Histopathology:

Non-neoplastic: the sponsor summarized statistically significant findings in the following tables:

Survivors

Organ	Finding	Dose group (mg/kg/day)							
		Male				Female			
		0	1	3	10	0	1	3	10
Pituitary	Anterior cyst	1/20	1/16	1/22	0/28	2/24	2/23	1/13	0/17
	Anterior hyperplasia	1/20	0/16	0/22	0/28	4/24	4/23	6/13	5/17
	Atrophy of intermediate part	0/20	0/16	6/22↑	11/28↑	0/24	0/23	3/13↑	10/17↑
Mammary glands	Acinar proliferation	0/20	0/16	0/22	0/29	5/24	3/23	6/13	6/17
Adrenal glands	Increased brown pigment deposition in cortico-medullary junction	7/20	4/16	3/22	2/29↓	11/24	9/23	7/13	9/17
Lungs	Mononuclear cell infiltration	4/20	1/16	0/22↓	5/29	4/24	6/23	2/13	5/17
Liver	Focal hepatocellular necrosis	0/20	0/16	1/22	0/29	0/24	0/23	0/13	0/17
Gallbladder	Luminal dilatation	4/20	3/16	1/21	6/29	6/24	2/23	2/13	3/17
Kidneys	Pelvic dilatation	8/20	3/16	0/22↓	2/29↓	1/24	4/23	1/13	1/17
Urinary bladder	Luminal dilatation (retention of urine)	3/20	2/16	0/22	2/29	0/24	0/23	0/13	0/17
Spleen	Increased extramedullary hematopoiesis	7/20	5/16	7/22	13/29	6/24	7/23	9/13↑	8/17
Mesenteric lymph node	Lymphoid cell hyperplasia	5/20	4/16	6/22	7/29	2/24	1/23	3/13	1/17
Spinal cord (lumbar)	Nerve fiber degeneration in nerve root	8/20	4/16	5/22	9/29	7/24	5/23	4/13	2/17
Sciatic nerves	Nerve fiber degeneration	14/20	8/16	11/22	20/29	11/24	15/23	9/13	9/17
Epididymides	Oligospermia	12/20	6/16	4/22↓	5/29↓				
	Fibrosis	4/20	0/16	0/22↓	0/29↓				
Seminal vesicles	Retention of secreted material	15/20	10/16	8/22↓	10/29↓				
Coagulating glands	Retention of secreted material	14/20	7/16	9/22	9/29↓				
Ovaries	Cyst					19/24	11/23↓	9/13	8/17↓
	Hematoma					2/24	0/23	0/13	0/17
Uterus	Cystic dilatation of glandular lumina					9/24	8/23	7/13	4/17
	Cystic hyperplasia of endometrial gland					7/24	6/23	1/13	2/17
	Endometrial proliferation					5/24	2/23	0/13	4/17
	Atrophy					0/24	0/23	1/13	2/17
Vagina	Persistent diestrus					7/24	14/23↑	7/13	8/17

The number (n/n) represents the number of animals with the lesions/the number of animals examined.
↑↓, $p<0.05$, ↑↓, $p<0.01$, statistically significant difference (Fisher's exact probability test)

Decedents and moribund sacrifices

Organ	Finding	Dose group (mg/kg/day)							
		Male				Female			
		0	1	3	10	0	1	3	10
Pituitary	Anterior cyst	4/40	0/44↓	1/38	1/31	0/36	0/36	0/46	0/43
	Anterior hyperplasia	0/40	1/44	0/38	0/31	0/36	3/36	8/46↑	14/43↑
	Atrophy of intermediate part	0/40	0/44	1/38	4/31↑	0/36	0/36	4/46	4/43
Mammary glands	Acinar proliferation	0/40	0/44	0/38	0/31	11/35	7/36	25/44↑	30/43↑
Adrenal glands	Increased brown pigment deposition in cortico-medullary junction	6/40	9/44	7/38	3/31	18/36	20/36	33/46↑	35/43↑
Lungs	Mononuclear cell infiltration	2/40	2/44	1/38	0/31	2/36	1/37	2/46	3/43
Liver	Focal hepatocellular necrosis	3/40	11/44↑	9/38↑	5/31	8/36	8/37	8/46	5/43
Gallbladder	Luminal dilatation	5/40	3/43	0/37↓	1/30	10/36	7/37	5/46↓	6/43
Kidneys	Pelvic dilatation	15/40	11/44	4/38↓	4/31↓	4/36	1/37	4/46	5/43
Urinary bladder	Luminal dilatation (retention of urine)	24/40	23/44	10/38↓	9/31↓	4/36	0/37	2/46	2/43
Spleen	Increased extramedullary hematopoiesis	20/40	18/44	21/38	16/31	19/36	17/37	32/46	20/43
Mesenteric lymph node	Lymphoid cell hyperplasia	1/40	2/43	1/38	2/31	0/36	3/36	5/46	4/43
Spinal cord (lumbar)	Nerve fiber degeneration in nerve root	10/40	4/44↓	6/38	5/31	11/36	6/37	10/46	14/43
Sciatic nerves	Nerve fiber degeneration	9/39	12/44	7/37	7/31	11/36	4/37↓	13/45	17/42
Epididymides	Oligospermia	6/40	3/44	3/38	3/31				
	Fibrosis	0/40	0/44	0/38	0/31				
Seminal vesicles	Retention of secreted material	11/40	14/44	10/38	5/31				
Coagulating glands	Retention of secreted material	11/40	14/44	7/38	4/31				
Ovaries	Cyst					22/36	15/37	22/46	15/43↓
	Hematoma					3/36	1/37	0/46	2/43
Uterus	Cystic dilatation of glandular lumina					10/36	1/37↓	4/46↓	4/43↓
	Cystic hyperplasia of endometrial gland					5/36	0/37↓	2/46	1/43
	Endometrial proliferation					4/36	4/37	1/46	4/43
	Atrophy					2/36	3/37	8/46	7/43
Vagina	Persistent diestrus					3/36	9/37	15/46↑	4/43↑

The number (n/n) represents the number of animals with the lesion/the number of animals examined.
↑↓, $p<0.05$, ↑↓, $p<0.01$, statistically significant difference (Fisher's exact probability test)

All animals

Organ	Finding	Dose group (mg/kg/day)							
		Male				Female			
		0	1	3	10	0	1	3	10
Pituitary	Anterior cyst	5/60	1/60	2/60	1/59	2/60	2/59	1/59	0/60
	Anterior hyperplasia	1/60	1/60	0/60	0/59	4/60	7/59	14/59↑	19/60↑
	Atrophy of intermediate part	0/60	0/60	7/60↑	15/59↑	0/60	0/59	7/59↑	14/60↑
Mammary glands	Acinar proliferation	0/60	0/60	0/60	0/60	16/59	10/59	31/57↑	36/60↑
Adrenal glands	Increased brown pigment deposition in cortico-medullary junction	13/60	13/60	10/60	5/60↓	29/60	29/59	40/59↑	44/60↑
Lungs	Mononuclear cell infiltration	6/60	3/60	1/60	5/60	6/60	7/60	4/59	8/60
Liver	Focal hepatocellular necrosis	3/60	11/60↑	10/60↑	5/60	8/60	8/60	8/59	5/60
Gallbladder	Luminal dilatation	9/60	6/59	1/58↓	7/59	16/60	9/60	7/59↓	9/60
Kidneys	Pelvic dilatation	23/60	14/60	4/60↓	6/60↓	5/60	5/60	5/59	6/60
Urinary bladder	Luminal dilatation (retention of urine)	27/60	25/60	10/60↓	11/60↓	4/60	0/60	2/59	2/60
Spleen	Increased extramedullary hematopoiesis	27/60	23/60	28/60	29/60	25/60	24/60	41/59↑	28/60
Mesenteric lymph node	Lymphoid cell hyperplasia	6/60	6/59	7/60	9/60	2/60	4/59	8/59↑	5/60
Spinal cord (lumbar)	Nerve fiber degeneration in nerve root	18/60	8/60↓	11/60	14/60	18/60	11/60	14/59	16/60
Sciatic nerves	Nerve fiber degeneration	23/59	20/60	18/59	27/60	22/59	19/59	22/58	26/59
Epididymides	Oligospermia	18/60	9/60↓	7/60↓	8/60↓				
	Fibrosis	4/60	0/60	0/60	0/60				
Seminal vesicles	Retention of secreted material	26/60	24/60	18/60	15/60↓				
Coagulating glands	Retention of secreted material	25/60	21/60	16/60	13/60↓				
Ovaries	Cyst					41/60	26/60↓	31/59	23/60↓
	Hematoma					5/60	1/60	0/59↓	2/60
Uterus	Cystic dilatation of glandular lumina					19/60	9/60↓	11/59	8/60↓
	Cystic hyperplasia of endometrial gland					12/60	6/60	3/59↓	3/60↓
	Endometrial proliferation					9/60	5/60	1/59↓	8/60
	Atrophy					2/60	3/60	0/59↑	9/60↑
Vagina	Persistent diestrus					10/60	23/60↑	22/59↑	22/60↑

The number (a/n) represents the number of animals with the lesion/the number of animals examined.
↑↓, $p<0.05$, ↑↓, $p<0.01$, statistically significant difference (Fisher's exact probability test)

The sponsor considered the following non-neoplastic findings to be drug-related: (a) acinar proliferation in mammary gland, (b) hyperplasia of the anterior lobe of the pituitary gland, (c) atrophy of the pars intermedia of the pituitary gland, and (d) uterine atrophy. The brown [ceroid] pigment deposition in the mammary gland was considered to be secondary to mammary gland tumors. All but the atrophy of the pars intermedia of the pituitary gland were considered secondary to elevations in serum prolactin; the mechanism underlying the pituitary gland atrophy was unknown. The sponsor did state that chlorpromazine "...is known to cause a decrease in content of melanocyte-stimulating hormone in the part intermedia..."

Non-neoplastic findings that were not significantly affected, but were notable, are summarized in the following table:

TISSUE	FINDING	PT/T*	MALES				FEMALES			
			C	LD	MD	HD	C	LD	MD	HD
submaxillary gland	fibrosis	PT	1/40	1/44	0/38	2/31	0/36	0/37	0/45	0/42
		T	0/20	0/16	1/22	3/29	0/24	0/23	0/13	0/17
		total	**1/60**	**1/60**	**1/60**	**5/60**	0/60	0/60	0/58	0/59
"sublingular" gland	fibrosis	P/T	0/40	0/44	0/38	1/31	0/36	0/37	0/45	0/42
		T	0/20	0/16	1/21	1/29	0/24	0/23	0/13	0/17
		total	**0/60**	**0/60**	**1/59**	**2/60**	0/60	0/60	0/58	0/59
kidney	tubular atrophy	P/T	2/40	2/44	2/38	5/31	0/36	0/37	0/46	2/43
		T	0/20	0/16	0/22	2/29	2/24	1/23	0/13	1/17
		total	**2/60**	**2/60**	**2/60**	**7/60**	2/60	1/60	0/59	3/60
	hyaline casts	P/T	0/40	0/44	0/38	0/31	1/36	1/37	2/46	0/43
		T	0/20	0/16	0/22	0/29	0/24	0/23	0/13	3/17
		total	0/60	0/60	0/60	0/60	1/60	1/60	2/59	3/60
	glomerular amyloidosis	P/T	2/40	2/44	0/38	0/31	1/36	1/37	0/46	3/43
		T	0/20	0/16	0/22	0/29	0/24	0/23	0/13	0/17
		total	0/60	0/60	0/60	0/60	0/60	1/60	0/59	3/60
heart	auricular thrombus	P/T	1/40	4/44	2/38	1/31	2/36	2/37	1/46	5/43
		T	0/20	0/16	1/22	1/29	0/24	0/23	0/13	0/17
		total	1/60	4/60	3/60	2/60	2/60	2/60	1/59	5/60
small intestine	amyloid deposition	P/T	2/40	2/44	0/38	0/31	0/36	1/37	1/46	4/43
		T	2/20	1/16	0/22	0/29	1/24	0/23	0/13	1/17
		total	4/60	3/60	0/60	0/60	1/60	1/60	1/59	5/60
liver	increased extramedullary hematopoiesis	P/T	1/40	3/44	0/38	3/31	1/36	2/37	3/46	5/43
		T	0/20	0/16	0/22	2/29	1/24	1/23	2/13	1/17
		total	1/60	3/60	0/60	5/60	2/60	3/60	5/59	6/60
	amyloid deposition	P/T	2/40	2/44	0/38	0/31	1/36	1/37	3/46	5/43
		T	0/20	0/16	0/22	1/29	0/24	1/23	1/13	1/17
		total	2/60	2/60	0/60	1/60	1/60	2/60	4/59	6/60
pancreas	islet cell hyperplasia	P/T	10/40	9/44	6/38	4/31	6/36	2/37	7/46	7/43
		T	9/20	7/16	7/22	8/29	2/24	6/23	4/13	5/17
		total	19/60	16/60	13/60	12/60	8/60	8/60	11/59	12/60
uterus	amyloid deposition	P/T					0/36	0/37	0/46	4/43
		T					0/24	0/23	0/13	0/17
		total					0/60	0/60	0/59	4/60

Neoplastic: the sponsor summarized statistically significant findings in the following tables:

Survivors

Organ	Findings	Dose group (mg/kg/day)							
		Male				Female			
		0	1	3	10	0	1	3	10
Pituitary	Anterior adenoma	0/20	0/16	0/22	0/28	1/24	2/23	2/13	8/17↑
Mammary glands	Adenocarcinoma	0/20	0/16	0/22	0/29	1/24	3/23	6/13↑	6/17↑
	Adenoacanthoma	0/20	0/16	0/22	0/29	0/24	0/23	7/13↑	3/17
Lungs	Adenoma	7/20	2/16	4/22	7/29	8/24	3/23	3/13	3/17
Liver	Hemangioma	2/20	2/16	2/22	2/29	1/24	0/23	0/13	1/17
Spleen	Hemangioma	0/20	1/16	0/22	1/29	0/24	0/23	1/13	0/17

Decedents and moribund sacrifices

Organ	Findings	Dose group (mg/kg/day)							
		Male				Female			
		0	1	3	10	0	1	3	10
Pituitary	Anterior adenoma	0/40	0/44	0/38	0/31	1/36	2/36	6/46	6/43
Mammary glands	Adenocarcinoma	0/40	0/44	0/38	0/31	0/35	2/36	7/44↑	13/43↑
	Adenoacanthoma	0/40	0/44	0/38	0/31	0/35	2/36	8/44↑	7/43↑
Lungs	Adenoma	4/40	8/44	6/38	9/31↑	4/36	2/37	9/46	4/43
Liver	Hemangioma	0/40	2/44	6/38↑	2/31	1/36	3/37	3/46	1/43
Spleen	Hemangioma	1/40	0/44	2/38	1/31	0/36	2/37	4/46	1/43

Total animals

Organ	Findings	Dose group (mg/kg/day)							
		Male				Female			
		0	1	3	10	0	1	3	10
Pituitary	Anterior adenoma	0/60	0/60	0/60	0/59	*2/60	4/59	8/59↑	14/60↑
Mammary glands	Adenocarcinoma	0/60	0/60	0/60	0/60	*1/59	5/59	13/57↑	19/60↑
	Adenoacanthoma	0/60	0/60	0/60	0/60	*0/59	2/59	15/57↑	10/60↑
Lungs	Adenoma	11/60	10/60	10/60	16/60	12/60	5/60	12/59	7/60
Liver	Hemangioma	2/60	4/60	8/60↑	4/60	2/60	3/60	3/59	2/60
Spleen	Hemangioma	1/60	1/60	2/60	2/60	0/60	2/60	5/59↑	1/60

The number (n/n) represents the number of animals with the designated lesions/the number of examined animals.

↑↓ $p<0.05$, ⇑⇓ $p<0.01$: statistically significant difference (Fisher's exact probability test)

* Tendency toward significant increase or decrease ($p<0.05$, Cochran-Armitage trend test)

Dosage (mg/kg/day)	No. of females with mammary gland tumors [a]		
	Survivors	Decedents and moribund sacrifices	All animals
0	2/24*	0/35*	2/59*
1	3/23	4/36	7/59
3	10/13↑	14/44↑	24/57↑
10	7/17↑	20/43↑	27/60↑

a The word tumor includes all types of tumors observed in this study (adenoma, adenocarcinoma, adenoacanthoma, and carcinosarcoma)

Dosage (mg/kg/day)	No. of females with pituitary tumors [a]		
	Survivors	Decedents and moribund sacrifices	All animals
0	1/24*	2/36	3/60*
1	2/23	2/36	4/59
3	2/13	6/46	8/59
10	8/17↑	6/43	14/60↑

a The word tumor includes all types of tumors (adenoma in anterior lobe and pars intermedia).

The sponsor considered the mammary gland [adenocarcinoma, adenoacanthoma] and pituitary gland [adenomas of the anterior lobe] tumors in females to be drug-related. The sponsor also noted that these tumors tended to appear earlier in treated females [as compared to CF]. These tumors were considered to be secondary to hyperprolactinemia, although serum prolactin was not measured in this study.

Tumors that were not significantly affected, but were of note, are summarized in the following table:

TISSUE	FINDING	PT/T*	MALES				FEMALES			
			C	LD	MD	HD	C	LD	MD	HD
hematopoietic/lymphatics	myelogenic leukemia	P/T	0/40	0/44	0/38	2/31	1/36	0/37	0/46	0/43
		T	0/20	0/16	0/22	0/29	0/24	0/23	0/13	0/17
		total	**0/60**	**0/60**	**0/60**	**2/60**	**1/60**	**0/60**	**0/59**	**0/60**
small intestine	adenocarcinoma	P/T	0/40	0/44	0/38	0/31	0/36	0/37	0/46	0/43
		T	0/20	0/16	0/22	2/29	0/24	0/23	0/13	0/17
		total	**0/60**	**0/60**	**0/60**	**2/60**	**0/60**	**0/60**	**0/59**	**0/60**
skin	Schwannoma	P/T	0/40	0/44	0/38	2/31	0/36	0/37	1/46	1/43
		T	0/20	0/16	1/22	0/29	0/24	0/23	0/13	0/17
		total	**0/60**	**0/60**	**1/60**	**2/60**	**0/60**	**0/60**	**1/59**	**1/60**
	leiomyosarcoma	P/T	0/40	0/44	0/38	0/31	0/36	0/37	0/46	0/43
		T	0/20	0/16	0/22	0/29	0/24	0/23	0/13	0/17
		total	**0/60**	**0/60**	**0/60**	**2/60**	**0/60**	**0/60**	**0/59**	**0/60**
mammary gland	adenoma	P/T	0/40	0/44	0/38	0/31	0/24	0/23	0/13	0/17
		T	0/20	0/16	0/22	0/29	0/35	0/36	0/44	2/43
		total	**0/60**	**0/60**	**0/60**	**0/60**	**0/59**	**0/59**	**0/57**	**2/60**

*PT = preterminal sacrifice/spontaneous death; T = terminal sacrifice

Toxicokinetics: TK data were collected only in 3/sex/grp/time point [satellite animals]. These data were summarized in the following sponsor's tables:

Table 1 Plasma concentration of OPC-31 in male mice of 104-week carcinogenicity study

Week 2		Week 52		Week 104	
Animal No.	Concentration(ng/ml)	Animal No.	Concentration(ng/ml)	Animal No.	Concentration(ng/ml)
OPC-31 1 mg/kg/day					
241		244		65	
242		245		67	
243		246		78	
Mean		Mean		Mean	
S.D.		S.D.		S.D.	
OPC-31 3 mg/kg/day					
249		252		121	
250		253		123	
251		254		126	
Mean		Mean		Mean	
S.D.		S.D.		S.D.	
OPC-31 10 mg/kg/da					
257		260		182	
258		261		183	
259		262		184	
Mean		Mean		Mean	
S.D.		S.D.		S.D.	

Table 2 Plasma concentration of OPC-31 in female mice of 104-week carcinogenicity study

Week 2		Week 52		Week 104	
Animal No.	Concentration(ng/ml)	Animal No.	Concentration(ng/ml)	Animal No.	Concentration(ng/ml)
OPC-31 1 mg/kg/day					
505		508		327	
506		509		330	
507		510		331	
Mean		Mean		Mean	
S.D.		S.D.		S.D.	
OPC-31 3 mg/kg/day					
513		516		392	
514		517		406	
515		518		412	
Mean		Mean		Mean	
S.D.		S.D.		S.D.	
OPC-31 10 mg/kg/da					
521		524		445	
522		525		447	
523		526		448	
Mean		Mean		Mean	
S.D.		S.D.		S.D.	

2. **Study title: 104-week carcinogenicity** [Study No. 010808, Volume #1.71, Conducting laboratory and location: [redacted], Date of study initiation: 3/2/95, GLP, QA'd report: Y]

Drug, lot #, and % purity: OPC-31 [OPC-14597], 93H80M[1] [redacted]
CAC concurrence: see Study No. 010379 review [#1 in this section]
Study Type (2 yr bioassay, alternative model etc.): 2-yr bioassay
Species/strain: ICR [CD-1] mouse [redacted]
Number/sex/group: 60/sex/grp
Initial age: 6 wks
Initial body wt: 15-25 gm for males, 14-23 gm for females
Animal housing: individually
Formulation/vehicle: diet
Drug stability/homogeneity: stated to be stable in diet [concentrations of 5 and 3000 ppm] for 17 days at rm temperature. Homogeneity was tested and found to be acceptable [supportive data were provided]. Drug concentration was assayed every other month [middle portion]; achieved concentrations were 95-102% of intended.
Methods
- Doses: 0, 30 mg/kg
- Basis of dose selection: dose-range finding studies, 2-yr bioassay [1, 3, 10 mg/kg]
- Restriction paradigm for dietary restriction studies: n/a
- Route of administration: diet
- Dual controls employed: no
- Interim sacrifices: no
- Satellite PK or special study group(s): 8/sex for analysis of TK

Observations and times:
- Clinical signs: animals were observed daily. Detailed examination [including palpation] was conducted weekly.
- Body weights: recorded in all main-study and satellite animals prior to the start of dosing, weekly from Wks 1 to 16, and bi-weekly during the rest of the dosing period.
- Food consumption: food intake was quantitated in all main-study and satellite animals prior to

start of dosing, weekly during the first 16 wks, and bi-weekly during the rest of the dosing period. Drug consumption was calculated on the basis of grp mean food consumption.

Hematology: blood samples were collected at the end of the dosing period [Wk 104 or 100] from all main-study survivors for analysis of the following parameters: hct, hgb, rbc ct, MCV, MCH, MCHC, platelet ct, wbc ct. Animals were not fasted prior to blood sampling.

Clinical chemistry: no

Organ weights: wts of the following organs were recorded in main-study animals [10/sex/grp]: brain, pituitary gland, heart, lungs, liver, kidney, spleen, adrenal gland, testes, ovary, seminal vesicle, coagulating gland, uterus, prostate.

Gross pathology: a complete necropsy was performed on all main-study animals. Males were sacrificed during Wk 104; females were sacrificed during Wk 100 due to increased mortality.

Histopathology: the following tissues were examined microscopically from all main-study animals: brain, spinal cord [cervical, thoracic, lumbar], sciatic nerve, pituitary gland, thymus, thyroid gland, parathyroid, adrenal gland, spleen, bone/bone marrow [sternum, femur, vertebrae], knee joints, lymph nodes [cervical, mesenteric], heart, aorta, salivary gland, tongue, esophagus, stomach [fore- and glandular], liver/gallbladder, pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, trachea, lungs/bronchi, kidney, urinary bladder, testes, epididymes, prostate, seminal vesicles, coagulating gland, ovary, uterus, vagina, eyeballs, Harderian gland, triceps surae muscle, skin, mammary gland [abdominal], gross lesions. Tissues were stained with H & E for examination. Adrenal gland was stained "...with PAS and an acid-fast stain, when necessary".

Statistical analysis: cf statistician's review.

Toxicokinetics: blood samples were collected from the posterior vena cava at 9:00 during Wks 2 and 52 from satellite animals [3/sex], and at Wks 104 (males) or 100 (females) from main-study animals [3/sex/grp]. Animals were not fasted prior to blood sampling. Plasma samples were prepared and shipped to Tokushima Research Institute of Otsuka for analysis. Plasma levels of OPC-31 were quantitated by the sponsor using GC-MS.

Results

Mortality: mortality rate was significantly higher in DTF and significantly lower in DTM compared to appropriate C. Final mortality rate was 75 [45/60] and 55% [33/60] in CM and DTM, and 58 [35/60] and 75% [45/60] in CF and DTF. The sponsor's survival curves are provided below:

Fig. 1 Survival curve in male mice (Main group) page 1 - 1

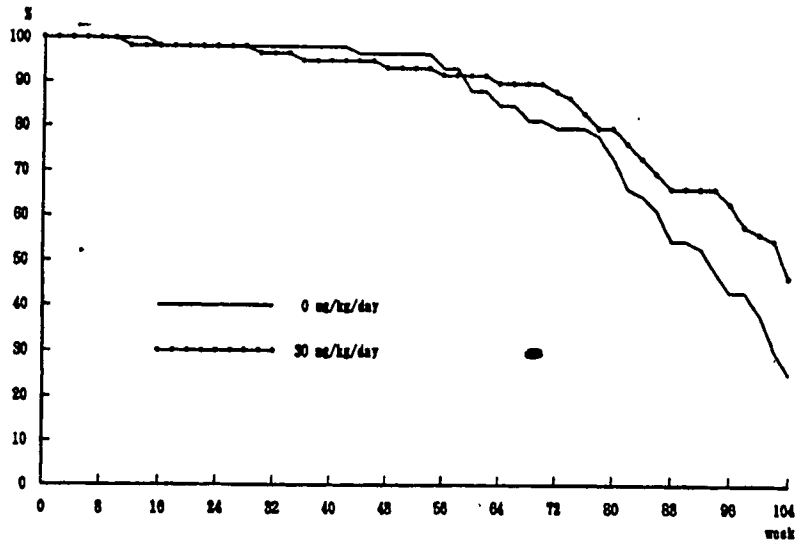
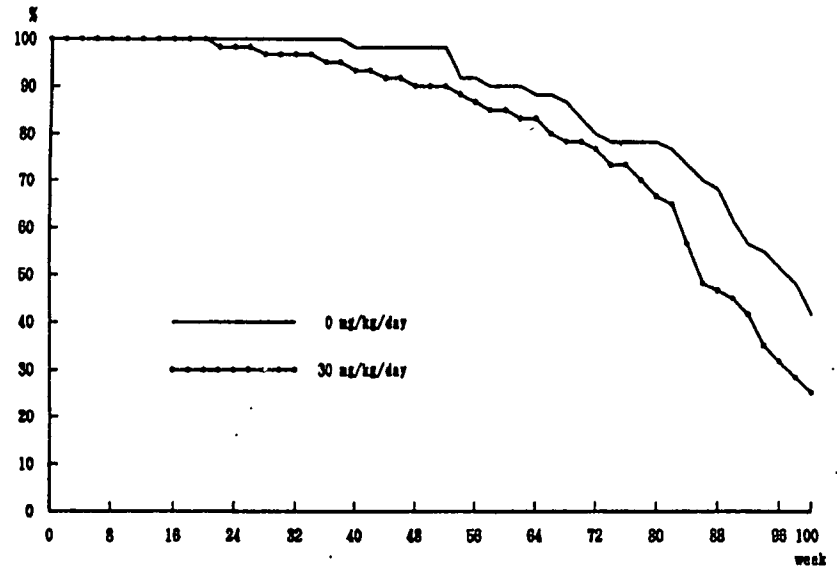
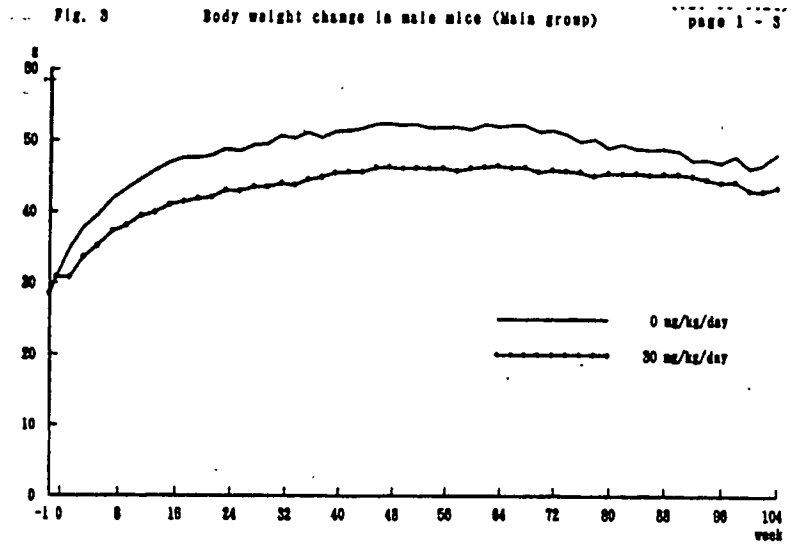


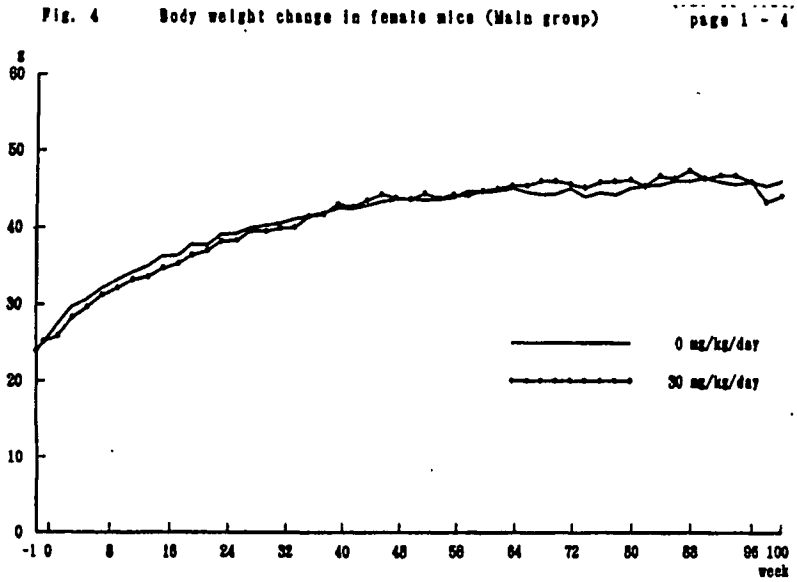
Fig. 2 Survival curve in female mice (main group) page 1 - 2



Clinical signs: the only significant findings in DTM were decreases in incidences of soiled fur, hair loss, scabs, skin erosions/ulcers, and skin/subcutaneous masses. In DTF, the incidences of hair loss and abdominal distension were lower than in CF; only the incidence of skin/subcutaneous masses was increased in DTF [11/60 CF, 28/60 DTF]. The incidences of decreased SMA and bradypnea tended to be higher in DTF compared to CF [SMA: 13/60 CF, 19/60 DTF; bradypnea: 19/60 CF, 25/60 DTF], although the differences were not statistically significant.

Body weights: mean body wt was reduced [10-11%] throughout the dosing period in DTM compared to CM. Body wt was not affected in DTF. The data are illustrated in the following sponsor's figures:





Food consumption: food intake in DTM was reduced throughout most of the dosing period [up to Wk 78-80]. The effect was greatest during the first wk [44%], but remained ≈10-20% lower than CM up to Wks 78-80. Overall mean daily food intake was 10% lower in DTM than in CM. Food intake was transiently reduced in DTF [24% during Wk 1, 0-14% during Wks 2-13]. Overall mean daily intake was similar between grps.

There were no significant effects on food efficiency, except for a decrease during the 1st wk of dosing in DTM.

Achieved doses: the achieved weekly dose ranged from 19.9 to 40.9 mg/kg in DTM [mean: 30.2 mg/kg] and from 22.0 to 39.6 mg/kg in DTF [mean: 30.2 mg/kg].

Hematology: there were no significant effects. Mean wbc ct was increased in DTF due to a marked elevation in 1 animal [#818; 35.5 x 10^3/mm^3 vs a mean of 3 x 10^3/mm^3 for CF and a high-CF value of 6.9 x 10^3/mm^3].

Gross pathology: there were a number of findings that had lower incidences in the DT grps. However, the incidences of skin/subcutaneous, lung, and pituitary masses and pituitary enlargement were increased in DTF. Selected findings are summarized in the table below:

TISSUE	FINDING	TS/MS#	MALES		FEMALES	
			C	DT	C	DT
external	soiled fur, genital region	TS	6/15 [40%]	6/27 [22%]	5/25 [20%]	2/15 [13%]
		MS	27/45 [60%]	16/33 [48%]	10/35 [28%]	11/45 [24%]
		total	**33/60 [55%]**	**22/60 [37%]***	15/60 [25%]	13/60 [22%]
spleen	enlargement	TS	1/15 [7%]	0/27 [0%]	5/25 [20%]	6/15 [40%]
		MS	11/45 [24%]	5/33 [15%]	19/35 [54%]	19/45 [42%]
		total	**12/60 [20%]**	**5/60 [8%]**	24/60 [40%]	25/60 [42%]
	spots	TS	0/15 [0%]	0/27 [0%]	1/25 [4%]	0/15 [0%]
		MS	1/45 [2%]	0/33 [0%]	4/35 [11%]	0/45 [0%]*
		total	**1/60 [2%]**	**0/60 [0%]**	**5/60 [8%]**	**0/60 [0%]***
lung	mass(es)	TS	5/15 [33%]	14/27 [52%]	8/25 [32%]	6/15 [40%]
		MS	15/45 [33%]	9/33 [27%]	7/35 [20%]	18/45 [40%]*
		total	**20/60 [33%]**	**23/60 [38%]**	**15/60 [25%]**	**24/60 [40%]**
intestine	mass(es)	TS	0/15 [0%]	1/27 [4%]		
		MS	0/45 [0%]	2/33 [6%]	no masses	no masses
		total	**0/60 [0%]**	**3/60 [5%]**		
kidney	pelvic dilatation	TS	4/15 [27%]	1/27 [4%]*	0/25 [0%]	1/15 [7%]
		MS	8/45 [18%]	1/33 [3%]*	0/35 [0%]	0/45 [0%]
		total	**12/60 [20%]**	**2/60 [3%]***	**0/60 [0]**	**1/60 [2%]**
seminal vesicle	distention	TS	7/15 [47%]	7/27 [26%]		
		MS	14/45 [31%]	2/33 [6%]*		
		total	**21/60 [35%]**	**9/60 [15%]***		
coagulating gland	distention	TS	7/15 [47%]	7/27 [26%]		
		MS	15/45 [33%]	2/33 [6%]*		
		total	**22/60 [37%]**	**9/60 [15%]***		
testis	softening	TS	4/15 [27%]	9/27 [33%]		
		MS	8/45 [18%]	4/33 [12%]		
		total	**12/60 [20%]**	**13/60 [22%]**		
	atrophy	TS	3/15 [20%]	9/27 [33%]		
		MS	6/45 [13%]	2/33 [6%]		
		total	**9/60 [15%]**	**11/60 [18%]**		
ovary	cysts	TS			16/25 [64%]	8/15 [53%]
		MS			15/35 [43%]	11/45 [24%]
		total			**31/60 [52%]**	**19/60 [32%]***
uterus	thickening of wall	TS			10/25 [40%]	0/15 [0%]*
		MS			8/35 [23%]	1/45 [2%]
		total			**18/60 [30%]**	**1/60 [2%]***
	mass(es)	TS			3/25 [12%]	0/15 [0%]
		MS			6/35 [17%]	1/45 [2%]*
		total			**9/60 [15%]**	**1/60 [2%]***
skin	hair loss	TS	0/15 [0%]	2/27 [7%]	11/25 [44%]	3/15 [20%]
		MS	8/45 [18%]	1/33 [3%]*	7/35 [20%]	7/45 [16%]
		total	**8/60 [13%]**	**3/60 [5%]**	18/60 [30%]	10/60 [2%]
	mass(es)	TS	2/15 [13%]	0/27 [0%]	1/25 [4%]	9/15 [60%]*
		MS	5/45 [11%]	1/33 [3%]	8/35 [23%]	19/45 [42%]
		total	**7/60 [12%]**	**1/60 [2%]***	**9/60 [15%]**	**28/60 [47%]***
pituitary	mass(es)	TS	0/15 [0%]	0/27 [0%]	2/25 [8%]	6/15 [40%]*
		MS	0/45 [0%]	0/33 [0%]	1/35 [3%]	6/45 [13%]
		total	**0/60 [0%]**	**0/60 [0%]**	**3/60 [5%]**	**12/60 [20%]***
	enlargement	TS	0/15 [0%]	0/27 [0%]	0/25 [0%]	0/15 [0%]
		MS	0/45 [0%]	0/33 [0%]	2/35 [6%]	11/45 [24%]
		total	**0/60 [0%]**	**0/60 [0%]**	**2/60 [3%]**	**11/60 [18%]***
abdominal cavity	ascites	TS	0/15 [0%]	0/27 [0%]	0/25 [0%]	1/15 [7%]
		MS	3/45 [7%]	2/33 [6%]	11/35 [31%]	2/45 [4%]*
		total	**3/60 [5%]**	**2/60 [3%]**	**11/60 [18%]**	**3/60 [5%]***

*statistically significant, #TS = terminal sacrifice, MS = moribund sacrifice or found dead

Organ wts: the primary findings were marked decreases in testis and ovary wts [absolute and

relative] in DT grps [testis: 33-28%, ovary: 78%]. An examination of the individual data indicates DTM #679, 682, 684, and 718 were particularly affected. The effect on ovaries was a combination of elevated wts in 3 CF [≈8-150% higher compared to mean] and markedly reduced wts in 2 DTF [#821, 834; 4 and 7% of CF mean].

Histopathology

Non-neoplastic: the sponsor summarized selected findings [i.e., those considered drug-related] in the following tables:

(1) **Non-neoplastic Findings in Mice Treated with OPC-31 That Were Terminally Killed at Week 104 (Males) or 100 (Females)**

Sex		Male		Female	
Dosage (mg/kg/day)		0	30	0	30
Organ	(No. of animals)	15	27	25	15
Pituitary gland	Atrophy of intermediate part	0/15	15/27**	0/25	4/15*
	Anterior hyperplasia	0/15	2/27	2/25	7/15**
Mammary glands	Acinar proliferation	0/15	0/27	2/25	4/15
Adrenal gland	Subcapsular cell hyperplasia	8/15	14/27	23/25	12/15
	Increased brown pigment deposition in corticomedullary junction	4/15	2/27	11/25	11/15
Eyeballs	Keratitis	2/15	0/27	0/25	0/15
Heart	Myocardial atrophy or fibrosis	1/15	0/27	0/25	1/15
Fore-stomach	Hyperkeratosis	3/15	2/27	3/25	2/15
Liver	Microgranuloma	7/15	13/27	17/25	7/15
Gallbladder	Luminal dilatation	5/15	3/27	8/25	2/15
Sciatic nerve	Degeneration of nerve fiber	8/15	9/27	20/25	10/14
Kidneys	Pelvic dilatation	5/15	1/27*	0/25	1/15
Urinary bladder	Cystitis	0/15	0/27	0/24	0/15
Seminal vesicles	Retention of secreted material	10/15	9/27*		
	Abscess	0/15	0/27		
Coagulating glands	Retention of secreted material	9/15	9/27		
	Abscess	0/15	0/27		
Prostate	Prostatitis	0/14	1/27		
Ovaries	Cyst			17/25	8/15
	Hematoma			0/25	1/15
Uterus	Atrophy			0/25	0/15
	Endometrial proliferation			7/25	1/15
Vagina	Estrus			8/25	0/15*
	Persistent diestrus			5/25	10/15**

(2) Non-neoplastic Findings in Mice Treated With OPC-31 That Died or Were Sacrificed Before Completion of Treatment

Sex		Male		Female	
Dosage (mg/kg/day)		0	30	0	30
Organ	(No. of animals)	45	33	35	45
Pituitary gland	Atrophy of intermediate part	0/45	7/33**	0/35	14/45**
	Anterior hyperplasia	1/45	0/33	0/35	17/45**
Mammary glands	Acinar proliferation	0/45	0/33	11/35	22/45
Adrenal gland	Subcapsular cell hyperplasia	13/45	11/33	28/35	28/45
	Increased brown pigment deposition in corticomedullary junction	16/45	6/33	18/35	36/45**
Eyeballs	Keratitis	4/45	0/33	0/35	1/45
Heart	Myocardial atrophy or fibrosis	10/45	2/33*	1/35	0/45
Fore-stomach	Hyperkeratosis	6/45	7/33	10/35	5/45*
Liver	Microgranuloma	3/45	2/33	5/35	4/45
Gallbladder	Luminal dilatation	2/45	0/32	3/35	1/45
Sciatic nerve	Degeneration of nerve fiber	19/45	12/33	14/35	12/45
Kidneys	Pelvic dilatation	12/45	3/33*	2/35	5/45
Urinary bladder	Cystitis	6/45	0/33*	0/35	0/45
Seminal vesicles	Retention of secreted material	12/45	3/33*		
	Abscess	7/45	0/33*		
Coagulating glands	Retention of secreted material	15/45	3/33*		
	Abscess	5/45	0/33		
Prostate	Prostatitis	8/45	0/33**		
Ovaries	Cyst			22/35	16/45*
	Hematoma			9/35	1/45**
Uterus	Atrophy			1/35	16/45**
	Endometrial proliferation			13/35	0/45**
Vagina	Estrus			7/35	1/45*
	Persistent diestrus			5/35	17/45*

(3) Non-neoplastic Findings in All Mice Treated With OPC-31

Sex		Male		Female	
Dosage (mg/kg/day)		0	30	0	30
Organ	(No. of animals)	60	60	60	60
Pituitary gland	Atrophy of intermediate part	0/60	22/60**	0/60	18/60**
	Anterior hyperplasia	1/60	2/60	2/60	24/60**
Mammary gland	Acinar proliferation	0/60	0/60	13/60	26/60**
Adrenal gland	Subcapsular cell hyperplasia	21/60	25/60	51/60	40/60*
	Increased brown pigment deposition in corticomedullary junction	20/60	8/60**	29/60	47/60**
Eyeballs	Keratitis	6/60	0/60*	0/60	1/60
Heart	Myocardial atrophy or fibrosis	11/60	2/60**	1/60	1/60
Fore-stomach	Hyperkeratosis	9/60	9/60	13/60	7/60
Liver	Microgranuloma	10/60	15/60	22/60	11/60*
Gallbladder	Luminal dilatation	7/60	3/59	11/60	3/60*
Sciatic nerve	Degeneration of nerve fiber	27/60	21/60	34/60	22/59*
Kidneys	Pelvic dilatation	17/60	4/60**	2/60	6/60
Urinary bladder	Cystitis	6/60	0/60*	0/59	0/60
Seminal vesicles	Retention of secreted material	22/60	12/60*		
	Abscess	7/60	0/60**		
Coagulating glands	Retention of secreted material	24/60	12/60*		
	Abscess	5/60	0/60*		
Prostate	Prostatitis	8/59	1/60*		
Ovaries	Cyst			39/60	24/60**
	Hematoma			9/60	2/60*
Uterus	Atrophy			1/60	16/60**
	Endometrial proliferation			20/60	1/60**
Vagina	Estrus			15/601	1/60**
	Persistent diestrus			0/60	27/60**

Values: Number of animals with lesions/Number of tissues or animals examined
Statistical significance (Fisher's exact probability test): *p<0.05, **p<0.01

Additional findings of note, but not included in the sponsor's summary tables, are provided below:

TISSUE	FINDING	TS/MS	MALES		FEMALES	
			C	DT	C	DT
bone marrow	increased hematopoiesis	TS	2/15 [13%]	6/27 [22%]	6/25 [24%]	7/15 [47%]
		MS	19/45 [42%]	12/19 [63%]	24/35 [68%]	26/45 [58%]
		total	**21/60 [35%]**	**18/60 [30%]**	**30/60 [50%]**	**33/60 [55%]**
	necrosis	TS	0/15 [0%]	0/27 [0%]	0/25 [0%]	0/15 [0%]
		MS	0/45 [0%]	2/33 [6%]	0/35 [0%]	1/45 [2%]
		total	**0/60 [0%]**	**2/60 [3%]**	**0/60 [0%]**	**1/60 [2%]**
spleen	increased extramedullary hematopoiesis	TS	2/15 [13%]	6/27 [22%]	10/25 [40%]	8/15 [53%]
		MS	21/45 [47%]	15/33 [45%]	17/35 [48%]	21/45 [47%]
		total	**23/60 [38%]**	**21/60 [35%]**	**27/60 [45%]**	**29/60 [48%]**
gallbladder	mucosal epithelial hyperplasia	TS	1/15 [7%]	4/27 [15%]		
		MS	0/45 [0%]	0/32 [0%]	none	none
		total	**1/60 [2%]**	**4/59 [7%]**		

Neoplastic: selected findings are provided in the following table:

TISSUE	FINDING	TS/MS#	MALES		FEMALES	
			C	DT	C	DT
lung	adenoma	TS	2/15 [13%]	6/27 [22%]	5/25 [20%]	3/15 [20%]
		MS	7/45 [16%]	5/33 [15%]	6/35 [17%]	9/45 [20%]
		total	**9/60 [15%]**	**11/60 [18%]**	**11/60 [18%]**	**12/60 [20%]**
	adenocarcinoma	TS	3/15 [20%]	12/27 [44%]	6/25 [24%]	3/15 [20%]
		MS	11/45 [24%]	8/33 [24%]	4/35 [11%]	6/45 [13%]
		total	**14/60 [23%]**	**20/60 [33%]**	**10/60 [17%]**	**9/60 [15%]**
small intestine	adenoma	TS	0/15 [0%]	0/27 [0%]		
		MS	0/45 [0%]	1/33 [3%]	none	none
		total	**0/60 [0%]**	**1/60 [2%]**		
	adenocarcinoma	TS	0/15 [0%]	0/27 [0%]		
		MS	0/45 [0%]	2/33 [6%]	none	none
		total	**0/60 [0%]**	**2/60 [3%]**		
liver	hepatocellular adenoma	TS	4/15 [27%]	9/27 [33%]	2/25 [8%]	0/15 [0%]
		MS	13/45 [29%]	12/33 [36%]	0/35 [0%]	0/45 [0%]
		total	**17/60 [28%]**	**21/60 [35%]**	**2/60 [3%]**	**0/60 [0%]**
	hepatocellular carcinoma	TS	1/15 [7%]	5/27 [18%]	2/25 [8%]	0/15 [0%]
		MS	11/45 [24%]	8/33 [24%]	0/35 [0%]	0/45 [0%]
		total	**12/60 [20%]**	**13/60 [22%]**	**2/60 [3%]**	**0/60 [0%]**
gallbladder	adenoma	TS	1/15 [7%]	3/26 [11%]	0/25 [0%]	0/15 [0%]
		MS	0/45 [0%]	0/33 [0%]	0/35 [0%]	1/45 [2%]
		total	**1/60 [2%]**	**3/59 [5%]**	**0/60 [0%]**	**1/60 [2%]**
pituitary	adenoma	TS	0/15 [0%]	0/27 [0%]	2/25 [8%]	7/15 [47%]*
		MS	1/45 [0%]	1/33 [3%]	3/35 [8%]	7/45 [16%]
		total	**0/60 [0%]**	**2/60 [3%]**	**5/60 [8%]**	**14/60 [23%]***
pancreas	acinar cell adenoma	TS			0/25 [0%]	0/15 [0%]
		MS	none	none	0/35 [0%]	1/45 [2%]
		total			**0/60 [0%]**	**1/60 [2%]**
mammary gland	adenocarcinoma	TS			0/25 [0%]	6/15 [40%]*
		MS	none	none	1/35 [3%]	8/45 [18%]*
		total			**1/60 [2%]**	**14/60 [23%]***
	adenoacanthoma	TS			0/25 [0%]	6/15 [40%]*
		MS	none	none	0/35 [0%]	5/45 [11%]
		total			**0/60 [0%]**	**11/60 [18%]***
	carcinosarcoma	TS			0/25 [0%]	1/15 [7%]
		MS	none	none	1/35 [3%]	2/45 [4%]
		total			**1/60 [2%]**	**3/60 [5%]**
uterus	endometrial stromal polyps	TS			5/25 [20%]	0/15 [0%]
		MS			3/35 [8%]	2/45 [4%]
		total			**8/60 [13%]**	**2/60 [3%]***

The sponsor summarized those findings they considered drug-related in the following tables:

(1) Neoplastic Findings in Mice Treated with OPC-31 That Were Terminally Killed at Week 104 (Males) or 100 (Females)

Sex		Male		Female	
Dosage (mg/kg/day)		0	30	0	30
Organ	(No. of animals)	15	27	25	15
Pituitary gland	Anterior adenoma	0/15	1/27	2/25	7/15**
Mammary gland	Adenocarcinoma	0/15	0/27	0/25	6/15**
	Adenoacanthoma	0/15	0/27	0/25	6/15**
	Animals with neoplasms in this organ(#a)	0/15	0/27	0/25	9/15**
Uterus	Endometrial stromal polyp			5/25	0/15

(2) Neoplastic Findings in Mice Treated With OPC-31 That Died or Were Sacrificed Before Completion of Treatment

Sex		Male		Female	
Dosage (mg/kg/day)		0	30	0	30
Organ	(No. of animals)	45	33	35	45
Pituitary gland	Anterior adenoma	0/45	1/33	3/35	7/45
Mammary gland	Adenocarcinoma	0/45	0/33	1/35	8/45*
	Adenoacanthoma	0/45	0/33	0/35	5/45
	Animals with neoplasms in this organ(#a)	0/45	0/33	2/35	15/45**
Uterus	Endometrial stromal polyp			3/35	2/45

#a) Neoplastic lesions: adenoma, adenocarcinoma, adenoacanthoma, and carcinosarcoma
Values: Number of animals with lesions/Number of tissues or animals examined
Statistical significance (Fisher's exact probability test/Peto's test): *p<0.05, **p<0.01

(3) Neoplastic Findings in All Mice Treated With OPC-31

Sex		Male		Female	
Dosage (mg/kg/day)		0	30	0	30
Organ	(No. of animals)	60	60	60	60
Pituitary gland	Anterior adenoma	0/60	2/60	5/60	14/60*/*
Mammary gland	Adenocarcinoma	0/60	0/60	1/60	14/60**/*
	Adenoacanthoma	0/60	0/60	0/60	11/60**/*
	Animals with neoplasms in this organ(#a)	0/60	0/60	2/60	24/60**/*
Uterus	Endometrial stromal polyp			8/60	2/60*/*

The sponsor noted that mammary gland tumors, and to a lesser extent, pituitary adenomas tended to appear earlier in DTF than in CF. The lung masses detected in females dying or sacrificed moribund were found to be due to mammary gland mesastasis upon microscopic examination. This was the case in 6 of the 18 DTF with lung masses. With these animals removed from the analysis, the incidences of primary lung masses in CF and DTF were 12/45 [27%] and 6/35 [17%]; this difference was not statistically significant.

The sponsor attributed the mammary and pituitary gland tumors in DTF to D_2-antagonsist induced hyperprolactinemia, and noted that these tumors "...caused a high mortality in the females". [Serum prolactin was not measured in this study.] The sponsor also noted that D_2 antagonists stimulate DNA synthesis in the pituitary gland. The non-neoplastic findings considered by the sponsor to be drug-related were as follows: (a) atrophy of the intermediate pituitary lobe in DTM and DTF, (b) "...hyperplasia of the anterior pituitary lobe, atrophy of the uterus, increased brown pigmentation in the corticomedullary junction of the adrenal gland, and persistent diestrus...", and acinar proliferation in mammary gland in DTF. The anterior pituitary and mammary gland hyperplasia and uterine atrophy were attributed to elevation in serum prolactin. The increased pigment deposition in adrenal gland was considered secondary to the mammary gland effects. No mechanism was proposed for the atrophy of the intermediate lobe of the pituitary; however, the sponsor noted that that this finding was also noted in a previous carcinogenicity study with OPC-31 and that the "antipsychotic chlorpromazine has been documented to reduce hormonal content in the intermediate pituitary lobe in rats..."

Toxicokinetics: the data were summarized in the following sponsor's tables:

Table 1 Plasma concentration of OPC-31 in male mice

Week 2		Week 52		Week 104	
Animal No.	Concentration(ng/ml)	Animal No.	Concentration(ng/ml)	Animal No.	Concentration(ng/ml)
OPC-31 30 mg/kg/d					
721		724		664	
722		725		666	
723		728		667	
Mean		Mean		Mean	
S.D.		S.D.		S.D.	

Table 2 Plasma concentration of OPC-31 in female mice

Week 2		Week 52		Week 100	
Animal No.	Concentration(ng/ml)	Animal No.	Concentration(ng/ml)	Animal No.	Concentration(ng/ml)
OPC-31 30 mg/kg/day					
849		852		791	
850		853		792	
851		854		797	
Mean		Mean		Mean	
S.D.		S.D.		S.D.	

3. **Study title: Mouse tumor-incidence data: supplemental statistical analysis** [Study No. DM00030, Volume #1.74, Conducting laboratory and location: Bristol-Myers Squibb Pharmaceutical Research Institute, report date 12/1/00, GLP, QA'd report:Y]

Study Type (2 yr bioassay, alternative model etc.): the report was a supplemental statistical analysis

conducted on tumor incidence data from Study No.'s 010379 and 010808. The analysis was conducted on all protocol-designated tissues. Tumors occurring in nonprotocol-designated tissues were deleted from the tumor output files in order to allow for the analysis. For trend-test analyses, the sponsor considered the following p-values indicative of a statistically significant response: (a) $p<0.005$ for a common tumor, (b) $p<0.025$ for a rare tumor [i.e., a tumor with an incidence of <1% based on concurrent and historical control data]. A more complete description and discussion of the statistical methods are provided in the statistical review [Statistical Review and Evaluation: Review of Mouse Carcinogenicity Studies, NDA#:21-438. Roswitha Kelly, M.S. (HFD-710)].

Results:

Study No. 010379: according to the sponsor's re-analysis, there was a significant negative trend in mortality in males and a [non-significant] positive trend in mortality in females. From an examination of the mortality data provided in the original study report, it would appear that the sponsor intended to state that the mortality rate was significantly [according to trend analysis] increased in males and significantly decreased in females. In the original report, it was stated that the mortality rate was not significantly affected in males or females.

The results of the re-analysis of the tumor incidence data were summarized in the following sponsor's table:

Text Table 1: Tumor Incidence Changes in BMS-337039-Dosed Female Mice
-Otsuka Study No. 010379-

Dose (mg/kg/day):	0	1	3	10
No. of Mice:	60	60	60	60
Mammary Gland:				
Adenoma	-	-	-	2
Adenocarcinoma	1	5	13	19
Adenoacanthoma	-	2	15	10
Carcinosarcoma	1	-	1	1
Pituitary Gland:				
Anterior adenoma	2	4	8	14
Adenoma in intermediate part	1	-	1	1

- Indicates absence of finding in group

The sponsor considered the following tumors drug-related: (a) mammary gland adenocarcinomas and adenoacanthoma in MDF and HDF [both analyzed as common tumors]; the sponsor noted that combined mammary tumors [i.e., adenoma, adenocarcinoma, adenoacanthoma, carcinosarcoma] were also significantly increased in MDF and HDF. (b) pituitary adenomas in MDF and HDF [both analyzed as common tumors; the trend test approached significance at the MD]. The sponsor noted that combined pituitary tumors [nos] were increased in MDF and HDF; however, the effect was statistically significant only at the HD. The sponsor attributed these findings to elevations in serum prolactin.

Study No. 010808: according to the sponsor's re-analysis, there was a significant negative trend in mortality in males and a positive trend in mortality in females. According to the data in the original report, survival was significantly increased in DTM and significantly decreased in DTF.

The results of the re-analysis of the tumor incidence data were summarized in the following sponsor's table:

Text Table 2: Tumor Incidence Changes in BMS-337039-Dosed Female Mice -Otsuka Study No. 010808-

Dose (mg/kg/day):	0	30
No. of Mice:	60	60
Mammary Gland:		
Adenoma	-	1
Adenocarcinoma	1	14
Adenoacanthoma	-	11
Carcinosarcoma	1	3
Pituitary Gland:		
Anterior adenoma	5	14

- Indicates absence of finding in group

The sponsor considered the following findings drug-related: (a) mammary gland adenocarcinoma, adenoacanthoma; the combination of mammary gland neoplasms was also significantly increased DTF; pituitary [anterior] adenomas in DTF. The sponsor attributed these findings to elevations in serum prolactin. The sponsor noted that the incidence of combined liver hemangiomas and hemangiosarcomas was increased in DTM, but that the p-value of 0.0475 did not reach the level of significance for common [hemangioma] or rare [hemangiosarcoma] tumors. It does not appear that the sponsor conducted an analysis of hemangiomas/hemangiosarcomas across organs/tissues.

3. Study title: **104-week carcinogenicity study of OPC-31 in rats** [Study No. IET 92-0157, Volume #1.75, Conducting laboratory and location: ——— Date of study initiation: 9/93, GLP, QA'd report:Y]

Drug, lot #, and % purity: OPC-31, lot no. 93H80M1, purity = ———

CAC concurrence: the sponsor submitted a protocol; however, the study was ongoing at the time of submission. The doses proposed [0, 1, 3, 10 mg/kg] were considered by the Exe-CAC [meeting, 2/8/94]. According to the draft minutes [a copy of the information fax'd to the sponsor (2/17/94) was not available], Exe-CAC did not comment on the doses proposed, but did note that the data indicated that the drug/diet admixture was unpalatable. The sponsor was informed that, due to the palatability issue, apparent adverse effects on body wt would not be sufficient to establish that an MTD had been achieved.

Study Type (2 yr bioassay, alternative model etc.): 2-yr bioassay

Species/strain: Fischer 344/DuCrj rat ———

Number/sex/group; age at start of study: 50/sex/grp

Initial body wts: 40-80 gm for males, 40-75 gm for females

Initial age: 4 wks

Animal housing: individually

Formulation/vehicle: drug-dietary admixture, prepared weekly

Drug stability/homogeneity: stability in the diet stated to have been confirmed for ≤17 days at rm temperature/homogeneity and drug concentrations were tested at the beginning of the study and periodically [bi-monthly] during the dosing period.

Methods:

Doses: 0, 1, 3, 10 mg/kg

Basis of dose selection: data from a 13-wk dietary dose-range finding study [Study No. IET 92-

0155]
Restriction paradigm for dietary restriction studies: no
Route of administration: oral [dietary]
Frequency of drug administration: daily for 104 wks [satellite grps: daily for 2 or 52 wks]
Dual controls employed: no
Interim sacrifices: no
Satellite PK or special study group(s): 8/sex/grp [treated grps only] for analysis of TK
Statistical methods: tumor data were analyzed using Cochran-Armitage trend test [one-sided] for overall incidence of neoplastic lesions and Peto's onset rate method [one-sided] for analysis of onset-time for mammary gland tumors in females. The statistical methods employed are described in detail in the biostatistical review [Statistical Review and Evaluation: Review of Rat Carcinogenicity Studies, NDA#21.436. Roswitha Kelly, M.S. (HFD-710)].

Observations and times
Mortality: all main-study animals were checked for death or morbidity twice daily [once on Saturday, Sunday] during the dosing period.
Clinical signs: all main-study animals were observed daily. More detailed examinations [including palpation for masses] were conducted weekly on all animals.
Body weights: body wts were recorded in all animals [including satellite-TK animals] prior to the start of dosing, weekly during the first 16 wks of dosing, and bi-weekly thereafter. Body wts were also recorded in main-study animals prior to blood sampling or sacrifice. [Data from satellite animals were not included in the calculation of grp means.]
Food consumption: food intake was measured in main-study and satellite animals once a week during the first 16 wks of dosing and bi-weekly thereafter. Food efficiency was calculated during the first 13 wks of dosing.
Hematology: blood samples were collected at Wk 104 for analysis of the following parameters: hct, hgb, rbc ct, MCV, MCH, MCHC, platelet ct, wbc ct [total, differential].
Clinical chemistry: no
Organ weights: wts of the following organs were recorded: brain, kidneys, seminal vesicles/coagulating gland, pituitary [postfixation], spleen, prostate, heart, adrenals, lung, testes/ovaries, lung, liver.
Gross pathology: a complete necropsy was conducted on all main-study animals, including animals dying premature or sacrificed moribund.
Histopathology: the following tissues were examined microscopically in all main-study animals terminated on schedule and those sacrificed moribund: brain [3 sections], spinal cord [cervical, thoracic, lumbar], sciatic nerve, pituitary, thymus [or thymic region], thyroid/parathyroid, adrenals, spleen [2 sections], bone/marrow [sternum, femur, vertebrae], tibio-femoral joint, lymph nodes [cervical, mesenteric], heart [2 sections], aorta, salivary gland, tongue, esophagus, stomach [forestomach, glandular], liver [2 sections], pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, trachea, lung/bronchi, kidneys, urinary bladder, teste, epididymides, prostate, seminal vesicles/coagulating glands, ovaries, uterus [cornua, cervix], vagina, eyes, Harderian glands, skeletal muscle [M. triceps surae], skin, mammary gland [abdominal region], gross lesions. Tissues from animals that died spontaneously during the study were collected when possible.

Tissues were paraffin-embedded and stained with H & E for examination.
Toxicokinetics: blood samples were collected in satellite animals [3/sex/grp/time point] and selected main-study animals [3/sex/grp except Cs]. [There was no explanation as to the fate of the satellite animals (2/sex/grp) not used for TK analysis.] Samples were

collected at 9:00 a.m. on sampling days. OPC-31 was quantitated in plasma using [redacted] analyses were conducted by the sponsor.

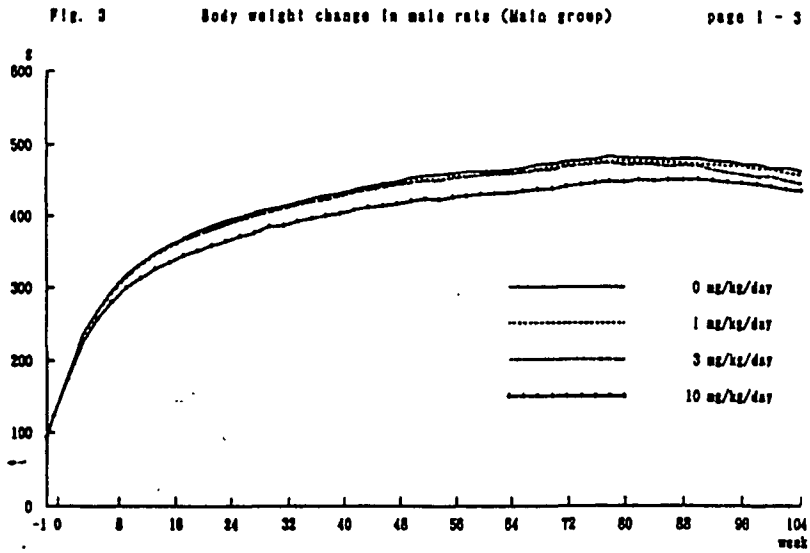
Results

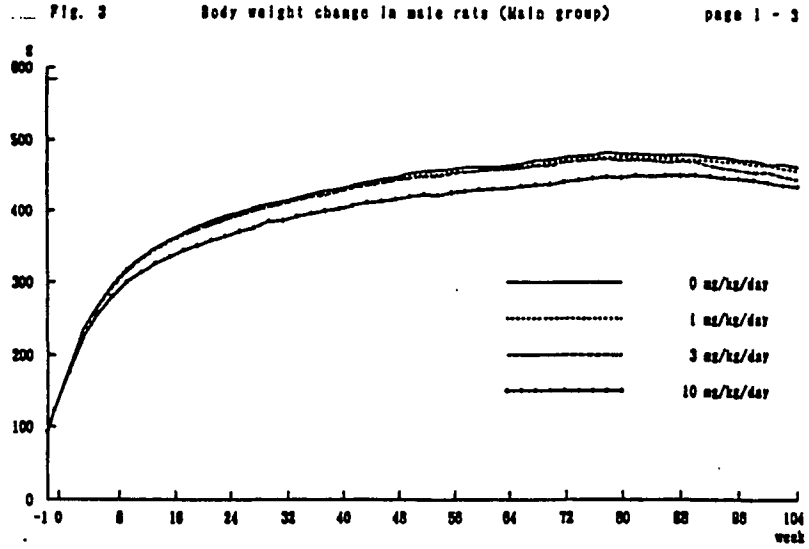
Dosing: data were provided documenting drug homogeneity and concentrations in the drug-diet admixture. Achieved doses were estimated to be [in general] with 10% of intended. At the early sampling time [Oct, 1993], the HD tended to be slightly higher [114%] than intended [only diets for females sampled]. The mean daily doses throughout the dosing period were estimated to be 1.002-0.999, 3.01, and 10.01-10.00 mg/kg at the LD, MD, and HD, respectively [M-F].

Mortality: there was no drug-related effect on mortality in either males or females. Overall mortality rates were as follows: 13/50 [26%], 7/50 [14%], 8/50 [16%], and 10/50 [20%] in CM, LDM, MDM, and HDM, respectively; and 7/50 [14%], 8/50 [16%], 13/50 [26%], and 12/50 [24%] in CF, LDF, MDF, and HDF, respectively.

Clinical signs: the primary clinical signs were pale eye color [M: 6/50, 6/50, 12/50, and 13/50 in C, LD, MD, and HD grps, respectively; F: 2/50, 6/50, 6/50, and 9/50 in C, LD, MD, and HD grps, respectively] and skin/subcutis masses [F: 15/50, 19/50, 20/50, and 29/50 in C, LD, MD, and HD grps, respectively]. Decreased SMA was noted primarily in MDF [3/50, 4/50, 11/50, and 9/50 in CF, LDF, MDF, and HDF, respectively].

Body weights: mean body wt was significantly lower in HDM [6-7%] throughout the dosing period, and in MDM during the last wks of dosing [3-4% during Wks92-104; significant only during Wks 94, 102, and 104]. Final mean body wts were 4 [MDM] and 6% [HDM] lower compared to CM at Wk 104. In females, mean body wts were significantly increased at all doses [≈3-4, 4-7, and 4-8% at LD, MD, and HD, respectively] during the mid-portion of the dosing period [Wks 52-68, 38-76, and 30-68 in LDF, MDF, and HDF, respectively]. The data are illustrated in the following sponsor's figures:





Food consumption: mean food intake was consistently reduced throughout the dosing period in HDM, and sporadically at the lower doses in males. Overall mean daily food intake was 9% lower in HDM compared to CM, but was similar among the other grps. The effect was similar in females. Overall mean daily food intake was 9% lower compared to CF, but was similar among the other grps. There were no significant effects on food efficiency in either males or females.

Hematology: the primary drug-related effect was an increase in wbc ct. In males, wbc ct was increased at all doses [11, 21, and 36% at LD, MD, and HD, respectively], although significantly only at the HD. Values in 1/40 LDM, 3/39 MDM, and 6/37 HDM exceeded the highest CM value. The increase in total wbc ct was due to increases in lymphocyte [35% at HD] and segmented neutrophil [36 and 32% at MD and HD, respectively] cts. In females, the effect on wbc ct was not dose-related [100, 56, and 41% at LD, MD, and HD, respectively]; lymphocyte and segmented neutrophil cts were increased at the HD [26 and 75%, respectively. Values in 2/39 LDF, 1/34 MDF, and 2/35 HDF markedly exceeding the highest CF value. The sponsor attributed these to various lesions detected during microscopic examination, and not a direct hematological effect of the drug. [Of the 12 HDM with high wbc ct values, 8 were found to have "causative lesions", e.g., "fibroma or ulcers of the skin, leukemia, lung adenoma, or adenoma or abscess of the preputial glands..." In females, all 7 HDF with high values had "causative lesions", e.g., "mammary gland tumors, clitoral gland tumors, or leukemia".

Organ weights: significant findings were summarized in the following sponsor's table:

Organ weights	Dose (mg/kg/day):	1		3		10	
	Sex:	M	F	M	F	M	F
Final body weight[a] at necropsy		109	96	102	94	99	88⇩
Brain:	Absolute	101	98	101	99	99	98
	Relative	80	102	96	103	96	110↑
Pituitary:	Absolute	100	94	73	154	64↓	244⇧
	Relative	86	94	68	158	61	279⇧
Adrenals:	Absolute	82	105	118	99	71↓	96
	Relative	75	105	115	105	70	110
Liver:	Absolute	105	95	99	103	86↓	92
	Relative	95	98	96	108	87⇩	105
Kidneys:	Absolute	95	97	92	101	87⇩	94
	Relative	84	100	87	107	84	108
Testes:	Absolute	90		95		59⇩	
	Relative	82		93		60⇩	
Seminal vesicles[b]:	Absolute	171		106		268⇧	
	Relative	150		100		260⇧	
Uterus:	Absolute		118		95		72⇩
	Relative		127		105		86

Sex: M, Male; F, Female
a: Percentage (%) of the control value
b: Including coagulating glands
Statistical significance (Dunnett's test): ↑ ↓, P<0.05; ⇧ ⇩, P<0.01

Gross pathology: the sponsor summarized significant findings in the following table:

Gross findings	Overall incidence in all animals examined							
	Dose (mg/kg/day):	0		1		3		10	
	Sex:	M	F	M	F	M	F	M	F
	No. of animals:	50	50	50	50	50	50	50	50
External Appearance:									
Emaciation		7	0	1↓	0	3	4	2	3
Soiled fur in external genital region		3	0	3	6↑	1	3	8	2
Eyes:									
Opacity		5	5	3	0↓	2	1	5	4
Skin/Subcutis:									
Hair loss		2	20	4	13	5	26	2	12
Callosity in hind paws		0	0	3	0	3	1	10⇧	0
Mass(es)		20	11	22	16	17	14	12	29⇧
Pituitary:									
Enlargement		0	0	0	1	0	0	0	7⇧
Spot(s)		4	10	1	14	1	5	2	9
Mass(es)		14	20	15	17	8	31↑	4⇩	27
Abdominal Cavity:									
Ascites		0	0	0	0	3	0	0	1
Spleen:									
Enlargement		6	4	9	8	4	9	7	11↑
Testes:									
Atrophy		18		8↓		14		8↓	
Mass(es)		43		42		46		26⇩	

Histopathology

Non-neoplastic: selected findings are summarized in the following table:

TISSUE	FINDING	PT/T#	MALES				FEMALES			
			C	LD	MD	HD	C	LD	MD	HD
heart	myocarditis	PT	0/13	0/7	0/8	0/10	0/7	0/8	0/13	0/12
		T	0/37	1/43	1/42	2/40	0/43	0/42	2/37	0/38
		total	0/50	1/50	1/50	2/50	0/50	0/50	2/50	0/50
liver	eosinophilic foci	PT	8/13	3/7	4/8	2/10	2/7	1/8	3/13	2/12
		T	22/37	23/43	24/43	17/40	19/43	18/42	17/37	24/38
		total	30/50	26/50	28/50	19/50*	21/50	19/50	20/50	26/50
pancreas	islet cell hyperplasia	PT	0/13	0/7	0/8	0/10	0/7	0/8	0/13	0/12
		T	0/33	0/43	0/42	2/40	0/43	0/42	0/37	0/38
		total	0/50	0/50	0/50	2/50	0/50	0/50	0/50	0/50
testis	interstitial cell hyperplasia	PT	3/13	3/7	4/8	4/10				
		T	5/37	7/43	9/42	20/40**				
		total	8/50	10/50	13/50	24/50**				
epididymis	atrophy	PT	8/13	4/7	4/8	1/10*				
		T	34/47	34/43	31/42*	13/40**				
		total	42/50	38/50	35/50	14/50**				
	fibrosis	PT	8/13	4/7	3/8	1/10*				
		T	35/37	37/43	34/42	19/40**				
		total	43/50	41/50	37/50	20/50**				
	oligospermia	PT	7/13	4/7	3/8	0/10**				
		T	34/37	37/43	34/42	17/40**				
		total	41/50	41/50	37/50	17/50**				
seminal vesicle	atrophy	PT	9/13	1/7*	2/8	1/10**				
		T	23/37	32/43	25/42	7/40**				
		total	32/50	33/50	27/50	8/50**				
	fibrosis	PT	8/13	17	1/8*	1/10*				
		T	22/37	28/43	23/42	5/40**				
		total	30/50	29/50	24/50	6/50**				
coagulating gland	atrophy	PT	9/13	1/7*	2/8	1/10**				
		T	23/37	32/43	26/42	7/40**				
		total	32/50	33/50	28/50	8/50**				
	fibrosis	PT	8/13	1/7	1/8*	1/10*				
		T	22/37	28/43	23/42	5/40**				
		total	30/50	29/50	24/50	6/50**				
prostate	prostatitis	PT	2/13	0/7	1/8	0/10				
		T	11/37	5/43*	5/42*	3/40*				
		total	13/50	5/50*	6/50	3/50**				
kidney	chronic nephropathy	PT	11/13	5/7	7/8	5/10	6/7	6/8	11/13	7/12
		T	37/37	43/43	42/42	40/40	41/43	36/42	29/37*	29/38*
		total	48/50	48/50	49/50	45/50	47/50	42/50	40/50*	36/50**
pituitary	atrophy of intermediate part	PT	0/12	0/7	1/8	7/10**	0/7	0/8	0/13	0/12
		T	2/37	1/42	7/42	30/40**	2/42	2/42	3/37	12/38**
		total	2/49	1/49	8/50*	37/50**	2/50	2/50	3/50	12/50**
	anterior cyst	PT	1/12	1/7	0/8	3/10	0/7	4/8	3/13	1/12
		T	2/37	1/42	5/42	2/40	18/43	24/42	14/37	7/38*
		total	3/49	2/49	5/50	5/50	18/50	28/50*	17/50	8/50*
Harderian gland	mononuclear cell infiltrates	PT	2/13	0/7	0/8	1/10	3/7	2/8	1/13	0/12*
		T	8/37	10/43	8/42	2/40*	17/43	16/42	9/37	8/38
		total	10/50	10/50	8/50	3/50*	20/50	18/50	10/50*	8/50**
skin	erosion/ulcer	PT	1/13	0/7	0/8	2/10	0/7	0/8	0/13	0/12
		T	0/37	3/43	3/42	6/40*	0/43	1/42	1/37	0/38
		total	1/50	3/50	3/50	8/50*	0/50	1/50	1/50	0/50
thyroid	C-cell hypeplasia	PT	6/13	3/7	5/8	6/10	5/7	4/8	9/13	7/12
		T	26/37	25/43	27/42	27/40	38/43	37/42	34/37	27/38*
		total	32/50	28/50	32/50	33/50	43/50	41/50	43/50	34/50*

TISSUE	FINDING	PT/T#	MALES				FEMALES			
			C	LD	MD	HD	C	LD	MD	HD
bone [sternum, femur, vertebra]	hyperosteosis	PT	1-2/13	0/7	0/8	0/10	3/7	1/8	2/13	3/12
		T	0-3/37	0/43	1-2/42	0/40	17-18/50	14/42	12/37	4/38**
		total	1-5/50	0/50	1-2/50	0/50	20-21/50	15/50	14/50	7/50**
uterus	atrophy	PT					2/7	2/8	7/13	10/12*
		T					2/43	1/42	3/37	24/38**
		total					4/50	3/50	10/50	34/50**
mammary gland	acinar proliferation	PT	1/13	0/7	0/8	0/10	5/7	6/8	12/13	10/12
		T	4/36	6/43	2/42	2/40	22/43	17/42	20/37	25/38
		total	5/49	6/50	2/50	2/50	27/50	23/50	32/50	35/50

#PT = premature sacrifice or spontaneous death, T = terminal sacrifice, *p<0.05, **p<0.01

The sponsor considered findings in the pituitary, male and female reproductive organ(s), kidney, liver, thyroid, Harderian gland, and bone drug-related. The paw [skin] findings were considered incidental. The uterine findings were considered secondary to drug-induced hyperprolactinemia. The male reproductive organ effects and the kidney effects were considered secondary to reduced food consumption. The effects on secondary male reproductive organs were considered to be the result of the decreased incidence of testicular interstitial cell tumors in HDM. The mechanism(s) underlying the atrophy of the pituitary pars intermedia was not clear; the sponsor noted that CPZ has been demonstrated to reduced the MSH-content of the pars intermedia [Wied DD. *Pharmacol Rev* 19:251-288, 1967].

Neoplastic: the only neoplastic finding of note was an increase in mammary gland fibroadenoma in HDF. The incidences [based on the data provided in the sponsor's summary table] are summarized in the following table:

PT/T*	CF	LDF	MDF	HDF
PT	1/7	1/8	1/13	1/12
T	5/43	8/42	7/37	16/38**
total	6/50	9/50	8/50	17/50**

*PT = premature termination or spontaneous death, T = terminal sacrifice, **p<0.01

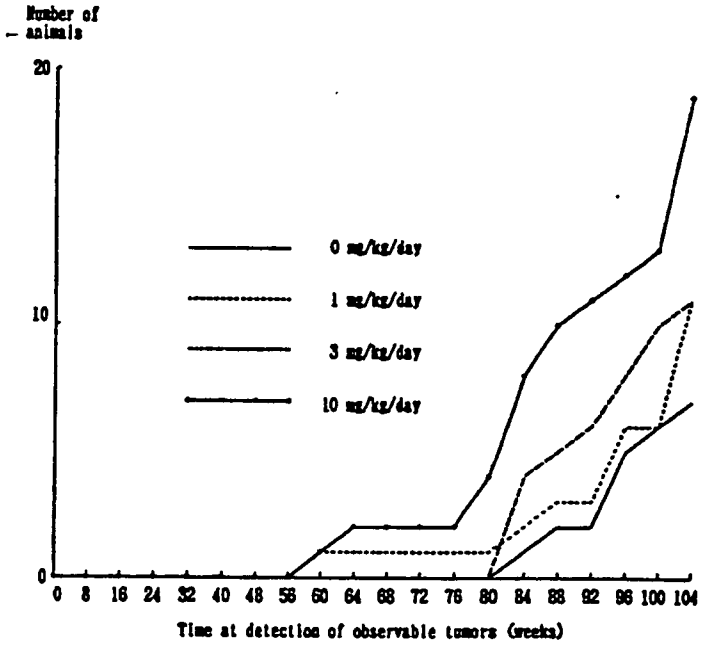
The no. of females with mammary gland tumors was summarized in the following sponsor's table:

Dose group (mg/kg/day)	No. of females with mammary tumors		
	A	B	Total (A+B)
0	5/43*	2/7	7/50*
1	9/42	2/8	11/50
3	9/37	2/13	11/50
10	18/38 ♀	1/12	19/50 ♀

A: Animals killed as scheduled after 104 weeks of treatment
B: Animals killed in extremis or found dead during the study
n/n: No. of animals with tumors/No. of animals examined
*: Significant increasing trend (P<0.05, Cochran-Armitage trend test)
♀: Significant increase (P<0.01, Fisher's exact test)

[There is a discrepancy between the two summary tables which needs to be resolved.]

The sponsor noted that the time of onset of the mammary gland tumors was earlier in HDF. This finding is illustrated in the following sponsor's figures:



The incidences of testicular interstitial cell tumor and pituitary [anterior] adenoma were significantly decreased in HDM [both PT and T animals], and the incidence of uterine endometrial stromal polyps was reduced in females [significant trend in survivors]. The incidence of anterior pituitary adenoma was slight, but not significantly higher in MDF and HDF [25/50, 25/50, 33/50, and 32/50 in CF, LDF, MDF, and HDF, respectively]

The sponsor considered the mammary gland fibroadenomas in HDF to be drug-related, and secondary to hyperprolactinemia [serum prolactin was not measured in this study]. The decreases in pituitary adenomas and interstitial cell tumors of the testis were considered secondary to reduced food consumption, whereas the decrease in uterine polyps was considered secondary to reduced food consumption and/or hyperprolactinemia.

Toxicokinetics: the data were summarized in the following sponsor's tables:

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Appendix 2-4 Chemical analysis - Plasma concentration of OPC-31 in rats

Table 1 Plasma concentration of OPC-31 in male rats of 104-week carcinogenicity study

Week 2		Week 52		Week 104	
Animal No.	Concentration(ng/ml)	Animal No.	Concentration(ng/ml)	Animal No.	Concentration(ng/ml)
OPC-31 1 mg/kg/day					
401		404		252	
402		405		253	
403		406		254	
Mean		Mean		Mean	
S.D.		S.D.		S.D.	
OPC-31 3 mg/kg/day					
409		412		301	
410		413		302	
411		414		303	
Mean		Mean		Mean	
S.D.		S.D.		S.D.	
OPC-31 10 mg/kg/day					
417		420		352	
418		421		353	
419		422		355	
Mean		Mean		Mean	
S.D.		S.D.		S.D.	

Appendix 2-5 Chemical analysis - Plasma concentration of OPC-31 in rats

Table 2 Plasma concentration of OPC-31 in female rats of 104-week carcinogenicity study

Week 2		Week 52		Week 104	
Animal No.	Concentration(ng/ml)	Animal No.	Concentration(ng/ml)	Animal No.	Concentration(ng/ml)
OPC-31 1 mg/kg/day					
901		904		752	
902		905		753	
903		906		755	
Mean		Mean		Mean	
S.D.		S.D.		S.D.	
OPC-31 3 mg/kg/day					
909		912		801	
910		913		805	
911		914		806	
Mean		Mean		Mean	
S.D.		S.D.		S.D.	
OPC-31 10 mg/kg/day					
917		920		851	
918		921		852	
919		922		853	
Mean		Mean		Mean	
S.D.		S.D.		S.D.	

4. Study title: **Oral carcinogenicity study in rats** [Study No. 99321, Volume #1.80-1.106, Conducting laboratory and location: —— Date of study initiation: 3/24/99, GLP **except for immunohistochemical analysis of adrenal gland**, QA'd report:Y]

Drug, lot #, and % purity: BMS-337039, lot (batch) no. C98G92(2)M [used for dosing from Wks 1 through 38], purity = ——, lot (batch) no. C98K78M [used for dosing from Wks 39 through end of study], purity = ——

CAC concurrence: see Study No. IET 92-0157 review [#3 in this section]

Study Type (2 yr bioassay, alternative model etc.): 2-yr
Species/strain: Sprague-Dawley rat
Initial age: 6 wks
Initial body wt: 140-192 gm for males, 119-160 gm for females
Number/sex/group: 55/sex/grp
Animal housing: individually
Formulation/vehicle: suspension/5% gum arabic
Drug stability/homogeneity: homogeneity tested during Wks 1, 6, 13, 39, and 52. Stability [protected from light, 2-8° C] was tested for periods of 8 and 15 days using drug suspensions prepared during Wk 1. Drug concentrations were tested during Wks 1, 13, 26, 52, 65, 78, 91, 96, and 104. The data provided documented drug suspension stability and adequate homogeneity, and verified drug concentrations.
Methods:
Doses: 0, 0, 10, 20, 40, 60 mg/kg [designated C1, C2, LD, MD-1, MD-2, HD]
Basis of dose selection: dose-range finding studies [5-wk, 4-wk diet vs gavage,], 4-, 13-, and 52-wk toxicity studies, previous dietary carcinogenicity study [doses: 0, 1, 3, 10 mg/kg]. In the 5-wk study [Sprague-Dawley rat], BMS-337039 was "well-tolerated" at doses up to 20 mg/kg; at 60 mg/kg, clinical signs were evident and body wt [19% in M, 17% in F] and food consumption were significantly decreased. In the 4-wk oral toxicity study [Sprague-Dawley rat], doses of 60 and 100 mg/kg were associated with clinical signs and decreases in body wt [15-19 and 25-34%, respectively] and food consumption [18-27 and 12-73%, respectively]. In the 4-wk diet vs gavage study [Fischer 344 male rat], doses of 10 and 30 mg/kg were associated with only minimal decreases in body wt [Day 7] and food consumption; at 100 mg/kg, clinical signs were noted, as well as decreases in body wt and food consumption [nos]. In the 13- and 52-wk studies [Sprague-Dawley rat], doses of 20 and 10 mg/kg were "well-tolerated". In the previous [dietary] carcinogenicity study [Fischer 344 rat], there was an increase in mammary gland fibroadenoma in F at 10 mg/kg [HD]; no drug-related tumors were evident at the lower doses [1, 3 mg/kg].
Restriction paradigm for dietary restriction studies: n/a
Route of administration: oral [gavage]
Frequency of drug administration: daily
Dual controls employed: y
Interim sacrifices: no
Satellite PK or special study group(s): no
Statistical methods: mortality data were analyzed using the Cox-Tarone trend test [2-sided]. Statistical analysis of nonpalpable and palpable tumors was conducted using the Peto and Pike [Peto, 1980] and the Cox-Tarone binary regression method, respectively. Detailed discussion of the sponsor's statistical evaluation is provided in the statistical review [ ].
Observations and times
Clinical signs: animals were observed twice daily for morbidity and mortality and once daily [Wks 1-4, 1-2 hrs postdose]; from Wk 5 on, animals were observed for clinical signs, morbidity, and mortality during the same observation periods.
Body weights: body wts were recorded at baseline, weekly during Wks 1-14, and every 4 wks thereafter.
Food consumption: food intake was recorded weekly during Wks 1-13 and every 4 wks thereafter.
Hematology: blood samples were collected from all survivors at Wks 105-106 for analysis of the following parameters: rbc ct, hgb, hct, MCV, MCH, MCHC, platelet ct, wbc ct [total, differential], reticulocyte smears [not examined].

Clinical chemistry: no

Organ weights: the following organs were weighed in the first 10/sex/grp sacrificed at the end of the dosing period: adrenals, brain, heart, kidneys, lung, ovaries, pituitary, prostate/seminal vesicles, spleen, testes, thyroids/parathyroids, uterus/cervix.

Gross pathology: a complete necropsy was conducted on all animals, including those that died spontaneously or were sacrificed moribund.

Histopathology: the following tissues were microscopically examined in all animals except as noted: adrenal (2), aorta, brain, cecum, cervix, colon, duodenum, epididymis (2), esophagus, eyes [preserved in Davidson's solution only in animals terminally sacrificed], fenur/bone marrow, Harderian gland, heart, ileum, jejunum, kidney (2), gross lesions, liver, lung/bronchi, lymph node [mandibular, mesenteric], mammary gland, optic nerve, ovary (2), pancreas, pituitary [including pars intermedia], prostate, salivary gland [mandibular (2)], sciatic nerve, seminal vesicle (2), skeletal muscle [biceps femoris], skin, spinal cord [cervical, thoracic, lumbar], spleen, sternum/bone marrow, stomach [nonglandular, fundic, pyloric], testis (2), thymus, thyroid (2)/parathyroid, tongue, trachea, urinary bladder, uterus, vagina, Zymbal's gland. Tissue sections were prepared (as appropriate) and stained with H & E for examination. Tissues from animals dying prematurely or sacrificed moribund were prepared and examined "...on an approximately monthly basis..."

In addition, the following analyses were performed: (a) adrenals (M) and ovaries from 3

provided from the combined control groups. Animals were selected for inclusion in these special studies based on absence of adrenocortical neoplasms.

Histopathology findings were peer-reviewed

Toxicokinetics: During Wk 26, blood samples were collected from 5/sex/grp/time point [randomly selected] at 4 and 24 hrs postdosing for analysis of BMS-330739 and metabolites, BMS-337040, BMS-337044, BMS-337045, BMS-337047, and 1-(2,3-dichlorophenyl)piperazine (DCPP) [using]. In addition, once during Wk 65, blood samples were collected at 1, 2, 4, 8, and 24 hrs postdosing from 3/sex/grp/time point for analysis of parent compound and 5 metabolites [as listed previously]. Samples were collected from C animals, but not analyzed. Samples were shipped to the sponsor for analysis.

Results

Mortality: the survival rate increased in a fairly dose-related manner. Survival rates were 36, 53, 53, 60, and 70% in CMs [combined], LDM, MD-1M, MD-2M, and HDM, respectively, and 39, 40, 58, 73, and 64% in CFs [combined], LDF, MD-1F, MD-2F, and HDF,

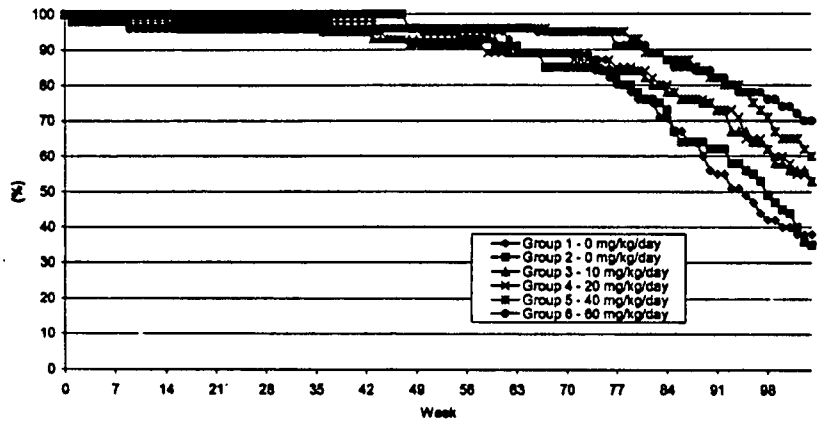
respectively. However, 1 MD-2M was found dead on Day 4 [clinical signs: hypoactivity, red nasal discharge, irregular respiration], 1 HDM and 5 HDF were either found dead [1 HDF] or were sacrificed moribund [1 HDM, 4 HDF] on Days 2-6 of dosing. In the HD animals, clinical sings consisted of "...hypoactivity, squinted eyes, tremors, irregular respiration, red nasal discharge, discolored haircoat (brown or yellow), and/or coolness to touch". Microscopic examination of the MD-2M and HDMs indicated presence of urinary tract obstruction/inflammation. Deaths in the HDF were "...histologically undetermined and were considered drug-related".

The survival data were summarized in the following sponsor's table and figures:

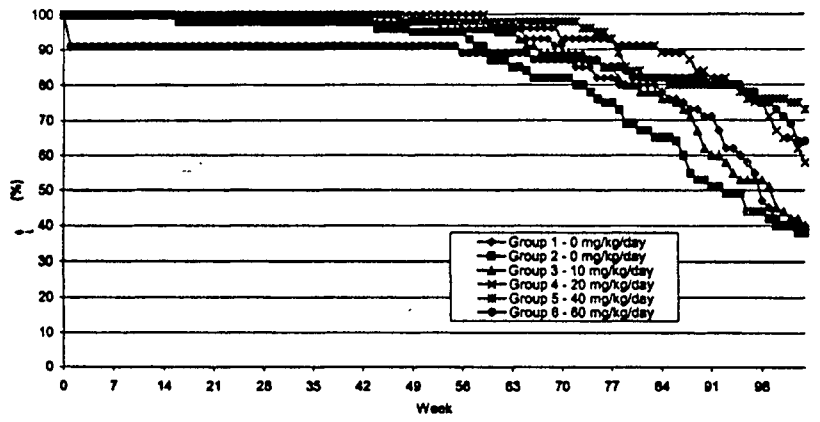
	Dose (mg/kg/day)					
	0	0	10	20	40	60
Number of males initially on study	55	55	55	55	55	55
Number of males surviving to study termination[a]	21	19	29	29	33	38
Number of females initially on study	55	55	55	55	55	55
Number of females surviving to study termination[a]	22	21	22	32	40	35

a Based on numbers of animals surviving to Week 104.

males



females



Clinical signs: the data were summarized only as the number of affected animals/grp during the entire dosing period. Therefore, the duration of the clinical signs in the affected animals could not be determined from the summary table. [Individual data were not examined to

determine duration.] Selected findings are summarized in the following table [n = 55/grp in all instances]:

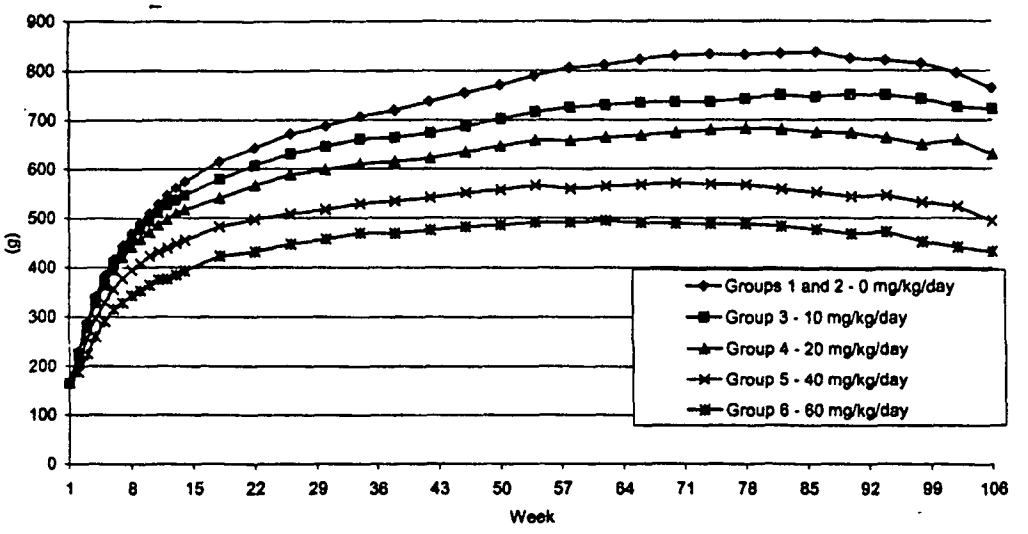
FINDING	MALES						FEMALES					
	C	C	LD	MD-1	MD-2	HD	C	C	LD	MD-1	MD-2	HD
convulsions	5	2	8	7	6	6	1	1	5	4	7	6
protruding penis	1	0	2	3	4	6						
aggressive behavior	1	1	3	2	0	10	0	0	1	0	0	0
hypoactivity												
unspecified	8	10	5	12	4	3	7	19	13	6	7	7
mild	0	1	0	0	1	1	0	0	0	0	0	11
moderate	0	0	0	0	0	1	0	0	0	0	0	9
hyperactivity												
unspecified	0	0	1	0	0	0	0	0	1	3	1	10
mild	0	0	0	0	0	0	0	0	0	0	0	1
clear oral discharge												
unspecified	2	1	6	4	7	10	0	1	0	1	8	11
mild	0	0	0	0	0	0	0	0	0	0	1	7
moderate	0	0	0	0	0	0	0	0	0	0	0	1
severe	0	0	0	1	0	0	0	0	0	0	0	0
eyes, cloudy discharge	0	0	0	0	0	0	0	0	1	0	0	4
eyes (R), opaque	2	0	0	1	0	0	0	0	0	0	1	3
peri-orbital squint	3	6	5	7	4	26	0	11	12	4	14	50
respiration, irregular	3	11	7	10	4	9	4	10	8	5	7	21
brown haircoat												
head-entire	0	0	1	3	3	12	3	4	4	2	10	36
head-cranial	0	0	0	0	0	9	1	0	0	0	15	40
dorsal-cervical	0	0	0	0	0	2	0	1	0	0	2	5
generalized	0	0	0	0	0	0	0	1	2	0	1	4
black skin, distal tail	0	0	0	0	0	5	0	0	0	0	0	1
red haircoat												
head-entire	3	1	3	4	4	14	6	11	4	10	15	23
head cranial	0	1	1	0	1	6	0	6	2	1	3	15
scrotum	0	0	0	1	1	2	--	--	--	--	--	--
ears, red skin	0	0	0	0	0	1	0	0	0	1	1	9
ears, sore/scab	2	0	2	1	0	1	0	0	0	0	1	13
head, sore/scab	1	1	2	2	4	1	0	1	2	0	2	6
tail, sore/scab	1	1	1	0	1	4	0	0	0	1	3	8
yellow hair coat, perineal	1	2	2	3	1	8	4	4	7	8	10	39
cold to touch, body	5	4	1	7	2	6	3	3	5	3	3	11

The sponsor attributed clinical signs such as eye squinting, aggressive behavior, tremors, changes in activity, coolness to touch, and irregular respiration to exaggerated pharmacological effects of BMS-337039. Other clinical signs, such as discoloration of haircoat and sores/scabs, to be due to "...the behavior and overall condition of the animals..."

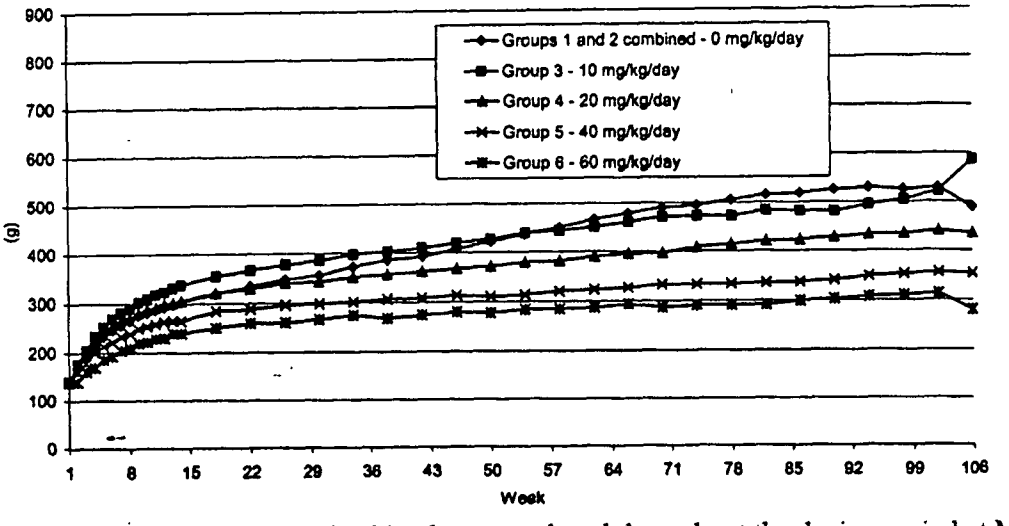
There were no clear drug-related increases in palpable masses. Overall, the number of affected animals per grp was low [i.e., ≤2/sex/grp].

Body weights: in males, mean body wt was reduced [compared to CMs] throughout the dosing period at the MD-2 and HD, and from Wk 4 on at MD-1, and from Wk 11 on at the LD. Mean body wts at Wk 102 were decreased by 8, 17, 34, and 44% in LDM, MD-1M, MD-2M, and HDM, respectively, compared to combined CM data. Body wts were recorded for 4-8/grp at Wk 106; in these animals, mean body wt was reduced by 5 (n.s.), 18, 35, and 43% in LDM, MD-1M, MD-2M, and HDM, respectively, compared to combined CM data. Overall body wt gain was decreased at all doses [11, 22, 43, and 56% in LDM,

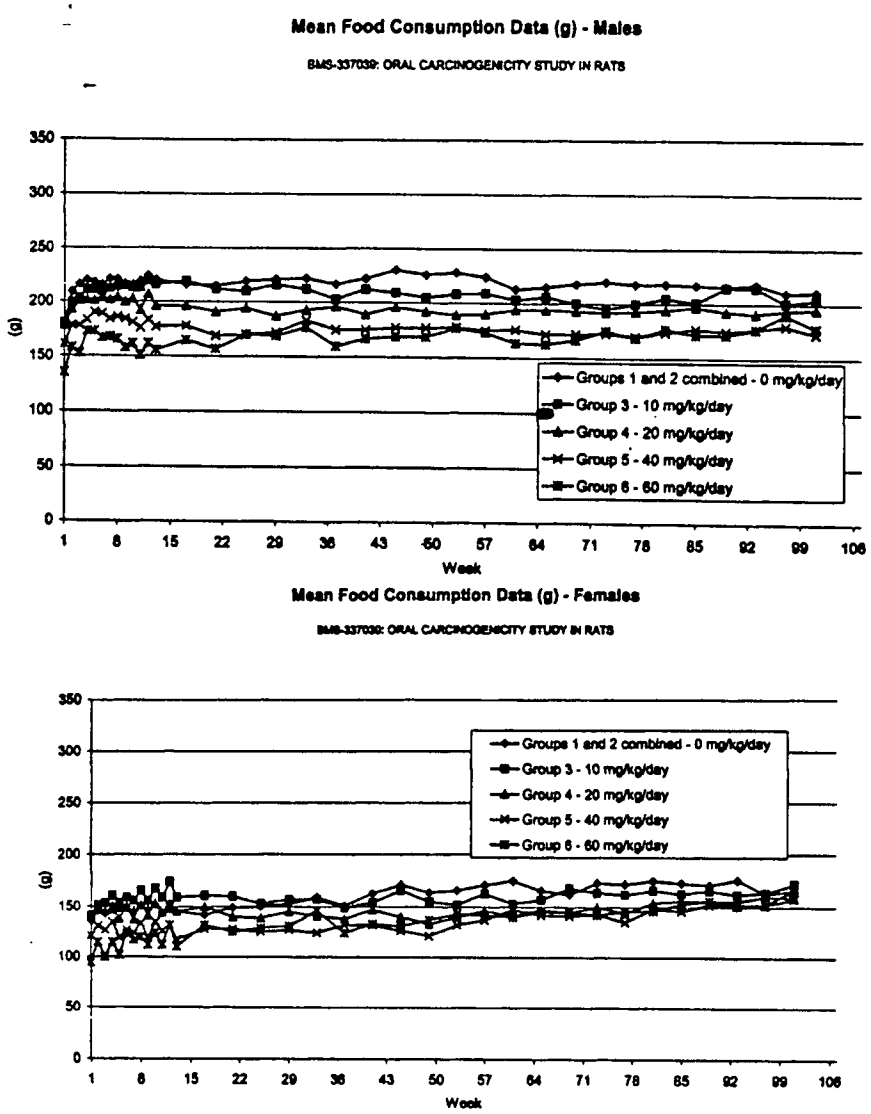
MD-1M, MD-2M, and HDM, respectively]. The data were illustrated in the following sponsor's figure:



In females, mean body wt was reduced compared to CFs throughout the dosing period at the MD-2 and HD and from Wk 34 on at the MD-1. At the LD, mean body wt was increased compared to CFs from Wk 2 through Wk 34. Mean body wts at Wk 102 were reduced by 17, 33, and 41% in MD-1F, MD-2F, and HDF, respectively, compared to combined CF data; mean body wt in LDF was comparable to CF. At Wk 106, body wts were recorded for 3-9/grp; mean body wts were reduced by 11, 28, and 43% in MD-1F, MD-2F, and HDF; mean body wt in LDF was 20% higher than in combined CFs. Overall body wt gain was reduced in MD-1F, MD-2F, and HDF [23, 44, and 55%, respectively]. The data were illustrated in the following sponsor's figure:



Food consumption: in males, food intake was reduced throughout the dosing period at MD-1, MD-2, and HD [6-17, 10-23, and 16-31%, respectively]. At the LD, food intake was reduced sporadically during dosing period [Wks 2-4, 7, 33-57, 65-77]. In females, food intake was reduced throughout the dosing period at MD-2 and HD [5-26 and 2-31%] and at MD-1 from Wk 21 on [0-19%]. At the LD, food intake was increased during the first 21 wks of dosing; thereafter, food intake was sporadically decreased [≤13%] at that dose. The data were illustrated in the following sponsor's figures:



Hematology: small increases in rbc ct [8-10%] and decreases [4-6%] in MCV and MCH were detected in both HDM and HDF; small decreases in MCV and MCH [4%] were also observed in MD-2F. Wbc ct was significantly increased in HDF [17%]; this increase was due to increases in segmented neutrophils [26%] and, perhaps, to an increase in lymphocytes [17% (n.s.) at the HD; 22% increase in MD-2F]. In males, wbc ct was not significantly affected, although there was a tendency for wbc ct to be increased at the mid-doses [47 and 21% (n.s.) at MD-1 and MD-2, respectively]. Segmented neutrophils were increased at the mid-doses and the HD [58, 45, and 34% in MD-1M, MD-2M, and HDM, respectively (significantly only at the mid-doses)]. Monocyte ct was increased in MD-1M [100%], but decreased in HDM [35%]; eosinophils were decreased [50%] at all but the LD. The sponsor noted that there were "...no obvious correlative anatomic pathology findings for these minor effects..."

Organ weights: the following findings were of note: (a) increases in absolute and relative [A-R] adrenal wt in males [130-220% (2.3-3.2 fold) and 150-310% (2.5-4 fold) at MD-2 and HD, respectively] and females [29-80% and 370-720% (4.7-8.2 fold) at MD-2 and HD, respectively], (b) increase in relative wt of lung in MD-2M and HDM [40 and 100%, respectively] and in absolute and relative lung wt in MD-2F [49-120%] and HDF [140-320% (2.4-4.2 fold)], (c) decrease in absolute pituitary wt in MD-1M, MD-2M, and

HDM [75, 78, and 84%, respectively]; relative wt was also decreased, but not in a dose-related manner [72-77%]. (d) a decrease in absolute and relative testis wt at the HD [54-21%], (e) an increase in absolute and relative thyroid/parathyroid wt in MD-2M [30-82%], but a decrease in absolute and relative thyroid/parathyroid wt in HDM [49-14%], (f) an increase in relative liver wt in MD-2F and HDF [25 and 61%, respectively], (g) a 68% increase in relative ovary wt in HDF, (h) an increase in relative spleen wt in MD-2F and HDF [40 and 84%, respectively], (i) an increase in relative uterus wt in MD-2F and HDF [35 and 51%, respectively].

The sponsor discussed the following microscopic correlates: (a) the increased adrenal wt "...appeared to be related primarily to hypertrophic changes in the cortex and lipofuscin pigment accumulation", (b) the increased lung wt was "...likely correlated with increased histiocyte infiltration within alveoli", (c) the decreased pituitary wt in males was "...considered secondary to the reduced incidence of neoplasia and increased incidence of atrophy of the pars intermedia", (d) the decreased testis wt was "...related to bilateral atrophy/degeneration...". The sponsor noted that decreases in absolute [but not relative] prostate/seminal vesicle wt may have been secondary to testis effects.

Gross pathology: selected findings are summarized in the following tables [data are provided as incidence and % affected animals (in brackets)]. The sponsor considered the following findings related to drug: (a) reduced incidence of "ventral brain compression and pituitary masses" at MD-2 and HD, (b) increased incidence of light areas/mottling of lung in MD-2M and HDM, (c) increased incidence of light areas/mottling/diffusely light lungs in females [all doses], (d) increased incidence of diffuse darkening of the adrenals in MD-1F, and MD-2 and HD animals, (e) increased incidence of enlarged adrenals in MD-2F and HD animals, (f) increased incidence of skin/mammary gland masses in males [MD-1, MD-2, HD], and a slight decrease in mammary gland masses in HDF; it was also noted that the incidence of multiple mammary gland masses was reduced in females at MD-2 and HD. (g) increased incidence of small seminal vesicles and epididymides in HDM, (h) increased incidence of testis findings [i.e., "diffuse reddening, small, contained fluid, diffuse darkening"] at the HD, (h) increased incidence of crusted tails in HD animals.

TISSUE	FINDING	PT/T*	GROUPS					
			C1	C2	LD	MD-1	MD-2	HD
MALES								
lung	light focus(i)/area(s)	PT	0/36 [0]	2/37 [5]	0/26 [[0]	1/26 [4]	6/22 [27]	5/17 [29]
		T	1/19 [5]	2/18 [11]	1/29 [3]	4/29 [14]	16/33 [48]	13/38 [34]
		total	**1/55 [2]**	**4/55 [7]**	**1/55 [[2]**	**5/55 [9]**	**22/55 [40]**	**18/55 [33]**
	mottled	PT	0/36 [0]	0/37 [0]	1/26 [4]	0/26 [0]	0/22 [0]	2/17 [12]
		T	0/19 [0]	0/18 [0]	0/29 [0]	0/29 [0]	0/33 [0]	19/38 [50]
		total	**0/55 [0]**	**0/55 [0]**	**1/55 [2]**	**0/55 [0]**	**0/55 [0]**	**21/55 [38]**
	diffusely light	PT	0/36 [0]	0/37 [0]	0/26 [0]	0/26 [0]	0/22 [0]	0/17 [0]
		T	0/19 [0]	0/18 [0]	0/29 [0]	0/29 [0]	0/33 [0]	2/38 [5]
		total	**0/55 [0]**	**0/55 [0]**	**0/55 [0]**	**0/55 [0]**	**0/55 [0]**	**2/55 [4]**
adrenal ctx	mass(es)	PT	0/36 [0]	1/37 [3]	1/26 [4]	0/26 [0]	0/22 [0]	0/17 [0]
		T	0/19 [0]	0/18 [0]	0/29 [0]	0/29 [0]	1/33 [3]	2/38 [5]
		total	**0/55 [0]**	**1/55 [2]**	**1/55 [2]**	**0/55 [0]**	**1/55 [2]**	**2/55 [4]**
	large	PT	0/36 [0]	3/37[8]	2/26 [8]	0/26 [0]	3/22 [14]	2/17 [12]
		T	1/19 [5]	0/18 [0]	3/29 [10]	2/29 [7]	0/33 [0]	10/38 [26]
		total	**1/55 [2]**	**3/55 [5]**	**5/55 [9]**	**2/55 [4]**	**3/55 [5]**	**12/55 [22]**
	diffusely dark	PT	0/36 [0]	0/37 [0]	0/26 [0]	1/26 [4]	1/22 [4]	0/17 [0]
		T	0/19 [0]	0/18 [0]	0/29 [0]	0/29 [0]	4/33 [12]	11/38 [29]
		total	**0/55 [0]**	**0/55 [0]**	**0/55 [0]**	**1/55 [2]**	**5/55 [9]**	**11/55 [20]**

TISSUE	FINDING	PT/T*	GROUPS					
			C1	C2	LD	MD-1	MD-2	HD
pituitary	masses	PT	12/36 [33]	21/37 [57]	7/26 [27]	11/26 [42]	5/22 [23]	2/17 [12]
		T	5/19 [26]	5/18 [28]	4/29 [14]	3/29 [10]	1/33 [3]	0/38 [[0]
		total	17/55 [31]	26/55 [47]	11/55 [20]	14/55 [25]	6/55 [11]	2/55 [4]
mammary gland	masses	PT	4/36 [11]	4/37 [11]	3/26 [12]	1/26 [4]	0/22 [0]	0/17 [0]
		T	2/19 [11]	3/18 [17]	4/29 [14]	0/29 [0]	3/33 [9]	0/38 [0]
		total	6/55 [11]	7/55 [13]	7/55 [13]	1/55 [2]	3/55 [5]	0/55 [0]
prostate	small	PT	3/36 [8]	2/37 [5]	0/26 [0]	0/26 [0]	1/22 [4]	1/17 [6]
		T	0/19 [0]	0/18 [0]	0/29 [0]	0/29 [0]	1/33 [3]	5/38 [13]
		total	3/55 [5]	2/55 [4]	0/55 [0]	0/55 [0]	2/55 [4]	6/55 [11]
seminal vesicles	small	PT	4/36 [11]	4/37 [11]	0/26 [0]	4/26 [15]	3/22 [14]	3/17 [18]
		T	0/19 [0]	0/18 [0]	2/29 [7]	1/29 [3]	2/33 [6]	12/38 [32]
		total	4/55 [7]	4/55 [7]	2/55 [4]	5/55 [9]	5/55 [9]	15/55 [27]
	gelatinous	PT	1/36 [3]	0/37 [0]	1/26 [4]	2/26 [8]	2/22 [9]	0/17 [0]
		T	0/19 [0]	0/18 [0]	0/29 [0]	1/29 [3]	2/33 [6]	4/38 [11]
		total	1/55 [2]	0/55 [0]	1/55 [2]	3/55 [5]	4/55 [7]	4/55 [11]
testis	diffusely red	PT	0/36 [0]	0/37 [0]	0/26 [0]	0/26 [0]	0/22 [0]	4/17 [23]
		T	0/19 [0]	0/18 [0]	0/29 [0]	0/29 [0]	1/33 [3]	8/38 [21]
		total	0/55 [0]	0/55 [0]	0/55 [0]	0/55 [0]	1/55 [2]	12/55 [22]
	small	PT	4/36 [11]	7/37 [19]	1/26 [4]	0/26 [0]	3/22 [14]	9/17 [53]
		T	1/19 [5]	1/18 [6]	3/29 [10]	1/29 [3]	7/33 [21]	28/38 [74]
		total	5/55 [9]	8/55 [14]	4/55 [7]	1/55 [2]	10/55 [18]	37/55 [67]
	diffusely dark	PT	0/36 [0]	0/37 [0]	0/26 [0]	0/26 [0]	0/22 [0]	0/17 [0]
		T	0/19 [0]	0/18 [0]	0/29 [0]	0/29 [0]	3/33 [9]	12/38 [32]
		total	0/55 [0]	0/55 [0]	0/55 [0]	0/55 [0]	3/55 [5]	12/55 [22]
epididymis	small	PT	1/36 [3]	2/37 [5]	0/26 [0]	0/26 [0]	2/22 [9]	1/17 [6]
		T	0/19 [0]	0/18 [0]	0/29 [0]	0/29[0]	2/33 [6]	5/38 [13]
		total	1/55 [2]	2/55 [4]	0/55 [0]	0/55 [0]	4/55 [7]	6/55 [11]
tail	crusted	PT	2/36 [6]	2/37 [5]	0/26 [0]	0/26 [0]	2/22 [9]	1/17 [6]
		T	0/19 [0]	1/19 [5]	1/29 [3]	1/29 [3]	1/33 [3]	7/38 [18]
		total	2/55 [4]	3/55 5]	1/55 [2]	1/55 [2]	3/55 [5]	8/55 [14]

*PT = premature deaths, T = terminal sacrifice

TISSUE	FINDING	PT/T*	GROUPS					
			C1	C2	LD	MD-1	MD-2	HD
FEMALES								
lung	light focus(i)/area(s)	PT	1/34 [3]	1/34 [3]	5/33 [15]	2/23 [9]	6/15 [40]	4/20 [20]
		T	1/21 [5]	2/21 [10]	3/22 [14]	10/32 [31]	18/40 [45]	8/35 [23]
		total	2/55 [4]	3/55 [5]	8/55 [14]	12/55 [22]	24/55 [44]	12/55 [22]
	mottled	PT	0/34 [0]	0/34 [0]	0/33 [0]	2/23 [9]	1/15 [7]	5/20 [25]
		T	0/21 [0]	0/21 [0]	0/22 [0]	0/32 [0]	16/40 40]	20/35 [57]
		total	0/55 [0]	0/55 [0]	0/55 [0]	2/55 [4]	17/55 [31]	25/55 [45]
	diffusely light	PT	0/34 [0]	0/34 [0]	0/33 [0]	0/23 [0]	2/15 [13]	2/20 [10]
		T	0/21 [0]	0/21 [0]	0/22 [0]	0/32 [0]	3/40 [8]	7/35 [20]
		total	0/55 [0]	0/55 [0]	0/55 [0]	0/55 [0]	5/55 [9]	9/55 [16]
lymph, mesenteric	diffusely red	PT	0/34 [0]	0/34 [0]	0/22 [0]	0/32 [0]	0/15 [0]	1/20 [5]
		T	0/21 [0]	0/21 [0]	0/22 [0]	1/32 [3]	2/40 [5]	3/35 [[8]
		total	0/55 [0]	0/55 [0]	0/55 [0]	1/55 [2]	2/55 [4]	4/55 [7]
adrenal ctx	masses	PT	1/34 [3]	0/34 [0]	0/33 [0]	0/32 [0]	1/15 [7]	1/20 [5]
		T	0/21 [0]	1/21 [5]	0/22 [0]	0/32 [0]	1/40 [2]	2/35 [6]
		total	1/55 [2]	1/55 [2]	0/55 [0]	0/55 [0]	2/55 [4]	3/55 [5]
	large	PT	5/34 [15]	4/34 [12]	6/33 [18]	4/23 [17]	5/15 [33]	8/20 [40]
		T	4/21 [19]	6/21 [28]	3/22 [14]	6/32 [19]	13/40 [32]	17/35 [49]
		total	9/55 [16]	10/55 [18]	9/55 [16]	10/55 [18]	18/55 [33]	25/55 [45]
	diffusely dark	PT	0/34 [0]	1/34 [3]	3/33 [9]	4/23 [17]	3/15 [20]	5/20 [25]
		T	2/21 [10]	2/21 [10]	1/22 [5]	3/32 [9]	7/40 [18]	5/35 [14]
		total	2/55 [4]	3/55 [5]	4/55 [7]	7/55 [13]	10/55 [18]	10/55 [18]
pituitary	masses	PT	25/34 [74]	27/34 [79]	22/33 [67]	12/23 [52]	5/15 [33]	1/20 [5]
		T	10/21 [48]	10/21 [48]	7/22 [32]	13/32 [41]	13/40 [32]	8/35 [23]
		total	35/55 [64]	37/55 [67]	29/55 [53]	25/55 [45]	18/55 [33]	9/55 [16]

TISSUE	FINDING	PT/T*	GROUPS					
			C1	C2	LD	MD-1	MD-2	HD
mammary gland	masses	PT	19/34 [56]	17/34 [50]	18/33 [54]	9/23 [39]	5/15 [33]	5/20 [25]
		T	13/21 [62]	12/21 [57]	12/22 [54]	16/32 [50]	19/40 [48]	12/35 [34]
		total	**32/55 [58]**	**29/55 [53]**	**30/55 [54]**	**25/55 [45]**	**24/55 [44]**	**17/55 [31]**
tail	crusted	PT	0/34 [0]	0/34 [0]	1/33 [3]	0/23 [0]	0/15 [0]	2/20 [10]
		T	1/21 [5]	0/21 [0]	0/22 [0]	0/32 [0]	0/40 [0]	5/35 [14]
		total	**1/55 [2]**	**0/55 [0]**	**1/55 [2]**	**0/55 [0]**	**0/55 [0]**	**7/55 [13]**

*PT = premature deaths, T = terminal sacrifice

Histopathology:

Non-neoplastic: selected findings are summarized in the following tables. The sponsor considered the following drug-related: (a) adrenal gland findings [i.e., adrenocortical cell loss in mid/inner cortex (MD-2, HD), diffuse hypertrophy/decreased vacuolation of cortical cells (MD-1, MD-2, HD), presence of lipofuscin pigment (MD-1, MD-2, HD), focal hypertrophy of cells in inner cortex (all doses)], (b) bilateral retinal degeneration [increased incidence and severity at MD-2, HD]. It was noted that the outer nuclear and photoreceptor cell layers were the most severely affected regions, and that "these morphologic features are similar to those seen in light-induced retinopathy". (c) an increase in skeletal muscle atrophy and sciatic nerve degeneration [increased incidence and severity in MD-2M, HDM, MD-1F, MD-2F, HDF], (d) alveolar histiocytosis in lung [increased incidence and severity in MD-1M, MD-2M, HDM and at all doses in F], (e) lipofuscin pigment in "Kupffer cells and macrophages" [increased incidence and severity in MD-2M, HDM, MD-1F, MD-2F, HDF], (f) hemorrhage and pigmented macrophage infiltrates in mesenteric lymph node [HDM]; in females, the "severity of pigmented macrophage infiltration was increased in those given 20, 40, or 60 mg/kg/day, while the incidence of hemorrhage was increased in those given 40 or 60 mg/kg/day only". (g) atrophy of the pituitary gland pars intermedia [all doses], (h) testicular atrophy/degeneration [increased severity] and hypospermia and degeneration of the multinuclear spermatogenic cells of the epididymides at MD-2 and HD [increased incidence, severity not scored]. (i) interstitial cell hyperplasia and lipofuscin pigment in ovary at MD-1, MD-2, and HD [increased severity]. The sponsor summarized these findings in Text Tables 3-10 (provided below).

TISSUE	FINDING	PT/T*	C1	C2	LD	MD-1	MD-2	HD
MALES								
eye	retinal degeneration (bilateral)	PT	0/36	0/37	0/25	0/26	0/21	1/17
		T	0/19	0/18	1/29	0/29	6/33	16/38
		total	**0/55**	**0/55**	**1/54**	**0/55**	**6/54**	**17/55**
	retinal degeneration (unilateral)	PT	0/36	0/37	0/25	0/26	0/21	0/17
		T	0/19	1/18	3/29	3/29	3/33	7/38
		total	**0/55**	**1/55**	**3/54**	**3/55**	**3/54**	**7/55**
brain	mineralization	PT	0/36	0/37	1/26	0/26	0/22	0/17
		T	0/19	1/18	0/29	0/29	0/33	7/38
		total	**0/55**	**1/55**	**1/55**	**0/55**	**0/55**	**7/55**
sciatic nerve	degeneration	PT	12/36	15.37	11/26	13/26	13/22	10/17
		T	17/19	13/17	19/29	10/29	29/33	36/37
		total	**29/55**	**28/54**	**30/55**	**32/55**	**42/55**	**46/55**
skeletal muscle	atrophy	PT	3/36	6/37	1/26	3/26	9/22	7/17
		T	8/19	7/17	7/29	2/29	14/33	23/38
		total	**11/55**	**13/54**	**8/55**	**5/55**	**23/55**	**30/55**
lung	histiocytosis	PT	10/36	17/37	10/26	17/26	18/22	15/17
		T	10/19	7/18	14/29	23/29	32/33	38/38
		total	**20/55**	**24/55**	**24/55**	**40/55**	**50/55**	**53/55**
liver	lipofuscin pigment, Kupffer cells	PT	0/32	5/31	0/20	3/23	2/19	4/14
		T	0/19	6/18	5/29	9/29	22/33	32/38
		total	**0/55**	**11/55**	**5/55**	**12/55**	**24/55**	**36/55**
lymph node, mesenteric	hemorrhage	PT	5/34	7/36	5/26	3/26	5/22	8/17
		T	3/19	3/18	1/29	8/29	10/33	17/37
		total	**8/53**	**11/54**	**6/55**	**11/55**	**15/55**	**25/54**
adrenal cortex	summarized in sponsor's text table 2							
adrenal medulla	hyperplasia	PT	5/35	1/36	5/26	4/26	2/22	2/17
		T	5/19	2/18	3/29	7/29	9/33	3/38
		total	**10/54**	**3/54**	**8/55**	**11/55**	**11/55**	**5/55**
pituitary	atrophy pars intermedia	PT	2/36	0/37	8/26	11/26	17/22	14/17
		T	0/18	0/18	17/29	20/29	30/33	35/38
		total	**2/54**	**0/55**	**25/55**	**31/55**	**47/55**	**49/55**
	hyperplasia	PT	6/36	4/37	5/26	4/26	3/17	1/17
		T	5/18	4/18	14/29	11/29	21/33	21/38
		total	**11/54**	**8/55**	**19/55**	**15/55**	**24/55**	**22/55**
Harderian gland	lymphohistiocytic infiltrate	PT	2/36	8/37	3/26	1/26	4/22	0/17
		T	3/19	3/18	3/29	2/29	9/33	10/38
		total	**5/55**	**11/55**	**6/55**	**3/55**	**13/55**	**10/55**
seminal vesicle	decreased secretion	PT	6/35	4/37	2/26	4/26	2/21	4/17
		T	1/19	1/18	3/29	1/29	6/33	13/38
		total	**7/54**	**5/55**	**5/55**	**5/55**	**8/54**	**17/55**
testis	bilateral atrophy/degeneration	PT	4/35	6/37	0/26	4/26	5/22	15/17
		T	1/19	1/18	2/29	3/29	16/33	36/38
		total	**5/54**	**7/55**	**2/55**	**7/55**	**21/55**	**51/55**
epididymides	multinuclear spermatogenic cell degeneration	PT	4/35	3/37	1/26	3/26	8/22	5/17
		T	2/19	1/18	1/29	5/29	21/33	12/38
		total	**6/54**	**4/55**	**2/55**	**8/55**	**29/55**	**17/55**
	hypospermia	PT	5/35	7/37	2/26	2/26	4/22	14/17
		T	2/19	2/18	5/29	4/29	12/33	33/38
		total	**7/54**	**9/55**	**7/55**	**6/55**	**16/55**	**47/55**

TISSUE	FINDING	PT/T*	C1	C2	LD	MD-1	MD-2	HD
FEMALES								
eye	retinal degeneration (bilateral)	PT	1/34	0/34	0/33	1/23	0/15	8/20
		T	4/21	3/21	5/22	3/32	15/40	33/35
		total	**5/55**	**3/55**	**5/55**	**4/55**	**15/55**	**41/55**
	retinal degeneration (unilateral)	PT	1/34	0/34	3/33	1/23	0/15	0/20
		T	1/21	0/21	1/22	4/32	4/40	0/35
		total	**2/55**	**0/55**	**5/55**	**5/55**	**4/55**	**0/55**
sciatic nerve	degeneration	PT	9/34	6/34	4/33	10/23	6/15	7/20
		T	8/21	15/21	15/22	23/32	33/40	30/34
		total	**17/55**	**21/55**	**19/55**	**33/55**	**39/55**	**37/54**
skeletal muscle	atrophy	PT	4/34	2/34	7/33	6/23	3/15	8/20
		T	4/21	6/21	3/22	15/32	20/40	17/34
		total	**8/55**	**8/55**	**10/55**	**21/55**	**23/55**	**25/54**
lung	histiocytosis	PT	22/34	19/34	27/33	20/23	15/15	14/20
		T	15/21	11/21	19/22	29/32	40/40	35/35
		total	**37/55**	**30/55**	**46/55**	**49/55**	**55/55**	**49/55**
liver	lipofuscin pigment, Kupffer cells	PT	8/34	7/34	7/33	8/23	1/15	2/20
		T	6/21	4/21	6/22	23/32	33/40	28/35
		total	**14/55**	**11/55**	**13/55**	**31/55**	**34/55**	**30/55**
	bile duct hyperplasia	PT	5/34	14/34	11/33	4/23	3/15	3/20
		T	12/21	9/21	11/22	14/32	16/40	29/35
		total	**17/55**	**23/55**	**22/55**	**18/55**	**19/55**	**32/55**
thymus	necrosis	PT	0/33	1/32	2/33	1/22	1/14	6/19
		T	0/21	0/20	0/20	0/32	0/39	0/35
		total	**0/54**	**1/52**	**2/53**	**1/54**	**1/53**	**6/54**
lymph node, mesenteric	hemorrhage	PT	3/34	3/34	4/33	5/23	7/15	9/20
		T	5/21	7/20	9/22	6/32	22/40	26/35
		total	**8/55**	**10/54**	**13/55**	**11/55**	**29/55**	**35/55**
adrenal cortex	summarized in sponsor's text table 2							
adrenal medulla	hyperplasia	PT	1/34	5/34	1/31	1/23	0/15	1/20
		T	4/21	2/19	4/22	6/32	4/40	15/32
		total	**5/55**	**7/53**	**5/53**	**7/55**	**4/55**	**16/52**
pituitary	atrophy pars intermedia	PT	9/34	10/34	11/33	13/23	8/15	12/20
		T	8/32	5/21	13/22	18/32	30/40	28/35
		total	17/55	**15/55**	**24/55**	**31/55**	**38/55**	**40/55**
	hyperplasia	PT	1/34	1/34	3/33	2/23	3/15	4/20
		T	1/21	3/21	2/22	2/32	4/30	6/35
		total	**2/55**	**4/55**	**5/55**	**4/55**	**8/55**	**10/55**

Text Table 3
Eye - Test Material-Related Finding

	BMS-337039 (mg/kg/day)											
	0	0	10	20	40	60	0	0	10	20	40	60
	Males						Females					
Number examined	55	55	54	55	54	55	55	55	55	55	55	55
Eye												
Degeneration, Retinal, Bilateral												
Unremarkable	55	55	53	55	48	38	50	52	50	51	40	14
Minimal	0	0	1	0	4	4	2	0	2	2	4	7
Slight	0	0	0	0	0	5	1	2	3	0	5	10
Moderate	0	0	0	0	2	8	2	1	0	2	6	24

Text Table 4
Skeletal Muscle and Sciatic Nerve - Test Material-Related Findings

	BMS-337039 (mg/kg/day)											
	0	0	10	20	40	60	0	0	10	20	40	60
	Males						Females					
Number examined	55	54	55	55	55	55	55	55	55	55	55	54
Muscle, Skeletal Atrophy												
Unremarkable	44	41	47	50	32	25	47	47	45	34	32	29
Minimal	3	5	5	4	16	13	8	8	8	14	17	18
Slight	6	6	3	1	5	14	0	0	1	6	6	5
Moderate	1	1	0	0	2	3	0	0	1	1	0	2
Moderately-severe	1	1	0	0	0	0	0	0	0	0	0	0
Number examined	55	54	55	55	55	54	55	55	55	55	55	54
Nerve, Sciatic Degeneration												
Unremarkable	26	26	25	23	13	8	38	34	36	22	16	17
Minimal	24	19	28	31	29	22	15	18	18	30	30	17
Slight	4	6	1	1	13	16	2	3	1	2	9	18
Moderate	1	3	1	0	0	8	0	0	0	1	0	2

Text Table 5
Lung - Test Material-Related Finding

	BMS-337039 (mg/kg/day)											
	0	0	10	20	40	60	0	0	10	20	40	60
	Males						Females					
Number examined	55	55	55	55	55	55	55	55	55	55	55	55
Lung Histiocytosis												
Unremarkable	35	31	31	15	5	2	18	25	9	6	0	6
Minimal	19	19	22	33	10	4	31	23	31	18	2	0
Slight	1	5	2	7	24	13	6	7	10	20	7	1
Moderate	0	0	0	0	13	22	0	0	5	10	15	13
Moderately-severe	0	0	0	0	3	10	0	0	0	0	31	35
Severe	0	0	0	0	0	4	0	0	0	1	0	0

Text Table 6
Liver - Test Material-Related Finding

	BMS-337039 (mg/kg/day)											
	0	0	10	20	40	60	0	0	10	20	40	60
	Males						Females					
Number examined	55	55	55	55	55	55	55	55	55	55	55	55
Liver Pigment, Lipofuscin, Kupffer Cell/Macrophage												
Unremarkable	55	44	50	43	31	19	41	44	42	24	21	25
Minimal	0	9	5	11	20	25	10	9	11	24	20	14
Slight	0	2	0	1	4	11	4	2	2	7	10	11
Moderate	0	0	0	0	0	0	0	0	0	0	4	5

Text Table 7
Mesenteric Lymph Node - Test Material-Related Findings

	BMS-337039 (mg/kg/day)											
	0	0	10	20	40	60	0	0	10	20	40	60
	Males						Females					
Number examined	53	54	55	55	55	54	55	54	55	55	55	55
Lymph Node, Mesenteric Infiltrate, Macrophage, Pigmented												
Unremarkable	13	16	26	23	15	17	0	1	0	1	0	5
Minimal	23	16	8	17	5	2	26	34	26	8	2	5
Slight	14	22	21	9	20	6	19	17	23	21	10	4
Moderate	3	0	0	6	15	25	10	2	6	23	26	23
Moderately-severe	0	0	0	0	0	4	0	0	0	2	17	18
Hemorrhage												
Not Present	45	43	49	44	40	29	47	44	42	44	26	20
Present	8	11	6	11	15	25	8	10	13	11	29	35

Text Table 8
Pituitary - Test Material-Related Finding

	BMS-337039 (mg/kg/day)											
	0	0	10	20	40	60	0	0	10	20	40	60
	Males						Females					
Number of Pars Intermedia examined	41	29	41	38	49	50	32	29	29	37	39	47
Pituitary												
Atrophy, Pars Intermedia												
Unremarkable	39	29	16	7	2	1	15	14	5	6	1	7
Minimal	1	0	17	26	23	16	12	10	8	8	11	5
Slight	1	0	8	5	22	29	4	5	13	12	16	12
Moderate	0	0	0	0	2	4	1	0	3	8	9	17
Moderately-severe	0	0	0	0	0	0	0	0	0	2	2	4
Severe	0	0	0	0	0	0	0	0	0	1	0	2

Text Table 9
Testes/Epididymides - Test Material-Related Findings

	BMS-337039 (mg/kg/day)					
	0	0	10	20	40	60
	Males					
Number examined	54	55	55	55	55	55
Testes						
Atrophy/Degeneration, Bilateral						
Unremarkable	49	48	53	48	34	4
Minimal	0	1	0	2	8	5
Slight	1	1	1	3	5	1
Moderate	2	1	0	1	2	6
Moderately-severe	0	1	1	1	4	3
Severe	2	3	0	0	2	36
Number examined	54	55	55	55	55	55
Epididymides						
Hypospermia						
Not Present	47	46	48	49	39	8
Present	7	9	7	6	16	47
Degenerate/Multinuclear Spermatogenic Cells						
Not Present	48	51	53	47	26	38
Present	6	4	2	8	29	17

Text Table 10
Ovary - Test Material-Related Findings

	BMS-337039 (mg/kg/day)					
	0	0	10	20	40	60
	Females					
Number examined	55	55	55	54	55	55
Ovary						
Hyperplasia, Interstitial Cell						
Unremarkable	7	5	4	1	1	6
Minimal	14	11	14	6	4	3
Slight	19	16	17	10	13	10
Moderate	14	22	16	29	29	21
Moderately-severe	1	1	4	8	7	13
Severe	0	0	0	0	1	2
Pigment, Lipofuscin						
Unremarkable	4	2	0	1	2	5
Minimal	49	51	51	37	13	0
Slight	2	2	4	16	28	14
Moderate	0	0	0	0	11	20
Moderately-severe	0	0	0	0	1	16

Other findings [e.g., in M: reduced incidence/severity of chronic progressive nephropathy, thymic lymphocytic depletion, ventral compression and ventricular dilatation in brain, prostatic inflammation, decreased seminal vesicle secretory

- material and increased splenic extramedullary hematopoiesis; in F: reduced incidence/severity of renal pelvis findings (mineralization, suppurative inflammation, transitional cell hyperplasia), ventral compression and ventricular dilatation in brain, thyroid C-cell hyperplasia, galactoceles in mammary gland, hepatocellular vacuolation] were considered secondary to the drug-related body wt effect.

Neoplastic: selected findings are summarized in the following table. The sponsor considered the adrenal gland tumors [i.e., adrenocortical carcinomas and combined adrenocortical tumors (adenomas, carcinomas) in HDF] the only drug-related effect. [The incidence of adrenocortical tumors were not statistically significant at the MD-2 when the HD data were removed from the sponsor's analyses.] The incidence of pheochromocytoma in M was not significantly increased (according to the sponsor's analyses), and was considered secondary to increased survival at the HD. Decreases in incidence/severity of pituitary adenoma [M,F], C-cell adenomas [F], and mammary tumors [F] were considered secondary to drug-related effects on body wt.

TISSUE	FINDING	PT/T*	C1	C2	LD	MD-1	MD-2	HD
MALES								
adrenal medulla	pheochromocytoma (B)	PT	1/35	1/36	2/26	2/26	3/22	2/17
		T	5/19	4/18	4/29	4/29	7/33	13/38
		total	**6/54**	**5/54**	**6/55**	**6/55**	**10/55**	**15/55**
	pheochromocytoma (M)	PT	1/35	1/36	0/26	0/26	0/22	0/17
		T	0/19	1/18	0/29	0/29	0/33	4/38
		total	**1/54**	**2/54**	**0/55**	**0/55**	**0/55**	**4/55**
FEMALE								
adrenal cortex	adenoma	PT	2/34	1/34	1/33	1/23	1/15	1/20
		T	0/21	2/21	0/22	2/32	3/40	5/35
		total	**2/55**	**3/55**	**1/55**	**3/55**	**4/55**	**6/55**
	carcinoma	PT	0/34	0/34	0/33	0/23	1/15	2/20
		T	0/21	0/21	0/22	0/32	1/40	4/35
		total	**0/55**	**0/55**	**0/55**	**0/55**	**2/55**	**6/55**
adrenal medulla	pheochromocytoma (B)	PT	1/34	0/34	2/31	2/23	0/15	0/20
		T	1/21	1/19	2/22	2/32	2/40	5/32
		total	**2/55**	**1/53**	**4/53**	**4/55**	**2/55**	**5/52**

*PT = premature deaths, T = terminal sacrifice

[The incidence of pheochromocytoma was not significantly increased in males when benign and malignant tumors were combined: 7/54, 7/54, 6/55, 10/55, and 16/55 in C1, C2, LD, MD-1, MD-2, and HD, respectively. The sponsor attributed the increased trend to the positive trend in survival rate.]

- The sponsor summarized the nonneoplastic and neoplastic adrenal gland findings in the following (sponsor's) table:

Text Table 2
Adrenal Gland - Selected Microscopic Findings

	BMS-337039 (mg/kg/day)											
	0	0	10	20	40	60	0	0	10	20	40	60
	Males						Females					
Number examined	54	55	55	55	55	55	55	55	55	55	55	55
Adrenal Cortex												
Adenoma												
Present	3	2	2	1	3	2	2	3	1	3	4	6
Carcinoma												
Present	2	0	0	0	0	2	0	0	0	0	2	6
Adenoma and Carcinoma, Combined												
Present	5	2	2	1	3	4	2	3	1	3	4[a]	12
Cortical Cell Loss, Mid/Inner Cortex												
Unremarkable	54	55	55	55	44	31	55	55	55	55	42	16
Minimal	0	0	0	0	5	5	0	0	0	0	3	6
Slight	0	0	0	0	4	9	0	0	0	0	2	8
Moderate	0	0	0	0	1	8	0	0	0	0	5	15
Moderately-severe	0	0	0	0	0	2	0	0	0	0	3	9
Severe	0	0	0	0	1	0	0	0	0	0	0	1
Hypertrophy/Decreased Vacuolation, Diffuse												
Unremarkable	54	55	53	45	23	20	55	55	54	48	23	29
Minimal	0	0	2	6	14	8	0	0	1	7	30	22
Slight	0	0	0	4	16	24	0	0	0	0	2	4
Moderate	0	0	0	0	2	3	0	0	0	0	0	0
Pigment, Lipofuscin												
Unremarkable	13	12	15	8	3	3	0	3	3	1	0	5
Minimal	33	36	29	20	4	0	19	19	18	8	0	0
Slight	8	7	11	27	21	6	29	29	32	27	5	2
Moderate	0	0	0	0	26	35	7	4	2	19	13	2
Moderately-severe	0	0	0	0	1	11	0	0	0	0	19	11
Severe	0	0	0	0	0	0	0	0	0	0	18	35
Hypertrophy, Focal, Inner Cortex												
Unremarkable	52	53	48	38	53	53	52	54	48	38	27	31
Minimal	2	2	4	8	0	1	3	0	6	13	19	8
Slight	0	0	3	9	0	0	0	1	1	4	7	6
Moderate	0	0	0	0	0	0	0	0	0	0	2	9
Moderately-severe	0	0	0	0	2	1	0	0	0	0	0	1

[a] Two animals had both tumor types (adrenocortical adenoma and carcinoma).

Additional analyses [Immunohistochemical and TUNEL analyses of adrenocortical findings]: these data were generated by the sponsor [Bristol-Myers Squibb] and were not collected under GLP.

According to the report,

> "The adrenocortical proliferation index was determined by counting the number of K_I-67 immunopositive cells along the interface of the zona glomerulosa and zona fasciculata. This region was selected for quantitation because it represents the primary region of normal adrenocortical mitotic activity."

Upon qualitative assessment of apoptosis, it was decided not to quantitate apoptosis since "...TUNEL immunostained sections revealed rare apoptotic adrenocortical epithelial cells in rats from all groups, including controls".