
Adenocarcinoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%)	P=0.043

Summary:
In the 106-week oral gavage carcinogenicity study with MK-0869 in Sprague Dawley rats, groups of animals (50/sex/group) received 0, 10, 50 and 250 mg/kg/day of the drug. The doses were administered twice a day (at least 6 hours apart) at oral doses of 5, 25 and 125 mg/kg. The doses were selected on the basis of saturation. The CDER ECAC did not concur with the dose selection because the AUC was determined for the parent compound only (see Appendix 1A). However, in a subsequent toxicokinetic study, it was demonstrated that saturation was achieved at the high dose (125 mg/kg b.i.d). No treatment-related effects on the body weights or survival were observed in any group. Treatment with MK-0869 was associated with higher incidences of thyroid follicular cell adenoma (control 1, 0/50 [0%], control 2, 0/50 [0%]; low dose, 1/50 [2%]; mid dose, 1/50 [2%]; high dose, 3/50 [6%]; P=0.014, Trend test) and carcinoma (control 1, 0/50 [0%], control 2, 0/50 [0%]; low dose, 1/50 [2%]; mid dose, 1/50 [2%]; high dose, 2/50 [4%]; P=0.036, Trend test) in the **male** rats. On the basis of CDER statistical standard, the incidences for these tumors were not significant as the P-values (0.014 and 0.036) exceeded the required P-value of 0.005 for common tumors. The incidences for thyroid follicular cell adenoma and carcinoma are higher than the historical control incidences from the sponsor's laboratory (follicular cell adenoma, 0%-4%; follicular cell carcinoma, 0%-2%). The incidences of thyroid follicular cell adenoma and carcinoma in males were similar to the spontaneous incidences for these tumors in this strain of rat (follicular cell adenoma, 1.67% to 12%; follicular cell carcinoma, 0.87% to 3.85%; [redacted] Treatment group **females** had higher incidences of hepatocellular adenoma (control 1, 1/50 [2%], control 2, 1/50 [2%]; low dose, 1/50 [2%]; mid dose, 4/50 [8%]; high dose, 6/50 [12%]; P=0.003, Trend test), thyroid follicular cell adenoma (control 1, 3/50 [6%], control 2, 1/50 [2%]; low dose, 1/50 [2%]; mid dose, 4/50 [8%]; high dose, 6/50 [12%]; P=0.018, Trend test) and adenocarcinoma of the uterus (control 1, 0/50 [0%], control 2, 0/50 [0%]; low dose, 0/50 [0%]; mid dose, 0/50 [0%]; high dose, 2/50 [4%]; P=0.043, Trend test). On the basis of CDER statistical standard, the incidences of thyroid follicular cell adenoma and uterine adenocarcinoma were not significant as the P-values (0.018 and 0.043) exceeded the required P-value of 0.005 for common tumors. Historical control incidences for thyroid follicular cell adenoma and uterine adenocarcinoma in female rats from the sponsor's laboratory were 0% - 3% and 0% - 3.85%, respectively. The incidences of thyroid follicular cell adenoma and adenocarcinoma of the uterus at the high dose were higher than the spontaneous incidences reported in this strain of rat (thyroid follicular cell adenoma, 1.43% to 6.12%; uterine adenocarcinoma, 1.67%; [redacted]

Analyses of the tumor incidences in male and female rats by the CDER Statistician (Dr. Mushfiqur Rashid) yileded the following p values for different tumors: Females- hepatocellular adenoma, p= 0.0076; thyroid follicular cell adenoma, p= 0.0444; adenocarcinoma of the uterus, p= 0.0441; Males- thyroid follicular cell adenoma, p= 0.0178; thyroid follicular cell carcinoma, p= 0.042. According to CDER statistical standard, only the incidences of thyroid follicular cell adenoma in the male mice were significant, as the p value is smaller than required p value of 0.025.

Twenty-Seven-Week Oral Toxicokinetic Study with MK-0869 (L-754030) in Rats (Study # 98-047-1):

Methods: The sponsor conducted a 27-week toxicokinetic study to determine the plasma pharmacokinetic parameters of MK-0869 (L-754030) after oral dosing in rats. This was an extension of the 106-week oral carcinogenicity study in rats (Study # 98-047-0) and the doses were the same used for the 106-week oral carcinogenicity study in rats (5, 25 and 125 mg/kg b.i.d; 10, 50 and 250 mg/kg/day). Male and female Sprague Dawley rats (10/sex/group; 39 days old) were used in the study and the doses were administered by oral gavage twice a day (6 hours apart). Samples of blood, for determination of plasma drug concentrations, were collected in weeks 13 and 27 (from 4 or 5 animals/sex/group; approximately 0.5, 2, 8 and 24 hours after the first daily dose). Plasma drug concentrations were determined by [redacted] The lower limit of detection for the assay was [redacted]

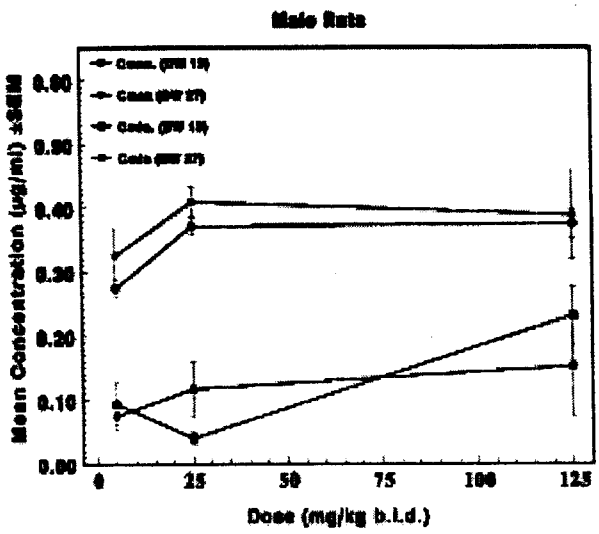
Results: After oral dosing of MK-0869 (L-754030) to the male and female rats, the C_{max} values in females were about 2-5 times higher than that of males. In females, there were increases in the C_{max} with increasing doses, but not dose-proportional. In males, no differences in the C_{max} values were observed between the mid and the high dose at both times of sampling. Thus, the steady state plasma concentrations were reached on Day-13 of dosing or before. The sponsor did not determine the plasma exposure levels (AUC values) for MK-0869 in male and female rats. The C_{max} and C_{min} values for MK-0869 in male and female rats in week-13 and week-27 are summarized in the sponsor's Tables below.

Plasma MK-0869 (L-754,030) Toxicokinetic Parameters
Drug Week 27 Mean Values± Standard Error of the Mean

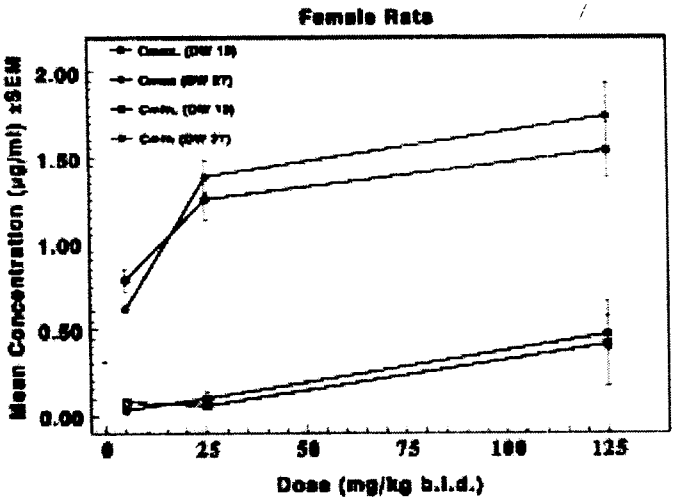
	L-754,030 (mg/kg b.i.d.)		
	Females		
	5	25	125
C_{max} (µg/mL)	0.616 ± 0.0294	1.39 ± 0.0944	1.74 ± 0.196
C_{min} (µg/mL)	0.0350 ± 0.00898	0.101 ± 0.0363	0.470 ± 0.103
	Males		
	5	25	125
C_{max} (µg/mL)	0.325 ± 0.0440	0.409 ± 0.0219	0.388 ± 0.0705
C_{min} (µg/mL)	0.0745 ± 0.0215	0.217 ± 0.0430	0.152 ± 0.0784

The C_{max} and C_{min} values for MK-0869 in male and female rats at weeks 13 and 27 during oral dosing for 27 weeks is shown in the sponsor's graphs below.

Comparison of Mean C_{max} and C_{min} in Male Rats Following Repeated Oral Dosing With MK-0869 in Drug Weeks (DW) 13 and 27



Comparison of Mean C_{max} and C_{min} in Female Rats Following Repeated Oral Dosing With MK-0869 in Drug Weeks (DW) 13 and 27



The sponsor conducted a 27-week toxicokinetic study to determine the plasma pharmacokinetic parameters of MK-0869 (L-754030) after oral dosing to rats. This is an extension of the 106-week oral carcinogenicity study in Sprague Dawley rats (Study # 98-047-0) and the doses used were 5, 25 and 125 mg/kg b.i.d. (10, 50 and 250 mg/kg/day). After oral dosing of MK-0869 (L-754030) to the male and female rats, the C_{max} values in females were about 2-5 times higher than that of males. In females, there were increases in the C_{max} values with increasing doses. However, the increases were not dose-proportional. In males, no differences in the C_{max} values were observed between the mid and the high dose at both times of sampling. The steady state plasma concentrations were reached on Day-13 of dosing or before. The sponsor did not determine the plasma exposure levels (AUC values) for MK-0869 in male and female rats.

CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT AND FDA CDER RODENT CARCINOGENICITY DATABASE FACT SHEET

P/T REVIEWER(s): Sushanta Chakder, Ph.D
DATE:
NDA: 21-549
DRUG CODE #: MK-0869 (L-754030)
CAS #: 170729-80-3
DIVISION: Gastrointestinal and Coagulation Drug Products (HFD-180)
DRUG NAME(s): EMEND (Aprepitant) Capsules
SPONSOR: Merck & Co., Inc.
LABORATORY: Merck Research Laboratories.
CARCINOGENICITY STUDY REPORT DATE: July 23, 2002
THERAPEUTIC CAREGORY: Anti-emetic.
PHARMACOLOGICAL/CHEMICAL CLASSIFICATION: NK1 (Substance P) Receptor Antagonist
MUTAGENIC/GENOTOXIC (y/n/equivocal/na; assay): No

MOUSE CARCINOGENICITY STUDY (multiple studies? Std1; Std2 etc.):

MOUSE STUDY DURATION (weeks): 105 Weeks
STUDY STARTING DATE: January 27, 1998
STUDY ENDING DATE: July 19, 2002
MOUSE STRAIN: Crl:CD-1 (ICR) BR mice
ROUTE: Oral (gavage)
DOSING COMMENTS: None

NUMBER OF MICE:

- Control 1 (C1): 50/sex (one female mouse of this group escaped in week-49 and was never found)
- Control 2 (C2): 50/sex
- Low Dose (LD): 50/sex
- Middle Dose (MD): 50/sex
- High Dose (HD): 50/sex

MOUSE DOSE LEVELS (mg/kg/day):

- Low Dose: 2.5 mg/kg/day
- Middle Dose: 25 mg/kg/day
- High Dose 1: 125 mg/kg/day
- High Dose 2: 500 mg/kg/day

(*Dose adjusted during study): Yes

BASIS FOR DOSES SELECTED (MTD; AUC ratio; saturation; maximum feasible): The doses were selected on the basis of saturation. The toxicology and toxicokinetic profiles of two MK-0869 formulations of different particle sizes were assessed in CD-1 mice during 5-week dosing period. Formulation M — average particle size) was administered at oral doses of 0 and 500 mg/kg/day. Formulation NB (average

particle size —— was administered using S.I.D. and B.I.D. regimens. For S.I.D. regimen, the doses were 0, 25, 500, 1000, 1250 and 1500 mg/kg/day, and for B.I.D. regimen, the doses were 0, 12.5, 250, 500. 625 and 750 mg/kg B.I.D. (total daily doses of 0, 25, 500, 1000, 1250 and 1500 mg/kg). Centrilobular hypertrophy was observed for male and female mice receiving the 500 mg/kg/day of the M formulation. In the S.I.D. regimen of the NB formulation, centrilobular hypertrophy was observed in males at ≥25 mg/kg/day and in females at ≥500 mg/kg/day of NB formulation. In the B.I.D. regimen, centrilobular hypertrophy was observed in male mice receiving ≥12.5 mg/kg and in female mice receiving ≥250 mg/kg B.I.D. doses. Toxicokinetic analysis was confined to the parent compound, MK-0869. Male and female mice receiving MK-0869 formulation NB at 25 to 1500 mg/kg/day doses, a plateau in systemic exposure to the parent compound was evident at ≥500 mg/kg/day. Animals receiving B.I.D. 12.5 to 750 mg/kg doses of the NB formulation, a plateau in the systemic exposure to the parent compound was evident at ≥500 mg/kg B.I.D. Corresponding total daily doses of NB formulation of MK-0869, using S.I.D. or B.I.D. regimens produced similar AUC values. Formulation NB at doses up to 1500 mg/kg/day or 750 mg/kg B.I.D. produced systemic exposures to the parent compound that were generally ≤2-fold that of formulation M at 500 mg/kg/day. The sponsor did not assess systemic exposure to the metabolites as requested by the Division (April 5, 1999 teleconference and August 20, 1999 letter). However, in a subsequent 5-week toxicokinetic study in mice, in which the plasma exposure levels of both the parent compound and the metabolite were determined, saturation of absorption was demonstrated at the high dose (500 mg/kg/day).

MOUSE CARCINOGENICITY (negative; positive; MF; M; F): positive in M and F.

PRIOR FDA DOSE CONCURRENCE (Div./CAC)? (y/n; Date): No.

MOUSE CARCINOGENICITY (conclusion: negative; positive; MF; M; F): MK-0869 was found to be carcinogenic in male and female mice in the 105-week oral carcinogenicity study. There were increased incidences of fibrosarcoma of the skin in males, and hepatocellular adenoma and harderian gland adenoma in females.

MOUSE TUMOR FINDINGS: Treatment with MK-0869 was associated with increased incidences of fibrosarcoma (Control 1 and 2, 0/50 [0%]; 2.5 mg/kg, 0/50 [0%]; 25 mg/kg, 0/50 [0%]; 125 mg/kg, 1/50 [2%]; 500 mg/kg, 2/50 [4%]; P=0.018, Trend test) of the skin in the **male** mice. The incidence of fibrosarcoma at the high dose (4%) is higher than and the historical control incidences from the sponsor's laboratory (0% - 1%, mean 0.09%) and the spontaneous incidences reported by — (1.54% to 2.00%; mean 1.77%) in this strain of mice. Treatment group **females** had higher incidences of hepatocellular adenoma (control 1, 1/49 [2%]; control 2, 0/50 [0%]; 2.5 mg/kg, 2/50 [4%]; 25 mg/kg, 0/50 [0%]; 125 mg/kg, 4/50 [8%]; 500 mg/kg, 4/50 [8%]; P=0.014, Trend test) and Harderian gland adenoma (Control 1, 2/49 [4%]; control 2, 1/50 [2%]; 2.5 mg/kg, 1/50 [2%]; 25 mg/kg, 2/50 [4%]; 125 mg/kg, 2/50 [4%]; 500 mg/kg, 4/50 [8%]; P=0.014, Trend test). On the basis of CDER statistical standard, the incidences of hepatocellular adenoma and Harderian gland adenoma in females were not significant, as the p values (0.014 for both) exceeded the required p value for common tumors (0.005). The incidences of hepatocellular adenoma at the two higher doses (8%) are higher than the historical control incidences from the sponsor's laboratory (1% - 4%, mean 2%) and similar to the range of spontaneous incidences in CD-1 mice, reported by — (range, 0.85% to 7.84%). The incidences of Harderian gland adenoma is similar to the the historical

control incidences (4% - 6%, mean 5.27%), and thespontaneously reported incidences for this tumor in this strain of mice (1.35% to 8.33%,).

MOUSE STUDY COMMENTS: The dose selection for the 106-week mouse carcinogenicity study was based on saturation of absorption. However, the sponsor did not take into consideration of the metabolites in determination of the exposure levels. So, the dose selection was not concurred by the CDER ECAC. However, in a subsequent toxicokinetic study, saturation of absorption was demonstrated at the high dose (500 mg/kg/day). The sponsor did not conduct the toxicokinetic study as part of the carcinogenicity study. Instead, an additional study was conducted to determine only the plasma drug concentrations, and no toxicokinetic data were provided..

COVERSHEET FOR CARCINOGENICITY STUDY IN MICE

1. Study No.: 98-016-0,-2
2. Name of Laboratory: Merck Research Laboratories, Merck & Co. Inc., West Point, PA 19486.
3. Strain: Crl:CD-1 (ICR) BR mice
4. No./sex/group: 50
5. Doses (0, L, M, and H): 0, 0, 2.5, 25, 125 and 500 mg/kg/day for both males and females.
6. Basis for dose selection stated: No.
7. Interim sacrifice: No
8. Total duration (weeks): 105
9. Week/site for first tumor:

	Male	**Female**
Control 1	52/lymphoma (primary site undetermined)	58/histiocytic sarcoma (primary site undetermined)
Control 2	79/hepatocellular adenoma, lung adenoma	51/lymphoma (primary site undetermined)
2.5 mg/kg/day	11/ lymphoma (primary site undetermined)	32/skin osteosarcoma
25 mg/kg/day	71/lung carcinoma	54/lung adenoma
125 mg/kg/day	50/lung carcinoma	74/skin malignant schwannoma
500 mg/kg/day	20/peritoneum, undifferentiated sarcoma	54/lymphoma (primary site undetermined)

10. No. alive at termination:

	Male	**% survival**	**Female**	**% survival**
Control 1	21/50	42%	24/49	48%
Control 2	29/50	58%	20/50	40%
2.5 mg/kg/day	22/50	44%	19/50	38%
25 mg/kg/day	33/50	66%	25/50	50%
125 mg/kg/day	23/50	46%	26/50	52%
500 mg/kg/day	27/50	54%	23/50	46%

11. Statistical methods used: For-evaluation of the carcinogenic potential of the compound, a trend analysis was performed to determine the significant effect on mortality in male and female mice. The incidence of various tumor types was analyzed for statistically significant ($P<0.05$) trend with adjustments made for potentially confounding factors such as, mortality, time-to-tumor onset.
12. Attach tumor and non-tumor data for each tissue: See Appendix 5 and Appendix 6.

Study title: One-hundred-five (105)-Week Oral Carcinogenicity Study with MK-0869 (L-754030) in Mice

Key study findings: MK-0869 was found to be carcinogenic in male and female mice in the 105-week oral carcinogenicity study. There were increased incidences of fibrosarcoma of the skin in males, and hepatocellular adenoma, metaststic histiocytic sarcoma and harderian gland adenoma in females.
Study number: 98-016-0, -2
Conducting laboratory and location: Merck Research Laboratories, Merck & Co., Inc., West Point, PA 19486.
Date of study initiation: January 27, 1998
GLP compliance: yes
QA report: yes (x) no ( )
Drug lot #, and % purity: MK-0869 (L-754,030); Lot Nos. 004H030, 004H032, 004H021, 004H026, 004H031, 004H048; Purity ≥ 99.2%
CAC concurrence: No.

Study Type: Long-term rodent carcinogenicity study
Species/strain: Crl:CD -1(ICR) BR mice
Number/sex/group; age at start of study: 50/sex/group; 44 days old at the start of the study. An additional 5 animals/sex/group were used in the study as replacement animals for mice sacrificed or found dead due to causes unrelated to treatment during the first 7 weeks of the study.
Animal housing: The animals were housed in plastic boxes (1 to 3 animals/box) with stainless steel lids and certified contact bedding. The room was environmentally controlled with high efficiency particulate air (HEPA) filters with a 12-hour light cycle.
Drug stability/homogenicity: The drug was suspended in 0.5% methylcellulose/0.02% sodium lauryl sulfate in deionized water. The suspensions were prepared daily. Samples of all dosing formulations were analyzed for stability and homogenicity during weeks 1, 7, 19, 27, 39, 41, 53, 61, 68, 77, 82, 88, 100 and 104. The sponsor stated that the compound was stable in the formulation under the conditions of the study and the concentrations were within the acceptable concentration range.

Methods:

Doses: 0, 2.5, 25, 125 and 500 mg/kg/day.

Two control groups received the vehicle only. The treatment groups received the drug at a constant volume (10 ml/kg/day), administered by oral gavage.

Basis of dose selection: The sponsor selected the doses on the basis of saturation. The toxicology and toxicokinetic profiles of two MK-0869 formulations of different particle sizes were assessed in CD-1 mice during 5-week dosing period. Formulation M (— particle size) was administered at oral doses of 0 and 500 mg/kg/day. Formulation NB (average particle size —) was administered using S.I.D. and B.I.D. regimens. For S.I.D. regimen, the doses were 0, 25, 500, 1000, 1250 and 1500 mg/kg/day, and for B.I.D. regimen, the doses were 0, 12.5, 250, 500, 625 and 750 mg/kg b.i.d. (total daily doses of 0, 25, 500, 1000, 1250 and 1500 mg/kg/day). Centrilobular hypertrophy was observed in male and female mice receiving the 500 mg/kg/day of the M formulation. In the S.I.D. regimen of the NB formulation, centrilobular hypertrophy was observed in males at ≥25 mg/kg/day and in females at ≥500 mg/kg/day. In the B.I.D. regimen,

centrilobular hypertrophy was observed in the male mice receiving ≥12.5 mg/kg and in the female mice receiving ≥250 mg/kg B.I.D. doses. Toxicokinetic analysis was confined to the parent compound, MK-0869. Male and female mice receiving MK-0869 formulation NB at 25 to 1500 mg/kg/day doses, a plateau in systemic exposure to the parent compound was evident at ≥500 mg/kg/day. Animals receiving B.I.D. 12.5 to 750 mg/kg doses of the NB formulation, a plateau in the systemic exposure to the parent compound was evident at ≥500 mg/kg B.I.D. Corresponding total daily doses of NB formulation of MK-0869, using S.I.D. or B.I.D. regimens produced similar AUC values. Formulation NB at doses up to 1500 mg/kg/day or 750 mg/kg B.I.D. produced systemic exposures to the parent compound that were generally ≤2-fold that of formulation M at 500 mg/kg/day. The sponsor did not assess systemic exposure to the metabolites as requested by the Divivsion (April 5, 1999 teleconference and August 20, 1999 letter). However, in a subsequent 5-week oral toxicokinetic study, it was demonstrated that saturation of absorption was achieved at the high dose (500 mg/kg/day).

Route of administration: Oral (gavage)

Frequency of drug administration: The drug was administered by oral gavage once daily.

Dual controls employed: Yes

Interim sacrifices: No

Satellite PK or special study group(s): None

Deviations from original study protocol: N/A

Statistical methods: For evaluation of the carcinogenic potential of the compound, a trend analysis was performed to determine the significant effect on mortality in male and female mice. The incidence of various tumor types was analyzed for statistically significant ($P<0.05$) trend with adjustments made for potentially confounding factors such as, mortality, time-to-tumor onset.

Observations and times:

Clinical signs: The animals were observed daily for mortality and once a week for physical signs. Beginning from administration week 26, all mice were examined every 4 weeks for palpable masses.

Body weights: The body weights were measured once in week-1, twice a week through week-13 and once a week thereafter.

Hematology: Blood samples for hematology examinations were collected from the surviving animals prior to the terminal necropsy.

Ophtahlmologic Examinations: Ophthalmic examinations were conducted of all animals before initiation of dosing and of the control-1 and the high dose animals during weeks 52 and 93 of dosing.

Gross pathology: All surviving animals were sacrificed at the end of the dosing period and complete necropsies done. Animals, those died or sacrificed moribund during the dosing period, also underwent complete necropsy examinations.

Histopathology: The following tissues from all animals were histologically examined after fixation and staining.

Salivary gland (submandibular/sublingual), esophagus, stomach, small intestine (duodenum, jejunum, ileum), large intestine (colon), liver, pancreas, adrenals, parathyroid, skin (from mammary region), mammary gland, lung, heart, spleen, lymph nodes (cervical and mesenteric), thymus, bone marrow, bone (femur, including femorotibial joint), skeletal muscle, pituitary, thyroid, kidneys, urinary bladder, ovaries, uterus, testes and epididymides, prostate, brain, spinal cord (cervical), peripheral nerve (sciatic), eyes (with optic nerves), Harder's glands, gallbladder.

Results:

Mortality: No treatment-related effects on mortality were observed in any group. The cumulative mortalities among males and females at different times of the treatment period are summarized in the Tables below.

Table: Cumulative mortalities in **male** mice receiving MK-0869 for 105 weeks.

Weeks	Control 1		Control 2		2.5 mg/kg/day		25 mg/kg/day		125 mg/kg/day		500 mg/kg/day	
	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death
52	3/50	6%	3/50	6%	5/50	10%	4/50	8%	4/50	8%	3/50	6%
65	8/50	16%	5/50	10%	7/50	14%	4/50	8%	7/50	14%	5/50	10%
78	11/50	22%	6/50	12%	11/50	22%	7/50	14%	12/50	24%	9/50	18%
91	21/50	42%	12/50	24%	21/50	42%	11/50	22%	19/50	38%	15/50	30%
105	29/50	58%	21/50	42%	28/50	56%	17/50	34%	27/50	54%	23/50	46%

Table: Cumulative mortalities in **female** mice receiving MK-0869 for 105 weeks.

Weeks	Control 1		Control 2		2.5 mg/kg/day		25 mg/kg/day		125 mg/kg/day		500 mg/kg/day	
	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death	No. Dead	% Death
52	2/49[a]	4%	2/50	4%	3/50	6%	0/50	0%	2/50	4%	2/50	4%
65	5/49[a]	10%	3/50	6%	4/50	8%	2/50	4%	4/50	8%	8/50	16%
78	7/49[a]	14%	8/50	16%	9/50	18%	7/50	14%	7/50	14%	13/50	26%
91	12/49[a]	25%	14/50	28%	19/50	38%	16/50	32%	15/50	30%	23/50	46%
105	26/49[a]	53%	30/50	60%	31/50	62%	25/50	50%	24/50	48%	27/50	54%

[a], One female mouse (#98-0179) escaped during case change in Week 49 and this mouse was not available for necropsy.

Clinical signs: No treatment-related clinical signs were observed in any group.

Body weights: The mean body weights of the control males and females at the beginning of dosing (week-1) were 29.8±1.9 g and 22.2±1.1 g, and at the end of the dosing (week-105) were 43.4±5.3 g and 34.7±4.0 g, respectively. The body weights of the males and females were not affected by treatment with MK-0869 at any time of the dosing period. The mean body weights and the percent changes in the body weights of the male and female mice receiving different doses of MK-0869 in weeks 13, 26, 54, 78 and 105 are summarized in the Table below.

Table: Body weights and changes in body weights (% of control 1) of the male and female mice receiving MK-0869.

Weeks	Males						Females					
	Control 1	Control 2	2.5 mg/kg	25 mg/k	125 mg/kg	500 mg/kg	Control 1	Control 2	2.5 mg/k	25 mg/k	125 mg/kg	500 mg/kg
Week-13												
Body Weight (g)	39.9	39.1	39.4	38.5	39.0	38.7	29.6	29.6	30.4	29.6	30.0	30.4
% of Control	100%	98.0%	98.8%	96.5%	97.7%	97.0%	100%	100%	102.7%	100%	101.4%	102.7%
Week-26												
Body Weight (g)	43.1	41.4	42.0	41.1	41.3	40.8	31.3	31.9	32.3	31.9	32.8	32.5
% of Control	100%	96.1%	97.5%	95.4%	95.8%	94.7%	100%	101.9%	103.2%	101.9%	104.8%	103.8%
Week-54												
Body Weight (g)	44.8	43.4	44.4	43.3	44.6	43.0	33.4	34.8	35.6	34.0	34.8	35.3
% of Control	100%	96.9%	99.1%	96.7%	99.6%	96.0%	100%	104.2%	106.6%	101.8%	104.2%	105.7%
Week-78												
Body Weight (g)	45.0	42.5	43.7	43.0	44.5	43.1	35.5	35.5	36.6	35.6	35.6	36.1
% of Control	100%	94.4%	97.1%	95.6%	98.9%	95.8%	100%	100%	103.1%	100.3%	100.3%	101.7%
Week-104												
Body Weight (g)	43.4	39.7	40.8	40.5	41.9	39.9	35.0	36.5	35.0	34.4	34.2	35.2
% of Control	100%	91.5%	94.0%	93.3%	96.6%	91.9%	100%	104.3%	100%	98.3%	97.7%	100.6%
Body Weight gain(g)	14.1	10.9	12.1	11.5	12.8	10.2	12.7	13.9	12.1	11.4	11.1	11.9
% of Control	100%	77.3%	85.8%	81.6%	90.8%	72.3%	100%	109.4%	95.3%	89.8%	87.4%	93.7%

The body weights (in g) of the male and female animals of different groups during the dosing period are shown in the sponsor's figure below.

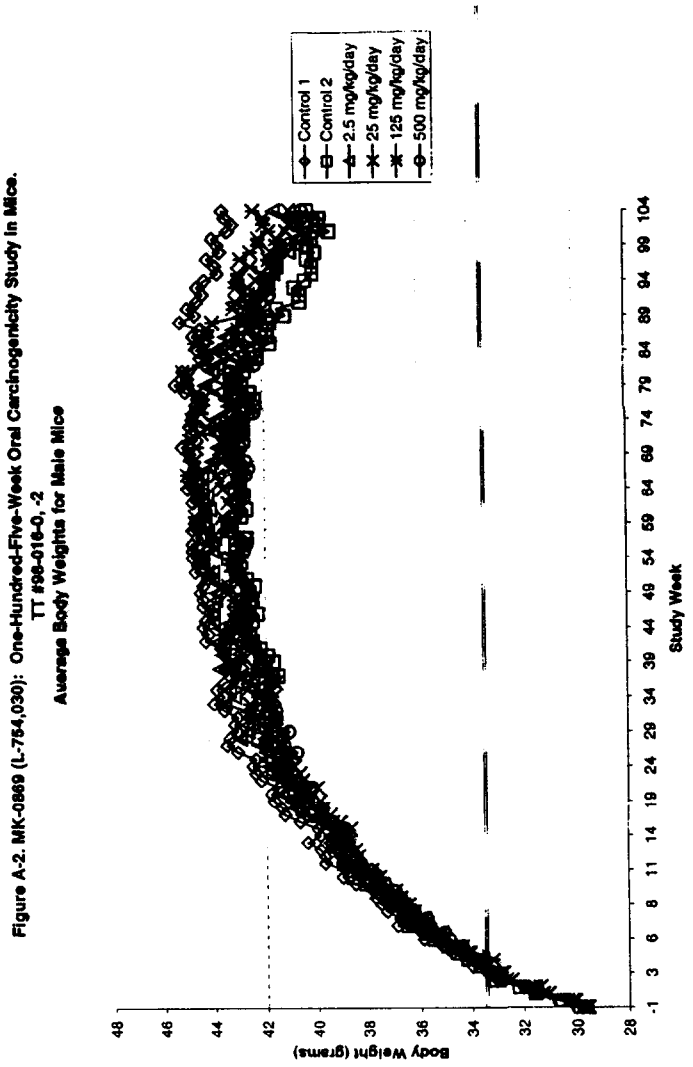
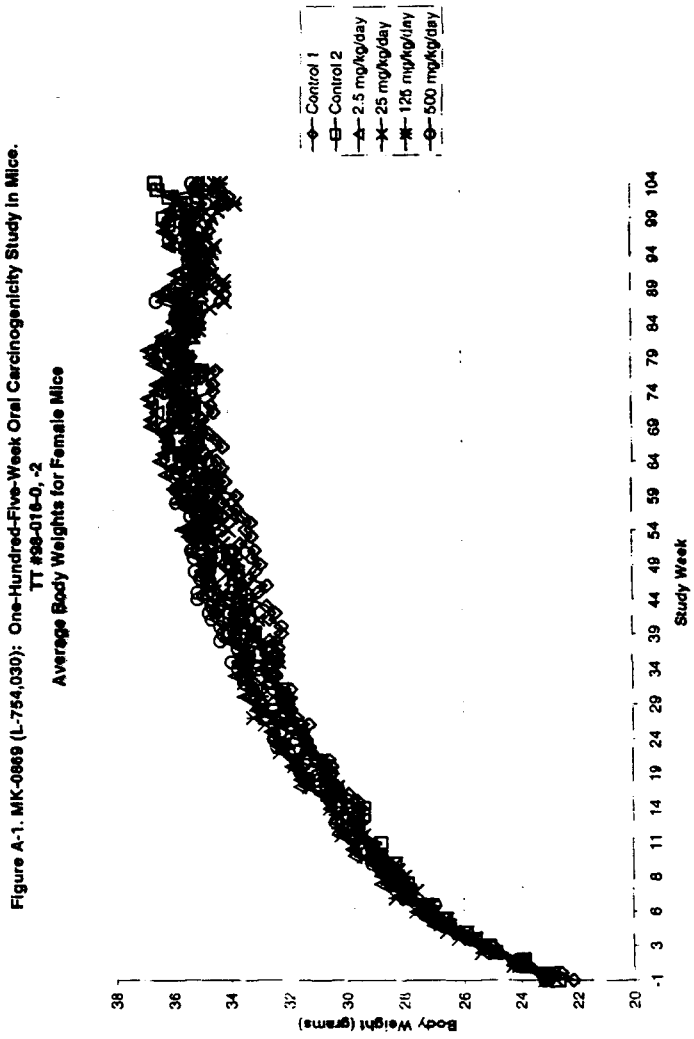


Figure A-2. MK-0869 (L-754,030): One-Hundred-Five-Week Oral Carcinogenicity Study in Mice.
TT #98-016-0, -2
Average Body Weights for Male Mice
Control 1
Control 2
2.5 mg/kg/day
25 mg/kg/day
125 mg/kg/day
500 mg/kg/day
Body Weight (grams)
Study Week



Ophthalmic Examinations: No treatment related ophthalmic changes were observed in any group.

Hematology: The following hematological parameters were determined: erythrocyte, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, RBC morphology, platelet count, leukocyte count and leukocyte differential count. No treatment-related changes in the hematological parameters were observed in any group.

Gross pathology: No treatment-related gross pathological changes were observed in any group. One female mice receiving125 mg/kg and one male receiving 500 mg/kg of the drug had acute necrotizing pancreatitis (there was no pancreatitis in any other group).

Histopathology:

Nonneoplastic: Male and female animals receiving 25 mg/kg and higher doses of MK-0869 had higher incidences of centrilobular hepatocellular hypertrophy. Nonneoplastic histopathological findings in the male and female mice are **summarized** in the Table below.

Table: Histopathological changes in the male and female mice receiving MK-0869 for 105 weeks

Observations	Control 1	Control 2	2.5 mg/kg/day	25 mg/kg/day	125 mg/kg/day	500 mg/kg/day
Males						
Small Intestine- Acute enteritis	1/50 (2%)	0/50 (0%)	0/50 (0%)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Liver- Centrilobular hepatocellular hypertrophy	11/50 (22%)	13/50 (26%)	12/50 (24%)	19/50 (38%)	20/50 (40%)	27/50 (54%)
Heart- Focal arteritis	1/50 (2%)	3/30 (6%)	2/50 (4%)	4/50 (8%)	5/50 (10%)	5/50 (10%)
Kidney- Hydronephrosis	5/50(10%)	6/60 (12%)	9/50 (18%)	8/50 (16%)	9/50 (18%)	11/50 (22%)
Females						
Small Intestine- Amyloidosis	6/49 (12%)	2/50 (0%)	6/50 (12%)	6/50 (12%)	10/50 (20%)	10/50 (20%)
Large Intestine- Lympholytic focal cellular infiltration	0/49 (0%)	1/50 (2%)	0/50 (0%)	4/50 (8%)	7/50 (14%)	9/50 (18%)
Liver- Centrilobular hepatocellular hypertrophy	4/49 (8%)	2/50 (4%)	2/50 (4%)	5/50 (10%)	7/50 (14%)	8/50 (16%)
Brain- Perivascular lymphocytic focal encephalitis	1/49 (2%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%)	2/50 (4%)

Neoplastic: Treatment with MK-0869 was associated with increased incidences of fibrosarcoma (Control 1 and 2, 0/50 [0%]; 2.5 mg/kg, 0/50 [0%]; 25 mg/kg, 0/50 [0%]; 125 mg/kg, 1/50 [2%]; 500 mg/kg, 2/50 [4%]; P=0.018, Trend test) of the skin in the male mice. The incidence of fibrosarcoma at the high dose (4%) is higher than the historical control incidences from the sponsor's laboratory (0% - 1%, mean 0.09%) in this strain of mice and the spontaneous incidences reported by (1.54% to 2.00%; mean 1.77%). Treatment group females had higher incidences of hepatocellular adenoma (control 1, 1/49 [2%]; control 2, 0/50 [0%]; 2.5 mg/kg, 2/50 [4%]; 25 mg/kg, 0/50 [0%]; 125 mg/kg, 4/50 [8%]; 500 mg/kg, 4/50 [8%]; P=0.014, Trend test) and Harderian gland adenoma (Control 1, 2/49 [4%]; control 2, 1/50 [2%]; 2.5 mg/kg, 1/50 [2%]; 25 mg/kg, 2/50 [4%]; 125 mg/kg, 2/50 [4%]; 500 mg/kg, 4/50 [8%]; P=0.014, Trend test). On the basis of CDER statistical standard, the incidences of hepatocellular adenoma and Harderian gland adenoma in females were not significant, as the p values (0.014 for both) exceeded the required p value for common tumors (0.005). The incidences of hepatocellular adenoma at the two higher doses (8%) are higher than the historical control incidences from the sponsor's laboratory (1% - 4%, mean 2%), and similar to the range of spontaneous incidences in CD-1 mice, reported by (range, 0.85% to 7.84%). The incidences of Harderian gland adenoma is similar to the historical control incidences (4% - 6%, mean 5.27%) from the sponsor's laboratory and the spontaneous incidences reported (1.35% to 8.33%, in this strain of mice. Tumor incidences ($P<0.05$) for the male and female animals

receiving different doses of MK0869 are summarized in the Tables below. Tumor incidences in all tissues are provided in Appendix 3.

Table: Tumor incidences of the male and female mice receiving different doses of MK-0869 for 105 weeks

Observation	Control 1	Control 2	2.5 mg/kg	25 mg/kg	125 mg/kg	500 mg/kg	P- value (Trend-test)
Males							
Skin- Fibrosarcoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)	2/50 (4%)	0.018
Females							
Liver- Hepatocellular adenoma	1/49 (2%)	0/50 (0%)	2/50 (4%)	0/50 (0%)	4/50 (8%)	4/50 (8%)	0.014
Eye- Harderian gland adenoma	2/49 (4%)	1/50 (2%)	1/50 (2%)	2/50 (4%)	2/50 (4%)	4/50 (8%)	0.014

Summary:

In the 105-week oral gavage carcinogenicity study with MK-0869 in CD-1 mice, groups of animals (50/sex/group) received 0, 2.5, 25, 125 and 500 mg/kg/day of the drug. The dose selection was based on saturation of absorption, however, it was not in concurrence with the CDER ECAC. However, in a subsequent toxicokinetic study, it was demonstrated that saturation of absorption was achieved at the high dose used in the carcinogenicity study. No treatment-related effects on the body weights or survival were observed in any group. Treatment with MK-0869 was associated with increased incidences of fibrosarcoma (Control 1 and 2, 0/50 [0%]; 2.5 mg/kg, 0/50 [0%]; 25 mg/kg, 0/50 [0%]; 125 mg/kg, 1/50 [2%]; 500 mg/kg, 2/50 [4%]; P=0.018, Trend test) of the skin in the male mice. The incidence of fibrosarcoma at the high dose (4%) is higher than the historical control incidences from the sponsor's laboratory (0% - 1%, mean 0.09%) in this strain of mice and the spontaneous incidences reported by [redacted] (1.54% to 2.00%; mean 1.77%). Treatment group females had higher incidences of hepatocellular adenoma (control 1, 1/49 [2%]; control 2, 0/50 [0%]; 2.5 mg/kg, 2/50 [4%]; 25 mg/kg, 0/50 [0%]; 125 mg/kg, 4/50 [8%]; 500 mg/kg, 4/50 [8%]; P=0.014, Trend test) and Harderian gland adenoma (Control 1, 2/49 [4%]; control 2, 1/50 [2%]; 2.5 mg/kg, 1/50 [2%]; 25 mg/kg, 2/50 [4%]; 125 mg/kg, 2/50 [4%]; 500 mg/kg, 4/50 [8%]; P=0.014, Trend test). On the basis of CDER statistical standard, the incidences of hepatocellular adenoma and Harderian gland adenoma in females were not significant, as the p values (0.014 for both) exceeded the required p value for common tumors (0.005). The incidences of hepatocellular adenoma at the two higher doses (8%) are higher than the historical control incidences from the sponsor's laboratory (1% - 4%, mean 2%), and similar to the range of spontaneous incidences in CD-1 mice, reported by [redacted] (range, 0.85% to 7.84%). The incidences of Harderian gland adenoma is similar to the historical control incidences (4% - 6%, mean 5.27%) from the sponsor's laboratory and the spontaneous incidences reported (1.35% to 8.33%, [redacted] in this strain of mice.

Analyses of the tumor incidences in male and female mice by the CDER Statistician (Dr. Mushfiqur Rashid) yileded the following p values for different tumors: Females- hepatocellular adenoma, p= 0.0147; Males- skin fibrosarcoma, p= 0.017; skin sarcoma, p= 0.0494. According to

CDER statistical standard, only the incidences of skin fibrosarcoma in the male mice were significant, as the p value is smaller than 0.025.

Twenty-Seven-Week Oral Toxicokinetic Study with MK-0869 (L-754030) in Mice (Study # 98-016-1):

Methods: The sponsor conducted a 27-week toxicokinetic study to determine the plasma pharmacokinetic parameters of MK-0869 (L-754030) after oral dosing to mice. This study is an extension of the 105-week oral carcinogenicity study in CD-1 mice (98-016-0,-2). Groups of animals received 2.5, 25,125 and 500 mg/kg/day doses of the drug. Samples of blood were collected in weeks 5 and 27 (from 5 animals/sex/group; approximately 2 and 10 hours after dosing) for determination of plasma drug concentrations. Plasma drug concentrations were determined by [redacted].

The lower limit of detection for the assay was [redacted]

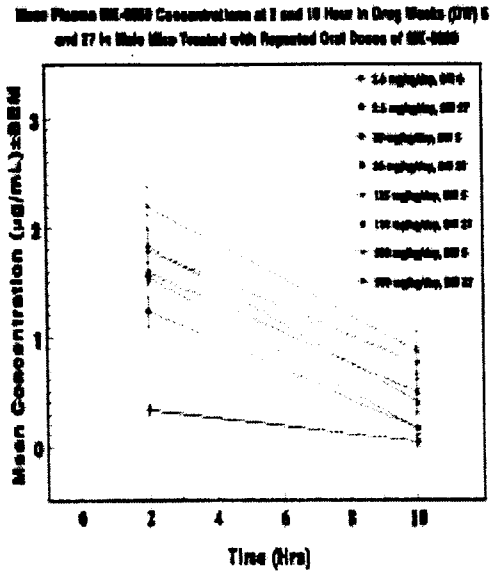
Results: After oral dosing of MK-0869 (L-754030) to male and female mice for 5 or 27 days, the plasma drug concentrations increased with increasing doses at 2 hours after dosing not dose-proportional). The plasma drug concentrations at 10 hours after dosing were lower than that at 2 hours after dosing. No apparent differences in the plasma drug concentrations were observed between week 5 and week 27, suggesting that the steady state plasma concentrations were reached in week 5 of dosing. There were no sex differences in the plasma drug concentrations at any time of the dosing period. The plasma MK-0869 concentrations of male and female mice in weeks 5 and 27 at 2 hr and 10 hr after dosing are summarized in the sponsor's Table below.

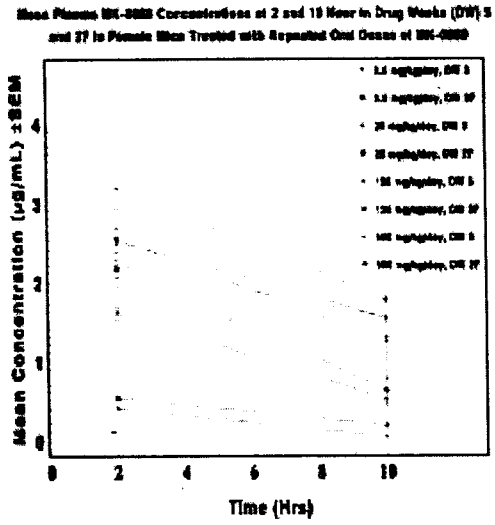
Plasma MK-0869 (L-754,030) Toxicokinetic Parameters
Drug Week 5 and 27 Mean Values

Females				
	C_{2hr} (µg/mL)		C_{10hr} (µg/mL)	
Dose (mg/kg/day)	DW5	DW27	DW5	DW27
2.5	0.394 ± 0.0175	0.527 ± 0.0371	0.0307 ± 0.001596	0.176 ± 0.0277
25	1.60 ± 0.0779	2.15 ± 0.111	0.500 ± 0.0961	0.633 ± 0.166
125	2.51 ± 0.165	2.19 ± 0.256	1.53 ± 0.228	1.54 ± 0.253
500	3.18 ± 0.280	2.54 ± 0.400	1.76 ± 0.294	1.24 ± 0.488
Males				
	C_{2hr} (µg/mL)		C_{10hr} (µg/mL)	
Dose (mg/kg/day)	DW5	DW27	DW5	DW27
2.5	0.339 ± 0.0221	0.333 ± 0.0481	0.0391 ± 0.00520	0.0368 ± 0.0148
25	1.55 ± 0.0667	1.24 ± 0.140	0.162 ± 0.0203	0.163 ± 0.0481
125	1.60 ± 0.0885	1.84 ± 0.282	0.486 ± 0.173	0.405 ± 0.113
500	2.20 ± 0.184	1.79 ± 0.188	0.870 ± 0.178	0.763 ± 0.146

Values are Mean ± Standard Error of the Mean.

The plasma MK-0869 concentrations at 2 and 10 hours in weeks 5 and 27 after daily oral dosing in male and female mice are shown in the sponsor's Figures below.





In the 27-week oral toxicokinetic study with MK-0869 in male and female mice, groups of animals received 2.5, 25, 125 and 500 mg/kg/day of the drug. At 2 hours after dosing, the plasma drug concentrations increased with increasing doses (not dose-proportional). The plasma drug concentrations at 10 hours after dosing were lower than that at 2 hours after dosing. The steady state plasma concentrations were reached in week 5 of dosing or before. There were no sex differences in

the plasma drug concentrations at any time of the dosing period. The sponsor did not calculate the C_{max} or AUC values for MK-0869 after oral dosing to mice.

Carcinigenicity study conclusions:

The sponsor conducted two 106-week oral carcinogenicity studies in Sprague Dawley rats and a 105-week oral carcinogenicity study in CD-1 mice with MK-0869. In the first carcinogenicity study in rats, oral doses of 0, 0.10, 0.50 and 2.0 mg/kg/day (0, 0.05, 0.25 and 1.0 mg/kg b.i.d.) were used and the exposure levels at the high dose were lower than that in humans at the proposed clinical dose. In this 106-week carcinogenicity study in rats, treatment with MK-0869 was not associated with an increase in any type of tumors in the male and female rats. In the second 106-week oral carcinogenicity study in rats, 0, 10, 50 and 250 mg/kg/day (0, 5, 25 and 125 mg/kg b.i.d) doses were used. The doses were selected on the basis of saturation of absorption at the high dose. However, in the dose-ranging study, the sponsor determined the exposure levels only of the parent compound, MK-0869. As the sponsor did not determine the exposure levels of the metabolites of MK-0869, the CDER Executive CAC did not concur with the dose selection for this study. However, in a subsequent 5-week oral toxicokinetic study, it was demonstrated that saturation of absorption was achieved at the 125 mg/kg b.i.d dose. In the second 106-week carcinogenicity study, MK-0869 was carcinogenic to both male and female rats. There were increased incidences of thyroid follicular cell adenoma and carcinoma in the male rats, and hepatocellular adenoma and thyroid follicular cell adenoma in the female rats.

In the 105-week oral carcinogenicity study in mice, 0, 2.5, 25, 125 and 500 mg/kg/day doses were used. The sponsor's dose selection was based on saturation of absorption of MK-0869. However, as the exposure levels of the metabolites were not determined, and only the parent compound was taken into account in determining the exposure levels, the CDER Executive CAC did not concur with the doses. However, in a subsequent 5-week oral toxicokinetic study, it was demonstrated that saturation was achieved at the high dose used in the carcinogenicity study. MK-0869 was found to be carcinogenic in male and female mice in the 105-week oral carcinogenicity study. There were increased incidences of fibrosarcoma of the skin in males, and hepatocellular adenoma and harderian gland adenoma in females.

Conclusions: Treatment with MK-0869 for 106 weeks was associated with higher incidences of thyroid follicular cell adenoma and carcinoma in the male SD rats, and hepatocellular adenoma and thyroid follicular cell adenoma in the female SD rats. Mice receiving MK-0869 for 105 weeks, had increased incidences of skin fibrosarcoma in males and hepatocellular adenoma and Harderian gland adenoma in females. The incidences of thyroid follicular cell tumors and hepatocellular adenoma may be related to the induction of CYP450 enzymes by the drug.

Labeling recommendations:
See the labeling section of the review.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

1. Segment I. Fertility and Reproductive Performance Study of I.V. L-758,298 in Female Rats (TT #96-714-0).

Testing Laboratory: Merck Research Laboratories
West Point, PA 19486

Compliance with Good Laboratory Practices and Quality Assurance Requirements: Sponsor provided statements of compliance.

Study Started: March 8, 1996

Study Completed: October 3, 1996

Animals: Female Sprague-Dawley rats (203 to 275 g; approximately 9 weeks of age).

Methods: In an exploratory intravenous toxicity study in rats (TT #95-2559), it was determined that the highest feasible concentration of L-758,298 for repeated administration was 0.4 mg/ml; higher concentrations produced vascular irritation. In a range-finding study (TT #96-703-5) of intravenously administered L-758,298 (0, 0.5, 1, 2 and 4 mg/kg/day from Gestation Day 6 through Lactation Day 21) in female rats, the 4 mg/kg/day dose produced a decrease in body weight gain (-26%; % of difference from control). There were no other treatment-related effects.

Thus, 4 groups of 24 female rats each were intravenously administered 0, 1, 2 and 4 mg/kg/day of L-758,298, respectively, via the tail vein for 14 days prior to cohabitation (Days 1 to 14), during cohabitation (Day 15 up to Day 34; females were mated with untreated males on a 1:1 ratio for a maximum of 20 nights), and through Gestation Day 7 (the day of finding a vaginal plug and/or sperm in the vagina was defined as Gestation Day 0). Vehicle was 0.9% saline solution; dosing volume was 10 ml/kg; injection rate was 2 ml/min.

Dams were observed daily for clinical signs of toxicity and mortality from initiation of treatment through Gestation Day 8, 12 or 15; dams were observed for 1 to 5 hr post-dosing. Body weights were recorded on Pre-cohabitation Days 1, 4, 8, 11 and 14; during cohabitation on Days 22 and 29; if not mated, on Days 36, 43 and 49; and on Gestation Days 0, 2, 4, 6, 8, 12 and 15. Food consumption was recorded on Pre-cohabitation Days 1 to 5 and 8 to 12 and on Gestation Days 1 to 5 and 8 to 12.

Dams were euthanized on Gestation Day 15, 16 or 17 by CO_2 asphyxiation. Numbers of corpora lutea, implantations, pre- and post-implantation loss, resorptions, and live and dead fetuses were determined. All dams were subjected to a thoracic and visceral examination. Fetuses were euthanized by rapid induction of hypothermia.

Data were statistically analyzed by trend tests and analyses of variance or covariance.

Results:

Dams

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 females were 236 and 245 g on Days 1 and 14 of the pre-cohabitation period, respectively. Mean body weights of control pregnant females were 256 and 346 g on Gestation Days 0 and 15, respectively. There were no treatment-related effects on body weight.

4. Food Consumption: Mean food consumption of control females was 19 and 18 g/day on Days 5 and 12 of the pre-cohabitation period, respectively. Mean food consumption of control pregnant females was 25 and 27 g on Gestation Days 5 and 12, respectively. There were on treatment-related effects on food consumption.

5. Fertility and Reproductive Performance: As shown in the following table, there were no treatment-related effects on fertility and reproductive performance in female rats.

Summary of Fertility and Reproductive Performance of Female Rats in a Segment I. Reproductive Toxicity Study.

Treatment Dose (mg/kg/day, i.v.)	Vehicle 0	L-758,298 1	2	4
Females cohabited	24	24	24	24
Mated females	24	24	24	23
Pregnant females	23	20	21	20
Matings per 4-day periods of cohabitation:				
Days 1-4	21	23	21	19
5-8	1	1	0	1
9-12	1	0	0	1
13-16	1	0	3	2
17 or later	0	0	0	0
Time to mating (4-day periods)	1.25	1.04	1.38	1.39
[a]Mating index	0.92	0.98	0.91	0.85
Mated females/ females cohabited (%)	100%	100%	100%	96%
[b]Fecundity index (%)	96%	83%	88%	87%
[c]Fertility index (%)	96%	83%	88%	83%

[a]Mean of (1/(Time to mating) for mated females and zero for females that did not mate.
[b]Pregnant females/mated females.
[c]Pregnant females/females cohabited.

6. Dam and Fetal Data: As shown in the following table, there were no treatment-related effects on number of pregnant females, corpora lutea, and implantations, and on % implantation loss and resorptions after euthanasia on Gestation Day 15, 16 or 17. There were no treatment-related effects on number of live fetuses.

Summary of Dam and Fetal Data After Euthanasia on Gestation Day 15, 16 or 17 in a Segment I. Study of Fertility and Reproductive Performance in Rats.

Treatment Dose (mg/kg/day, i.v.)	Vehicle 0	L-758,298 1	2	4
Total females	24	24	24	24
No. Pregnant females	23	20	21	20
No. Died	0	0	0	0
Mean Corpora lutea/dam	17.5	17.0	16.8	16.2
Mean Implantations/dam	16.1	15.8	15.8	15.3
% Pre-implantation loss/litter	7.5%	8.0%	7.5%	7.9%
% Post-implantation loss/litter	5.2%	4.5%	7.3%	9.1%
% Resorptions/implantation	5.2%	4.5%	7.3%	7.6%
Mean Dead fetuses/dam	0	0	0	1.5
Mean Live fetuses/dam	15.3	15.0	14.6	13.8

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

In summary, there were no treatment-related effects of i.v. L-758,298 (0, 1, 2 and 4 mg/kg/day) on fertility and reproductive performance of female rats. Furthermore, in a previous 4-week i.v. toxicity study of L-758,298 (0, 0.25, 1 and 4 mg/kg/day) in male and female rats, 4 mg/kg/day was the no effect dose. Thus, since the high dose of L-758,298 did not produce any toxicity in either of the above studies, it does not appear to be adequate. However, 4 mg/kg/day was originally selected as the high dose for the reproductive toxicity studies because it produced a decrease in body weight gain (-26%; % of difference from control) in a range-finding study where female rats received i.v. L-758,298 from Gestation Day 6 through Lactation Day 21. Furthermore, in an exploratory intravenous study using rats, it was determined that the highest feasible concentration of L-758,298 for repeated i.v. administration was 0.4 mg/ml; higher concentrations produced vascular irritation.. Thus, based upon data from these preliminary studies, the selection of a high i.v. dose of 4 mg/kg/day for the reproductive toxicity study appeared to be reasonable.