Additionally, time to onset of mammary gland tumors in females revealed that these tumors tended to occur earlier in the high-dose group than in the control group (Peto's onset rate method).

2.2 Reviewer's Findings for Study 009489

The intercurrent mortality among the female rats of this study showed a few more animals dying in the mid- and high dose groups than in the controls, but not to a statistically significant degree (p=0.2378, Tables 1-2, Figure 1). There was a statistically significant increase in fibroadenomas of the mammary gland (p=0.002 vs. α=0.005, Table 3).

Among the males, there was a lack of difference between the mortality experience of the various dose groups (p=0.9028, Tables 4-5, Figure 2)). No individual tumor finding reached statistical significance (Table 6).

2.3 Validity of the Male Rats of Study 009489

As there were no statistically significant tumor trends among the male rats in this study, its validity needs to be assessed. Two criteria are set up for this purpose (Haseman[12], Chu et al.[3], and Bart et al.[4]):

i) was a sufficient number of animals exposed long enough to allow for late-developing tumors, and

ii) did the high dose provide a sufficient tumor challenge?

The number of animals and length of exposure can be assessed at weeks 52, 80-90, and at termination, but are generally considered satisfied if 20-30 animals survive through weeks 80-90. Only seven high dose males had died by week 91 and 80% lived to terminal sacrifice, easily satisfying this criterion. The high dose is expected to be close to the MTD to present a sufficient tumor challenge. Suppression in survival when compared to the controls and/or average body weight differences of about 10 percent, especially during the first year of treatment, are indicators that the high dose is close to the MTD. For this study, the mortality pattern of the high dose group did not distinguish itself from the other groups, including the controls. The sponsor reported average body weight data being 3-8 percent lower for the high-dose males than the controls for most of the study, which suggests that the high dose was close to the MTD. Therefore, the long-term administration of aripiprazole to male rats can be considered a valid study.

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[1] Haseman: Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, *Environmental Health Perspectives*, Vol. 58, pp 385-392, 1984.

[2] Haseman: Issues in Carcinogenicity Testing: Dose Selection, *Fundamental and Applied Toxicology*, Vol. 5, pp. 66-78, 1985.

[3] Chu, Cueto, Ward: Factors in the Evaluation of 200 National Cancer Institute Carcinogenicity Bioassays, *Journal of Toxicology and Environmental Health*, Vol. 8, pp 251-280, 1981.

[4] Bart, Chu, Tarone: Statistical Issues in Interpretation of Chronic Bioassay Tests for Carcinogenicity, *Journal of the National Cancer Institute*, pp. 957-974, 1979.

3.0 BMS Study No. 99321 in Rats

Crl:CD®(SD)IGS BR rats were assigned randomly to groups receiving either the vehicle (two groups) or aripiprazole at doses of 10, 20, 40, and 60 mg/kg/day via gavage for two years. Group size was 55 per gender. Implanted microchip identification devices held the permanent identification number. Animals were housed individually and water and food was available ad lib. All tissues were microscopically examined from each animal. Mortality data were evaluated using a two-sided Cox-Tarone test for trend. Differences in non-palpable tumor rates were analyzed using the method of Peto and Pike[5]. The two control groups were pooled for these analyses. Palpable tumors were analyzed by the Cox-Tarone binary regression method using the first palpation time as onset time. Levels of significance were set at p-values of 0.005 and 0.025 for common and rare tumors, respectively.

3.1 Sponsor's Findings for Study 99321

The sponsor observed dose-dependent increases in survival for each gender, though five maximum dose females could not tolerate the dosing during week one and were found dead or euthanatized moribund.

Dose Group (mg/kg/day)	Males	Females
0	34/55 (62%)	33/55 (60%)
0	36/55 (65%)	34/55 (62%)
10	26/55 (47%)	33/55 (60%)
20	26/55 (47%)	23/55 (42%)
40	22/55 (40%)	15/55 (27%)
60	17/55 (31%)	20/55 (36%)

Average bodyweights were decreased in a dose-dependent way for males (9-44% at week 102). Low dose females experienced no effect on bodyweight. Mid-, high-, and maximum-dose females had average bodyweights 17-41% lower than controls at week 102.

Among the females, adrenocortical carcinoma and combined adrenocortical adenomas and carcinomas showed a statistically significant trend. The trend excluding the maximum dose was not statistically significant and the two carcinomas in the 40 mg/kg dose were considered not to be clearly drug related. The maximum dose was considered to markedly exceed the MTD. No other statistically significant positive trends in tumors were observed in either gender.

[5] Peto et al.: Guidelines for simple sensitive significance tests for carcinogenic effects in long-term animal experiments. In: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 2: Long-term and Short-term Screening Assays for Carcinogens: A Critical Appraisal, Lyon, International Agency for Research on Cancer, 1980: 311-346.

3.2 Reviewer's Findings for Study 99321

The intercurrent mortality for the female rats in this study was extremely statistically significant (p=0.0000, Tables 7-8), but in the direction of better survival with dose. The significant lack of homogeneity indicates that the separation among the survival curves does not strictly follow the increasing doses. The Kaplan-Meier graphs make visually apparent what these p-values convey (Figure 3). Among the tumor findings, malignant carcinoma of the adrenal cortex was highly statistically significant (p=0.0001 vs. α=0.025, Table 9). Combining carcinomas and adenomas of the adrenal cortex resulted in a significant p-value of 0.0002 (based on the asymptotic test due to tumors being both incidental and fatal).

The male rats of this study had similar mortality experience as the female rats, in that the treated animals experienced significantly better survival than the controls (p=0.0000, Tables 10-11). The significant p-value for homogeneity indicates that the survival curves crossed occasionally, but, in general, survival increased with dose. The Kaplan-Meier curves bear out these observations (Figure 4). Among the tumor findings, none reached statistical significance among the male rats (combining benign and malignant pheochromocytoma of the adrenal, medullar, resulted in a p-value of 0.0334, which is not close to statistical significance for common tumors).

3.3 Validity of Male Rat Study 99321

The same criteria as noted above to evaluate the male rat study of Study 009489 are being applied to the male rats of Study 99321, as no statistically significant increase in tumors were observed. Survival was excellent for all groups and the number of animals living long enough is not an issue. Survival was better for the treated than for the control groups. Average bodyweight for the maximum dose animals was 44 % lower than the controls' at week 102. By week 2 of the study, an 18.5% lower average body weight was observed for the maximum dose, and the difference steadily increased. This would indicate as the sponsor had noted, that the maximum dose exceeded the MTD. As there is another valid study in male rats available (Study No. 009489), no further investigation of this study was done (e.g. excluding the top dose and evaluating the remaining data as a potentially valid study).

4.0 Summary -

The following table summarizes the major statistically significant findings of the two rat studies.

	Otsuka Study 009489		BMS Study 99321	
	Females	Males	Females	Males
Survival	NS	NS	Sign. increased	Sign. increased
Mammary Gland, Fibroadenoma	Sign. increased	NS	NS	NS
Adrenal Cortex, Carcinoma	NS	NS	Sign. increased	NS
Validity	N/A	Yes	N/A	MTD exceeded

Otsuka Study 009489 used doses of 0, 1, 3, and 10 mg/kg/day in the diet. Survival was not affected by treatment and the only statistically significant tumor finding were fibroadenomas of the mammary gland among female rats. Among the males, no increase in tumor incidence reached statistical significance, but the study was considered valid based on length of exposure and number of animals available at study end. The high dose was judged to be close to the MTD due to the suppressed average body weights of 3-8 %.

In BMS Study 99321 doses of 10, 20, 40, and 60 mg/kg/day were administered via gavage. Two identical vehicle controls were also available. For either gender, survival was much better for the treated that the control groups. The only statistically significant tumor finding were carcinoma of the adrenal cortex, and carcinoma and adenoma of the adrenal cortex combined. The males showed no statistically significant increase in tumors. The length of exposure and the number of animals available at study end were satisfactory. However, the high average body weight suppression of the top dose compared to the controls suggested that this dose far exceeded the MTD.

The summary results for the two mice studies are given as well:

MICE	Otsuka Study 011487		Otsuka Study 011932	
	Females	Males	Females	Males
Survival	NS	Sign. increased	Sign. decreased	Sign. increased
Anterior Pituitary, Adenoma	Sign. increased	NS	Sign. increased	NS
Mammary Gland, Adenocarcinoma	Sign. increased	NS	Sign. increased	NS
Mammary Gland, Adenoacanthoma	Sign. increased	NS	Sign. increased	NS
Validity	N/A	Yes	N/A	Yes

Overall, it appears that the administration of aripiprazole in the doses given results in increased tumor findings in female rats or mice. The p-values in each case are highly statistically significant. No increase in tumor incidence rates was observed among the males of any of the studies. All but one of these male studies were judged to be valid. The maximum dose in Study No. 99321 was judged to be well beyond the MTD, based on much lower average body weights of these animals compared to the controls.

Table 1: Number of Deaths per Time interval for Female Rats in Study 009489

	Treatment Group				Total
	CTRL	LOW	MED	HIGH	
	N	N	N	N	N
Week					
53-78	.	1	2	1	4
79-91	3	2	4	1	10
92-103	3	4	7	9	23
104-104	44	43	37	39	163
Total	50	50	50	50	200

Table 2: Dose Mortality Trend Test* for Female Rats in Study 009489

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.39	0.2378
	Depart from Trend	2.87	0.2384
	Homogeneity	4.26	0.2346
Kruskal-Wallis	Dose-Mortality Trend	1.29	0.2562
	Depart from Trend	2.88	0.2368
	Homogeneity	4.17	0.2437

* Program used: Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute.

Figure 1: Kaplan-Meier Survival Curves for Female Rats in Study 009489

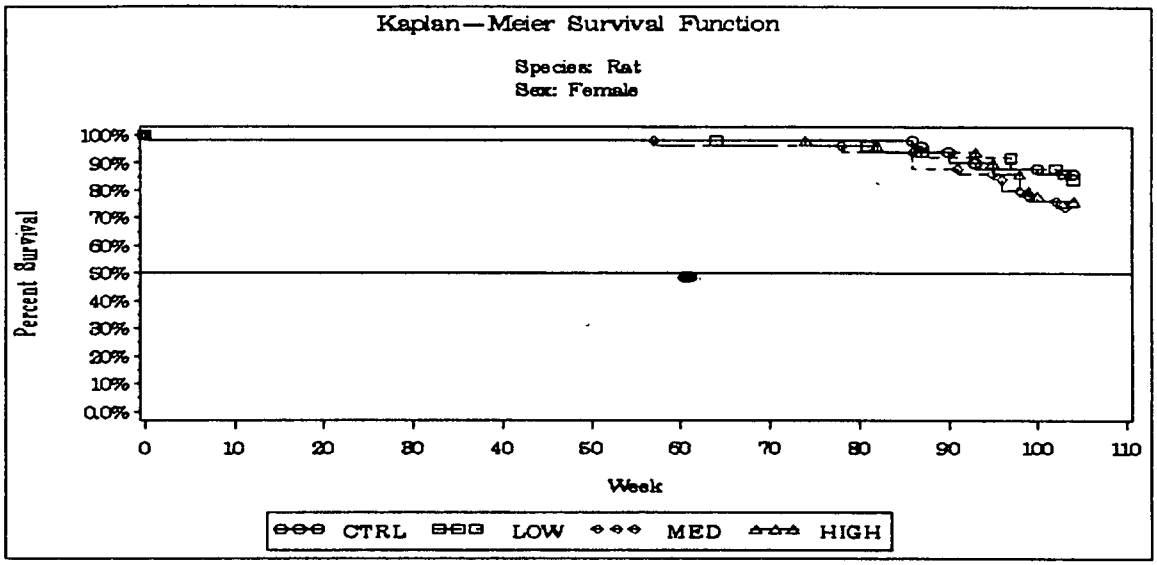

Table 3: Tumor Trend Tests for Female Rats in Study 009489

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL	LOW	MED	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
Lung	18	Adenoma (Lung)	1835	2%	1	1	1	1	IN	0.4750	0.4922
Lung	18	Adenocarcinoma (Lung)	1865	2%	1	0	1	1	IN	0.4593	0.4521
Liver	34	Cholangiocarcinoma (Liver	3467	.0%	0	0	1	0	IN	0.4663	0.5853
Pancreas	37	Islet cell adenoma (Pancr	3736	.0%	0	0	1	2	IN	0.0516	0.0309
Kidney	38	Adenoma (Kidney)	3835	.0%	0	0	1	0	IN	0.4663	0.5853
Kidney	38	Liposarcoma (Kidney)	3871	.0%	0	0	1	0	FA	0.4888	0.5999
Ovary	52	Granulosa cell tumor (Ova	5232	2%	1	0	1	0	IN	0.7167	0.7770
Uterus	54	Endometrial stromal polyp	5431	12%	6	8	6	1	IN	0.9892	0.9843
Uterus	54	Hemangioma (Uterus)	5442	4%	2	0	0	0	MX	1.0000	0.9085
Clitoral gland	58	Adenoma (Clitoral gland)	5835	4%	2	3	2	5	IN	0.1074	0.1008

Clitoral gland	58	Adenocarcinoma (Clitoral	5865	2%	1	2	0	3	MX	0.1390	0.1195
Pituitary	59	Anterior adenoma (Pituita	5935	50%	25	25	33	32	MX	0.0335	0.0330
Pituitary	59	Anterior adenocarcinoma (	5965	2%	1	0	2	0	FA	0.6548	0.7503
Thyroid	60	C-cell adenoma (Thyroid)	6036	6%	3	2	7	4	IN	0.2438	0.2467
Thyroid	60	C-cell carcinoma (Thyroid	6066	2%	1	3	1	3	IN	0.2105	0.2065
Adrenal	62	Pheochromocytoma (Adrenal	6239	2%	1	4	0	2	IN	0.4892	0.4945
Adrenal	62	Malignant pheochromocytom	6269	.0%	0	2	0	0	IN	0.7850	0.8276
Ear	84	Zymbal's gland carcinoma	8465	2%	1	1	0	0	IN	0.9283	0.8702
Auricle	85	Schwannoma (Auricle)	8550	.0%	0	0	0	1	IN	0.2393	0.0564
Auricle	85	Malignant schwannoma (Aur	8580	.0%	0	0	1	0	FA	0.4889	0.5986
Skin	86	Papilloma (Skin)	8631	2%	1	0	1	1	IN	0.3564	0.3550
Skin	86	Malignant schwannoma (Ski	8680	2%	1	0	0	0	FA	1.0000	0.8471
Mammary gland	95	Adenoma (Mammary gland)	9535	2%	1	3	2	1	IN	0.6872	0.7187
Mammary gland	95	Fibroadenoma (Mammary gla	9539	12%	6	9	8	17	IN	0.0020	0.0015
Mammary gland	95	Fibroma (Mammary gland)	9540	.0%	0	1	0	2	IN	0.0966	0.0584
Mammary gland	95	Adenocarcinoma (Mammary g	9565	2%	1	1	2	1	IN	0.5897	0.6204
Abdominal cavity	98	Paraganglioma (Abdominal	9831	.0%	0	1	0	0	FA	0.7381	0.7664
Abdominal cavity	98	Malignant mesothelioma (A	9886	.0%	0	0	0	1	FA	0.2528	0.0633
General	99	Malignant lymphoma (Gener	9989	.0%	0	0	1	1	MX	0.1764	0.1520
General	99	Mononuclear cell leukemia	9993	12%	6	6	6	7	MX	0.3225	0.3298

Table 4: Number of Deaths per Timer Interval for Male Rats in Study 009489

	Treatment Group				Total
	CTRL	LOW	MED	HIGH	
	N	N	N	N	N
Week 53-78	2	1	1	2	6
79-91	3	2	2	5	12
92-103	7	4	5	3	19
104-104	38	43	42	40	163
Total	50	50	50	50	200

Table 5: Dose Mortality Trend * Test for Male Rats in Study 009489

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.01	0.9028
	Depart from Trend	1.90	0.3874
	Homogeneity	1.91	0.5910
Kruskal-Wallis	Dose-Mortality Trend	0.03	0.8642
	Depart from Trend	1.85	0.3958
	Homogeneity	1.88	0.5971

Figure 2: Kaplan Meier Survival Curves for Male Rats in Study 009489

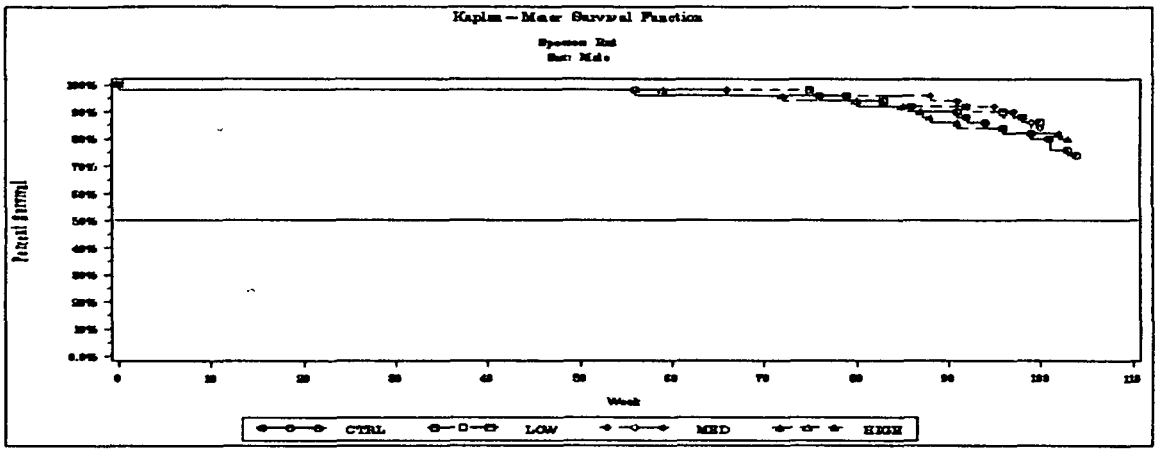

Table 6: Tumor Trend Tests for Male Rats in Study 009489

Organ Code	Organ Name	Tumor Code	Tumor Name	CTRL	LOW	MED	HIGH	pValue (Exact)	pValue (Asymp)	Natural Tumor # in control group	Natural Rate (in ctrl group)	Tumor type
03	Bone marrow(femur)	0342	Hemangioma (Bone marrow)	0	0	1	0	0.5031	0.6012	0	.0%	IN
03	Bone marrow(femur)	0354	Histiocytoma (Bone marrow	1	1	1	0	0.8379	0.8527	1	2%	IN
04	Bone marrow(sternum)	0354	Histiocytoma (Bone marrow	1	1	1	0	0.8379	0.8527	1	2%	IN
05	Bone marrow(vertebra)	0354	Histiocytoma (Bone marrow	1	1	1	0	0.8379	0.8527	1	2%	IN
07	Thymus	0740	Thymoma (Thymus)	0	0	2	0	0.4969	0.6072	0	.0%	IN
13	Spleen	1372	Hemangiosarcoma (Spleen)	0	0	2	0	0.4969	0.6072	0	.0%	IN
18	Lung	1835	Adenoma (Lung)	2	1	4	4	0.1298	0.1280	2	4%	IN
18	Lung	1865	Adenocarcinoma (Lung)	1	1	1	2	0.2580	0.2393	1	2%	IN
31	Small intestine	3165	Adenocarcinoma (Small int	0	1	1	0	0.6337	0.7386	0	.0%	IN

31	Small intestine	3176	Leiomyosarcoma (Small int	0	0	1	0	0.5031	0.6012	0	.0%	IN
34	Liver	3465	Hepatocellular carcinoma	1	0	0	0	1.0000	0.8491	1	2%	IN
37	Pancreas	3735	Acinar cell adenoma (Panc	0	0	1	0	0.5031	0.6012	0	.0%	IN
37	Pancreas	3736	Islet cell adenoma (Pancr	3	2	1	1	0.8189	0.8183	3	6%	IN
38	Kidney	3865	Adenocarcinoma (Kidney)	0	0	1	0	0.5027	0.5969	0	.0%	FA
41	Urinary bladder	4131	Papilloma (Urinary bladde	0	0	1	0	0.4211	0.5092	0	.0%	IN
43	Testis	4337	Interstitial cell tumor (	42	41	46	18	1.0000	1.0000	42	84%	IN
48	Prostate	4835	Adenoma (Prostate)	2	2	1	0	0.9391	0.9244	2	4%	IN
50	Preputial gland	5035	Adenoma (Preputial gland)	1	2	2	1	0.5828	0.6293	1	2%	MX
50	Preputial gland	5065	Adenocarcinoma (Preputial	1	3	2	1	0.6925	0.7229	1	2%	IN
59	Pituitary	5935	Anterior adenoma (Pituita	21	21	14	6	0.9999	0.9997	21	42%	MX
59	Pituitary	5936	Adenoma in intermediate p	0	0	1	0	0.5062	0.6025	0	.0%	IN
60	Thyroid	6036	C-cell adenoma (Thyroid)	10	8	6	8	0.5696	0.5776	10	20%	IN
60	Thyroid	6066	C-cell carcinoma (Thyroid	2	2	3	1	0.7337	0.7563	2	4%	IN
62	Adrenal	6239	Pheochromocytoma (Adrenal	2	3	5	1	0.7839	0.7904	2	4%	IN
62	Adrenal	6268	Malignant ganglioneuroma	0	0	0	1	0.2513	0.0629	0	.0%	FA
62	Adrenal	6269	Malignant pheochromocytom	1	0	2	0	0.6875	0.7726	1	2%	IN
75	Bone(others)	7278	Osteosarcoma (Bone)	0	0	1	0	0.5031	0.6012	0	.0%	IN
79	Skeletal muscle(others)	7977	Rhabdomyosarcoma (Skeleta	0	1	0	0	0.7500	0.8339	0	.0%	IN
85	Auricle	8550	Schwannoma (Auricle)	0	2	0	2	0.1874	0.1621	0	.0%	MX
85	Auricle	8580	Malignant schwannoma (Aur	0	0	1	0	0.5031	0.6012	0	.0%	IN
86	Skin	8631	Papilloma (Skin)	1	3	1	0	0.9216	0.9193	1	2%	IN
86	Skin	8632	Keratoacanthoma (Skin)	1	2	3	2	0.3483	0.3712	1	2%	IN

86	Skin	8633	Trichoepithelioma (Skin)	1	0	0	1	0.4317	0.3220	1	2%	IN
86	Skin	8640	Fibroma (Skin)	8	4	5	3	0.9123	0.9093	8	16%	IN
86	Skin	8641	Lipoma (Skin)	2	0	1	0	0.8970	0.8846	2	4%	IN
86	Skin	8643	Hemangiopericytoma (Skin)	1	0	0	0	1.0000	0.8472	1	2%	FA
86	Skin	8644	Hemangioleiomyoma (Skin)	0	0	0	1	0.2454	0.0600	0	.0%	IN
86	Skin	8650	Schwannoma (Skin)	0	1	0	0	0.7669	0.7805	0	.0%	IN
86	Skin	8660	Squamous cell carcinoma (	0	1	0	0	0.7527	0.7751	0	.0%	FA
86	Skin	8661	Basal cell carcinoma (Ski	0	1	0	0	0.7526	0.7786	0	.0%	FA
86	Skin	8672	Hemangiosarcoma (Skin)	2	0	0	0	1.0000	0.9129	2	4%	FA
95	Mammary gland	9539	Fibroadenoma (Mammary gla	1	3	1	0	0.9066	0.9076	1	2%	IN
95	Mammary gland	9540	Fibroma (Mammary gland)	1	0	2	0	0.6911	0.7754	1	2%	IN
95	Mammary gland	9565	Adenocarcinoma (Mammary g	1	0	0	0	1.0000	0.8503	1	2%	IN
98	Abdominal cavity	9841	Lipoma (Abdominal cavity)	0	0	1	0	0.5031	0.6012	0	.0%	IN
98	Abdominal cavity	9842	Hemangioma (Abdominal cav	1	0	0	0	1.0000	0.8479	1	2%	FA
98	Abdominal cavity	9886	Malignant mesothelioma (A	0	0	1	0	0.5000	0.5985	0	.0%	FA
99	General	9989	Malignant lymphoma (Gener	0	0	0	1	0.2487	0.0617	0	.0%	FA
99	General	9993	Mononuclear cell leukemia	5	3	2	6	0.1971	0.1980	5	10%	MX

Table 7: Number of Deaths per Time Interval for Female Rats in Study 99321

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR1	0-52	55	1	54	98.2	1.8
	53-78	54	10	44	80.0	20.0
	79-91	44	5	39	70.9	29.1
	92-104	39	17	22	40.0	60.0
	FINALKILL105-106	22	22	0		
CTR2	0-52	55	3	52	94.5	5.5
	53-78	52	12	40	72.7	27.3
	79-91	40	12	28	50.9	49.1
	92-104	28	7	21	38.2	61.8
	FINALKILL105-106	21	21	0		
LOW	0-52	55	1	54	98.2	1.8
	53-78	54	9	45	81.8	18.2
	79-91	45	12	33	60.0	40.0
	92-104	33	11	22	40.0	60.0
	FINALKILL105-106	22	22	0		
MED	53-78	55	5	50	90.9	9.1
	79-91	50	5	45	81.8	18.2
	92-104	45	13	32	58.2	41.8
	FINALKILL105-106	32	32	0		
HIGH	0-52	55	1	54	98.2	1.8
	53-78	54	5	49	89.1	10.9
	79-91	49	5	44	80.0	20.0
	92-104	44	4	40	72.7	27.3
	FINALKILL105-106	40	40	0		
MAX	0-52	55	5	50	90.9	9.1
	53-78	50	3	47	85.5	14.5
	79-91	47	3	44	80.0	20.0
	92-104	44	9	35	63.6	36.4
	FINALKILL105-106	35	35	0		

Table 8: Dose Mortality Trend Test for Female Rats in Study 99321

Dose-Mortality Trend Tests

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	7.8514	0.0972	8.9348	0.0628
Dose-Mortality Trend	17.8748	0.0000	16.4303	0.0001
Homogeneity	25.7262	0.0001	25.3651	0.0001

Figure 3: Kaplan Meier Curves for Female Rats in Study 00321

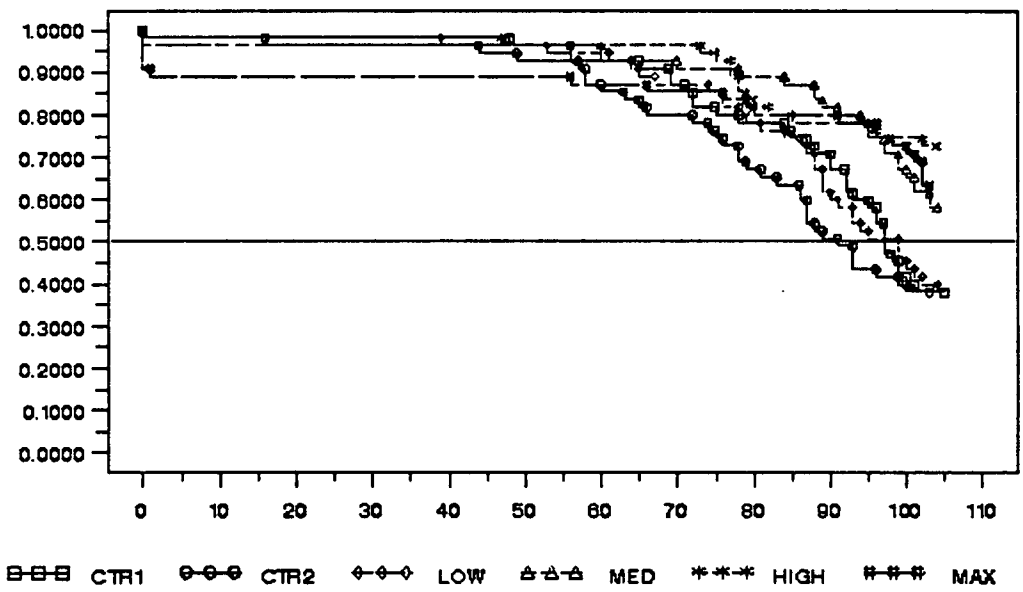

Table 9: Tumor Trend Tests for Female Rats in Study 99321

Organ Code	Organ Name	Tumor Code	Tumor Name	CTRL1	CTRL2	LOW	MED	HIGH	MAX	pValue (Exact)	pValue (Asymp)	Natural Tumor # in control group	Natural Rate (in ctrl group)	Tumor type
AC	ADRENAL, CORTEX	265	B-ADENOMA	2	3	1	3	4	6	0.0495	0.0416	5	5%	IN
AC	ADRENAL, CORTEX	90	M-CARCINOMA	0	0	0	0	2	6	0.0001	0.0001	0	.0%	MX
AS	AUDITORY SEB GL	445	M-CARCINOMA	0	0	0	0	1	0	0.4327	0.2776	0	.0%	IN
BR	BRAIN	121	M-ASTROCYTOMA	0	1	1	1	0	0	0.8689	0.8617	1	.9%	MX
BR	BRAIN	191	B-OLIGODENDROGLIOMA	1	0	1	0	0	0	0.8750	0.8532	1	.9%	IN
BR	BRAIN	192	B-GRANULAR CELL TUMOR	0	1	0	0	0	0	1.0000	0.7721	1	.9%	IN
CV	CERVIX	456	B-POLYP, ENDOMETRIAL STRO	0	0	1	0	0	0	0.7500	0.7791	0	.0%	IN
CV	CERVIX	468	M-LEIOMYOSARCOMA	0	0	0	1	0	0	0.6221	0.6244	0	.0%	IN
CV	CERVIX	54	M-SARCOMA, STROMAL	1	0	0	0	0	0	1.0000	0.8423	1	.9%	FA
HN	HEMATONEOPLASIA	178	M-LYMPHOMA	0	0	0	1	0	2	0.0753	0.0457	0	.0%	MX
HN	HEMATONEOPLASIA	264	M-SARCOMA, HISTIOCYTIC	0	2	0	0	1	0	0.8233	0.8024	2	2%	MX
HT	HEART	446	B-RHABDOMYOMA	0	0	0	0	1	0	0.4360	0.2785	0	.0%	IN
LI	LIVER	241	B-ADENOMA, HEPATOCELLULAR	1	3	2	1	0	1	0.9498	0.9362	4	4%	IN
LI	LIVER	451	B-CHOLANGIOMA	0	0	0	0	1	0	0.4360	0.2785	0	.0%	IN
LI	LIVER	466	M-CARCINOMA, HEPATOCELLUL	0	0	0	1	0	0	0.6221	0.6244	0	.0%	IN
LU	LUNG	369	M-CHORDOMA	0	0	0	1	0	0	0.4262	0.4624	0	.0%	IN
MA	ADRENAL, MEDULLA	218	B-PHEOCHROMOCYTOMA	2	1	4	4	2	5	0.2007	0.1867	3	3%	IN
MF	MAMMARY, FEMALE	205	B-ADENOMA	6	6	8	6	4	7	0.6408	0.6317	12	11%	MX
MF	MAMMARY, FEMALE	46	B-FIBROADENOMA	26	22	19	20	19	15	0.9947	0.9938	48	44%	MX
MF	MAMMARY, FEMALE	73	M-CARCINOMA	16	16	15	10	6	2	1.0000	1.0000	32	29%	MX
OV	OVARY	444	M-MALIGNANT GRANULOSA/THE	0	0	0	0	1	0	0.4386	0.2796	0	.0%	IN
OV	OVARY	475	B-ADENOMA	0	1	0	0	0	0	1.0000	0.8888	1	.9%	IN
PA	PANCREAS	244	M-CARCINOMA, ISLET CELL	0	1	1	2	0	0	0.8913	0.8762	1	.9%	MX
PA	PANCREAS	286	B-ADENOMA, ISLET CELL	5	2	3	2	2	1	0.9428	0.9315	7	6%	IN

PI	PITUITARY	292	M-CARCINOMA	2	1	2	0	1	1	0.8580	0.8422	3	3%	MX
PI	PITUITARY	49	B-ADENOMA	50	46	43	49	39	29	1.0000	1.0000	96	87%	MX
PN	PINNA	300	M-FIBROSARCOMA	0	0	0	1	0	0	1.0000	0.8473	0	0%	FA
PT	PARATHYROID	326	B-ADENOMA	0	2	0	1	0	0	0.9402	0.9144	2	2%	IN
SK	SKIN	207	M-FIBROSARCOMA	0	1	0	1	0	0	0.8351	0.8207	1	1%	FA
SK	SKIN	267	B-TRICHOEPITHELIOMA	1	0	0	1	0	0	0.6553	0.6735	1	1%	IN
SK	SKIN	358	M-CARCINOMA, SEBACEOUS GL	0	0	1	0	0	0	0.6066	0.6506	0	0%	IN
SK	SKIN	386	M-CARCINOMA, SQUAMOUS CEL	0	1	0	0	0	0	1.0000	0.8074	1	1%	IN
SM	MUSCLE, SKELETAL	243	M-SARCOMA, UNDIFFERENTIAT	1	0	0	0	0	0	1.0000	0.8546	1	1%	FA
SM	MUSCLE, SKELETAL	277	M-FIBROSARCOMA	0	1	0	0	0	0	1.0000	0.8598	1	1%	FA
SP	SPLEEN	448	B-HEMANGIOMA	0	0	0	0	2	0	0.2649	0.1979	0	0%	IN
SU	STOMACH, NONGL	413	B-PAPILLOMA, SQUAMOUS CEL	0	0	1	1	0	1	0.3188	0.3066	0	0%	IN
TH	THYMUS	318	B-THYMOMA	1	0	0	1	0	0	0.8028	0.7868	1	1%	IN
TH	THYMUS	403	M-THYMIC CARCINOMA	1	0	0	0	0	1	0.5160	0.4248	1	1%	IN
TI	TAIL	342	B-PAPILLOMA, SQUAMOUS CEL	0	0	1	0	0	0	1.0000	0.8461	0	0%	IN
TY	THYROID	128	B-ADENOMA, FOLLICULAR CEL	2	2	0	0	0	0	1.0000	0.9863	4	4%	IN
TY	THYROID	340	M-CARCINOMA, C-CELL	0	0	0	1	1	0	0.3991	0.3060	0	0%	IN
TY	THYROID	81	B-ADENOMA, C-CELL	7	7	14	4	5	1	0.9996	0.9993	14	13%	IN
UT	UTERUS	232	B-POLYP, ENDOMETRIAL, STR	1	1	0	3	5	2	0.0719	0.0593	2	2%	MX
UT	UTERUS	349	M-LEIOMYOSARCOMA	1	0	0	0	0	0	1.0000	0.8806	1	1%	FA
UT	UTERUS	354	M-CARCINOMA	1	0	0	0	0	0	1.0000	0.8074	1	1%	IN
UT	UTERUS	469	M-SARCOMA, ENDOMETRIAL, S	0	0	0	1	0	0	0.6221	0.6244	0	0%	IN
VA	VAGINA	370	B-POLYP, STROMAL	0	0	0	1	0	1	0.2597	0.1951	0	0%	FA

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Table 10: Number of Deaths per Time Interval for Male Rats in Study 99321

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR1	0-52	55	2	53	96.4	3.6
	53-78	53	9	44	80.0	20.0
	79-91	44	14	30	54.5	45.5
	92-104	30	9	21	38.2	61.8
	FINALKILL105-106	21	21	0		
CTR2	0-52	55	3	52	94.5	5.5
	53-78	52	8	44	80.0	20.0
	79-91	44	10	34	61.8	38.2
	92-104	34	15	19	34.5	65.5
	FINALKILL105-106	19	19	0		
LOW	0-52	55	4	51	92.7	7.3
	53-78	51	5	46	83.6	16.4
	79-91	46	6	40	72.7	27.3
	92-104	40	11	29	52.7	47.3
	FINALKILL105-106	29	29	0		
MED	0-52	55	5	50	90.9	9.1
	53-78	50	3	47	85.5	14.5
	79-91	47	7	40	72.7	27.3
	92-104	40	11	29	52.7	47.3
	FINALKILL105-106	29	29	0		
MEDHI	0-52	55	2	53	96.4	3.6
	53-78	53	1	52	94.5	5.5
	79-91	52	7	45	81.8	18.2
	92-104	45	12	33	60.0	40.0
	FINALKILL105-106	33	33	0		
HIGH	0-52	55	2	53	96.4	3.6
	53-78	53	3	50	90.9	9.1
	79-91	50	5	45	81.8	18.2
	92-104	45	7	38	69.1	30.9
	FINALKILL105-106	38	38	0		

Table 11: Dose Mortality Trend Test for Male Rats in Study 99321

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	3.1335	0.5357	2.7301	0.6040
Dose-Mortality Trend	16.8969	0.0000	16.5506	0.0000
Homogeneity	20.0304	0.0012	19.2807	0.0017

Figure 4: Kaplan Meier Survival Curves for Male Rats in Study 99321

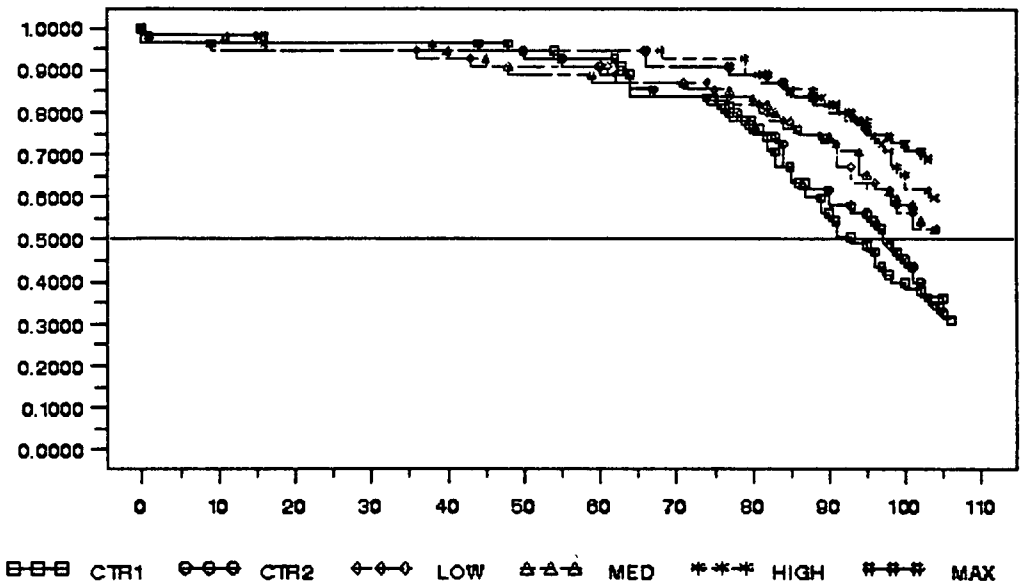

Table 12: Tumor Trend Tests for Male Rats in Study 99321

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL1	CTRL2	LOW	MED	HIGH	MAX	Tumor type	pValue (Exact)	pValue (Asymp)
ADRENAL, CORTEX	AC	B-ADENOMA	15	5%	3	2	2	1	3	2	IN	0.6410	0.6279
ADRENAL, CORTEX	AC	M-CARCINOMA	424	2%	2	0	0	0	0	2	IN	0.3591	0.3175
AUDITORY SEB GL	AS	M-CARCINOMA, SEBACEOUS-SQ	133	2%	0	2	1	1	0	0	FA	0.9488	0.9326
AUDITORY SEB GL	AS	B-ADENOMA	431	.0%	0	0	0	0	0	1	IN	0.2216	0.0692
BONE, OTHER	BO	B-ODONTOMA	305	.9%	1	0	0	0	0	0	IN	N/A	N/A
BRAIN	BR	M-ASTROCYTOMA	296	4%	1	3	6	1	0	0	MX	0.9985	0.9956
BRAIN	BR	M-GRANULAR CELL TUMOR	332	.9%	0	1	0	0	0	0	FA	1.0000	0.8679
COLON	CO	M-CARCINOMA	447	.0%	0	0	0	0	0	1	IN	0.2249	0.0713
BONE, FEMUR	FE	M-OSTEOSARCOMA	350	.0%	0	0	1	0	0	0	FA	0.7261	0.7462

)OT/FOOTPAD	FP	M-FIBROSARCOMA	395	.0%	0	0	0	0	1	0	FA	0.4062	0.2383
HEMATO NEOPLASIA	HN	M-SARCOMA, HISTIOCYTIC	145	.9%	0	1	2	2	3	1	MX	0.4140	0.3949
HEMATO NEOPLASIA	HN	M-LEUKEMIA, GRANULOCYTIC	262	.0%	0	0	0	0	1	1	FA	0.1090	0.0516
HEMATO NEOPLASIA	HN	M-LYMPHOMA	89	.9%	0	1	2	2	1	0	MX	0.8186	0.8031
HEART	HT	M-ENDOCARDIAL SCHWANNOMA	454	.0%	0	0	0	0	0	1	IN	0.2249	0.0713
ILEUM	IL	M-CARCINOMA	496	.0%	0	0	0	1	0	0	IN	0.5952	0.6239
JEJUNUM	JE	M-CARCINOMA	404	.0%	0	0	0	0	1	0	FA	0.4211	0.2808
KIDNEY	KD	M-RENAL MESENCHYMAL TUMOR	341	.9%	1	0	0	0	1	1	MX	0.3186	0.2667
LIVER	LI	B-ADENOMA, HEPATOCELLULAR	123	5%	2	3	1	2	0	0	IN	0.9939	0.9856
LIVER	LI	M-CARCINOMA, HEPATOCELLUL	342	2%	2	0	1	0	0	0	IN	0.9686	0.9346
IVER	LI	M-HEMANGIOSARCOMA	444	.0%	0	0	0	0	0	1	IN	0.2249	0.0713
LUNG	LU	M-CARCINOMA, BRONCHIOLAR	310	.9%	0	1	0	0	0	0	IN	1.0000	0.7907
ADRENAL, MEDULLA	MA	B-PHEOCHROMOCYTOMA	188	10%	6	5	6	6	10	15	IN	0.0163	0.0141
ADRENAL, MEDULLA	MA	M-MALIGNANT PHEOCHROMOCYT	387	3%	1	2	0	0	0	4	MX	0.1704	0.1467
MAMMARY, MALE	MM	B-FIBROADENOMA	407	3%	1	2	0	0	0	0	IN	1.0000	0.9783
MAMMARY, MALE	MM	B-ADENOMA	433	.0%	0	0	0	0	0	1	IN	0.2333	0.0785
LN, MESENTERIC	MS	M-HEMANGIOSARCOMA	443	.9%	1	0	0	0	0	0	IN	1.0000	0.8832
PANCREAS	PA	M-CARCINOMA, ACINAR CELL	158	2%	2	0	0	0	0	1	MX	0.5759	0.5326
ANCREAS	PA	M-CARCINOMA, ISLET CELL	213	4%	1	3	3	0	1	0	IN	0.9701	0.9552

ANCREAS	PA	B-ADENOMA, ISLET CELL	286	9%	6	4	4	2	2	3	IN	0.9450	0.9366
PANCREAS	PA	B-ADENOMA, ACINAR CELL	52	.0%	0	0	2	0	0	0	IN	0.8340	0.8105
CAVITY, ABDOM	PC	M-MESOTHELIOMA	316	.0%	0	0	0	1	0	0	FA	0.4000	0.3566
CAVITY, ABDOM	PC	M-LIPOSARCOMA	334	.9%	0	1	0	0	0	0	FA	1.0000	0.7861
PITUITARY	PI	B-ADENOMA	61	63%	29	40	26	29	24	15	MX	1.0000	1.0000
PINNA	PN	B-ADENOMA, BASAL CELL	402	.9%	1	0	0	0	0	0	IN	1.0000	0.8643
PINNA	PN	B-PAPILLOMA, SQUAMOUS CEL	403	.9%	1	0	0	0	0	0	IN	1.0000	0.8643
PARATHYROID	PT	B-ADENOMA	102	4%	1	3	1	1	2	0	IN	0.8250	0.8103
SALIV GL, MANDIB	SG	M-CARCINOMA	372	.9%	1	0	0	0	0	0	FA	1.0000	0.8773
SKIN	SK	B-KERATOACANTHOMA	274	3%	2	1	2	1	0	0	IN	0.9748	0.9588
SKIN	SK	M-LIPOSARCOMA	287	.9%	1	0	0	0	0	0	FA	1.0000	0.8585
KIN	SK	M-CARCINOMA, BASAL CELL	412	.0%	0	0	1	1	0	0	IN	0.6767	0.6998
SKIN	SK	M-CARCINOMA, SQUAMOUS CEL	417	.0%	0	0	1	0	0	0	IN	0.6308	0.6792
SKIN	SK	B-TRICHOEPITHELIOMA	418	.0%	0	0	0	1	0	0	IN	0.4615	0.4886
SKIN	SK	B-PAPILLOMA, SQUAMOUS CEL	441	.9%	0	1	1	0	0	3	IN	0.1463	0.1251
SKIN	SK	B-FIBROMA	450	2%	1	1	3	0	1	0	IN	0.9623	0.9495
SKIN	SK	B-LIPOMA	465	.0%	0	0	0	0	2	0	IN	0.2527	0.2013
SKIN	SK	B-ADENOMA, SEBACEOUS/SQUA	470	.9%	0	1	0	0	0	0	IN	1.0000	0.8841
SKIN	SK	M-FIBROSARCOMA	62	4%	2	2	3	0	0	0	MX	0.9972	0.9901
MUSCLE, SKELETAL	SM	M-FIBROSARCOMA	304	.9%	1	0	1	0	0	0	FA	0.9266	0.8959
SPLEEN	SP	M-HEMANGIOSARCOMA	338	2%	1	1	0	0	0	0	IN	1.0000	0.9350

ГОМАСН, GL	ST	M- LEIOMYOSARCOMA -	437	.9%	1	0	0	0	0	0	IN	1.0000	0.8841
TESTIS	TE	B- INTERSTITIAL CELL TUMOR	201	5%	2	3	2	2	0	1	IN	0.9355	0.9209
TAIL	TI	B- KERATOACANTHOMA	493	.0%	0	0	1	0	0	0	IN	0.8333	0.8982
THYROID	TY	B-ADENOMA, FOLLICULAR CEL	108	5%	3	2	2	1	1	2	IN	0.6827	0.6707
THYROID	TY	B-ADENOMA, C-CELL	205	11%	5	7	8	3	3	4	IN	0.9524	0.9455
THYROID	TY	M- CARCINOMA, FOLLICULAR C	480	.0%	0	0	0	0	1	0	IN	0.4201	0.2813
THYROID	TY	M- CARCINOMA, C-CELL	495	.0%	0	0	0	2	0	0	IN	0.6938	0.6633

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- Statistical Review and Evaluation

Review of Mouse Carcinogenicity Studies

NDA#: 21-436

APPLICANT: **Otsuka Pharm**

NAME OF DRUG: **Aripiprazole**

INDICATION: **Schizophrenia**

STUDIES REVIEWED: **Mouse Studies: Otsuka Study No. 011487 and Otsuka Study No. 011932 in Volumes 1.67 and 1.71**

PHARMACOLOGY REVIEWER: **Lois Freed, Ph.D. (HFD-120)**

STATISTICAL REVIEWER: **Roswitha Kelly, M.S. (HFD-710)**

Roswitha Kelly, M.S.
Mathematical Statistician

George Chi, Ph.D.
Director, Division of Biometrics 1

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HDS-700/Charles Anello, Sc.D.

This review consists of 7 pages of text and 14 pages of Tables and Figures.
File Directory: c:\Data\My Documents\aripiprazole_mice.doc

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1.0 Introduction

The sponsor has submitted two rat and two mouse carcinogenicity studies. As there is basically double the information of the usual bioassay, the multiplicity problem inherent in carcinogenicity analyses is increased. This reviewer, however, performed no further adjustment on the usual 0.025 and 0.005 levels of significance in trend for rare and common tumors, as there is no guidance on this issue. High levels of significance and consistency across gender and studies should be considered when interpreting any findings. This reviewer wrote a separate review for each species but presented the main findings from both species in the summary section.

2.0 Otsuka Study No. 011487 in Mice

This is a 104 week study of the aripiprazole in the diet of ICR (Crj:CD-1) mice at dose levels of 0, 1, 3, and 10 mg/kg/day. Groups of 60 animals/gender comprised the main study. Additional 8 animals per treatment group were maintained for 52 weeks to study plasma concentrations. The animals were housed individually and food and water were available ad lib. All main-study animals were fully histopathologically examined. The sponsor used a two-tailed log-rank test for mortality and one-tailed Cochran-Armitage trend tests for incidence of neoplastic lesions and number of females with pituitary or mammary gland tumors. Further, one-tailed Peto's onset rate and death rate methods were used for the incidence of mammary gland tumors and pituitary tumors respectively.

2.1 Sponsor's Findings for Study 011487

The sponsor observed no statistically significant differences in mortality between groups for either gender. The final mortality rates (number of animals killed in extremis or found dead) were as follows:

Dose Group (mg/kg/day)	Males	Females
0	40/60 (67%)	36/60 (60%)
1	44/60 (73%)	37/60 (62%)
3	38/60 (63%)	46/60 (78%)
10	31/60 (52%)	43/60 (72%)

Average body weight of the male mice in the high dose was slightly lower (about 5%) than the controls throughout the administration period. Differences reached statistical significance for Week 1 to Week 40. The average body weight of the high dose females was slightly lower than the controls (about 3-4%) in the early weeks, but became similar to the controls for the remainder of the study.

Among the females, incidence of adenocarcinoma and of adenoacanthoma in the mammary glands and of adenoma in the anterior pituitary was significantly higher in the 3- and 10 mg/kg doses when compared to the controls. The corresponding trend tests reached statistical significance as well. No statistically significant increase in neoplastic findings was seen among the males, except for a comparison of hemangiomas in the liver

between male control and mid dose animals. The corresponding trend test or control-high dose comparison was not statistically significant. Similar findings were observed when considering decedents and moribund sacrifices and terminal sacrifices separately.

2.2 Reviewer's Findings for Study 011487

The intercurrent mortality among the female mice of this study showed an increase in mortality with dose, however the trend did not reach statistical significance (p=0.0821, Tables 1-2, Figure 1). Tumor findings in the pituitary and mammary gland were highly statistically significant: adenoma in the anterior pituitary: p=0.0000; adenocarcinoma in the mammary gland: p=0.0000, and adenoacanthoma in the mammary gland: p=0.0011, (Table 3).

Among the males, there was statistically significantly better survival among the treated than among the control group (p=0.0138, Table 4-5, Figure 2). There were no positive increases in tumor findings that reached statistical significance (Table 6).

2.3 Validity of the Male Mouse of Study 011487

As there were no statistically significant tumor trends among the male mice in this study, its validity needs to be assessed. Two criteria are set up for this purpose (Haseman[12], Chu et al.[3], and Bart et al.[4]):

i) was a sufficient number of animals exposed long enough to allow for late-developing tumors, and

ii) did the high dose provide a sufficient tumor challenge?

The number of animals and length of exposure can be assessed at weeks 52, 80-90, and at termination, but are generally considered sufficient if 20-30 animals survive through weeks 80-90. The high dose is expected to be close to the MTD to present a sufficient tumor challenge. Suppression in survival when compared to the controls and/or average body weight differences of about 10 percent, especially during the first year of treatment, are indicators that the high dose is close to the MTD. For this study, 19 animals had died by the end of week 91 and 50% survived till terminal sacrifice. Therefore, there was a sufficient number of animals living long enough to satisfy the first criterion. There was no reduction in survival with dose. The sponsor reported average body weights of the high dose group being below the controls'. Though the difference is only about 5 percent, it was observed very early in the study and was maintained for most of the two years. These findings may sufficiently indicate that the high dose was close to the MTD and that the study can be considered valid.

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[1] Haseman: Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, *Environmental Health Perspectives*, Vol. 58, pp 385-392, 1984.

[2] Haseman: Issues in Carcinogenicity Testing: Dose Selection, *Fundamental and Applied Toxicology*, Vol. 5, pp. 66-78, 1985.

[3] Chu, Cueto, Ward: Factors in the Evaluation of 200 National Cancer Institute Carcinogenicity Bioassays, *Journal of Toxicology and Environmental Health*, Vol. 8, pp 251-280, 1981.

[4] Bart, Chu, Tarone: Statistical Issues in Interpretation of Chronic Bioassay Tests for Carcinogenicity, *Journal of the National Cancer Institute*, pp. 957-974, 1979.

3.0 Otsuka Study No. 011932 in Mice

This study consisted only of two groups of ICR (Crj:CD-1) SPF mice: a control group of 60 animals/gender and a 30 mg/kg/day group of another 60 animals/gender. Animals were randomly allocated on the basis of body weight measured 1 week prior to the assignment. The compound was administered orally in the diet for 104 weeks for the males. Dosing was terminated at week 100 for females due to 75% mortality. The animals were housed individually and water and diet were available ad lib. Additional 8 animals per gender were dosed and maintained for 52 weeks for determination of plasma concentrations. All tissues were histopathologically examined for all animals of the main study. Mortality was assessed by a two-tailed life table analysis. Tumor incidences were analyzed by a one-tailed Peto test.

3.1 Sponsor's Findings of Study 011932

The sponsor found increased survival in the treated males but decreased survival in the treated females compared to their controls. The final mortality rates (number of animals killed in extremis or found dead) at week 104 (males) or week 100 (females) were as follows:

Dose Group (mg/kg/day)	Males	Females
0	45/60 (75%)	35/60 (58%)
30	33/60 (55%)	45/60 (75%)

Mean body weight in the treated males was approximately 10% lower than the controls throughout the treatment period. This difference was statistically significant at almost all weeks. The body weight of the treated females was approximately 5% lower than the controls from Week 1 through Week 16. Thereafter, the average weight became similar to the controls' with no statistically significant differences at any time.

There were no significant differences in neoplastic lesions among the control and treated males. Among the females, there were statistically significant increases in adenoma in the anterior pituitary and in adenocarcinoma and adenoacanthoma in the mammary glands. Also, the number of animals with epithelial mammary gland tumors was significantly greater than the controls'.

3.2 Reviewer's Findings for Study 011932

There was only one control and one treated (30 mg/kg/day) group per gender. Therefore, all statistical tests are pair-wise comparisons, two-sided for mortality and one-sided for tumor findings. The intercurrent mortality for the female mice showed higher mortality in the treated group, which reached statistical significance (p=0.0391, Table 7-8, Figure 3). Among the tumor findings, adenoma in the anterior pituitary (p=0.0023),

adenocarcinoma in the mammary gland (p=0.0000), and adenoacanthoma in the mammary gland (p=0.0000) were highly statistically significant (Table 9). These findings are consistent with the sponsor's.

The male mice of this study had statistically significant better survival in the treated group than in the control (p=0.0234, Table 10-11, Figure 4). Among the tumor findings, none reached statistical significance (Table 12).

3.3 Validity of Male Mouse Study 011932

The same criteria as noted above to evaluate the male mice of Study 011487 are being applied to the male mice of this study, as no statistically significant increase in tumors were observed. Survival was good for both the control and the treated group, and the number of animals living long enough is not an issue. Survival was significantly better for the treated than for the control group, and therefore mortality cannot be used as a criterion for assessing whether 30 mg/kg/day presented a sufficient tumor challenge in these animals. The sponsor's average bodyweight data indicated an early and sustained differential of about 10% for the treated males compared to the controls. This finding implies that the high dose was close to the MTD for these animals.

4.0 Summary

For Study 011487, 60 animals/gender received aripiprazole in the diet at levels of 0, 1, 3, and 10 mg/kg/day. The sponsor observed no statistically significant difference in mortality patterns for either the male or female mice. This reviewer, however, observed that the increased survival among males reached statistical significance and that the decreased survival among females approached statistical significance. This difference in conclusion about survival is minor, since all tumor findings were tested by age-adjusted methods. The conclusions based on the tumor findings are the same as the sponsor's, except that the sponsor did not note the very high levels of statistical significance. Adenoma in the anterior pituitary gland, and adenocarcinoma and adenoacanthoma in the mammary glands were highly statistically significantly increased among the females. Among the male mice, there were no statistically significant increases in tumor findings, however, the length of exposure and number of animals alive at study end were acceptable. Whether the high dose presented a sufficient tumor challenge is assessed by suppressed body weights, since there was no increased mortality for these animals. The sponsor reported an early and sustained reduction of about 5% in average body weights for the high dose males compared to the controls. This reviewer assumes that this differential is sufficient to conclude that this was a valid study.

For Study 011932, where 60 control animals/gender were compared to 60 mice treated with 30 mg/kg/day in the diet, the sponsor's and this reviewer's findings and conclusions agree. Mortality of 75% prompted the sponsor to stop dosing the females at week 100. The increased mortality reached statistical significance. Among the females, highly significant increases in tumor incidence rates were found for adenoma in the anterior

pituitary gland and for adenocarcinoma and adenoacanthoma in the mammary gland. For the males, survival was significantly better among the treated than among the controls. There were no statistically significant increases in neoplastic findings among the males, however, length of exposure, number of animals alive at study end, and suppressed body weights indicated that this was a valid study.

The major findings of the two mouse studies are summarized below:

MICE	Otsuka Study 011487		Otsuka Study 011932	
	Females	Males	Females	Males
Survival	NS	Sign. increased	Sign. decreased	Sign. increased
Anterior Pituitary, Adenoma	Sign. increased	NS	Sign. increased	NS
Mammary Gland, Adenocarcinoma	Sign. increased	NS	Sign. increased	NS
Mammary Gland, Adenoacanthoma	Sign. increased	NS	Sign. increased	NS
Validity	N/A	Yes	N/A	Yes

For completeness, the major findings of the two rat studies are given as well:

RATS	Otsuka Study 009489		BMS Study 99321	
	Females	Males	Females	Males
Survival	NS	NS	Sign. increased	Sign. increased
Mammary Gland, Fibroadenoma	Sign. increased	NS	NS	NS
Adrenal Cortex, Carcinoma	NS	NS	Sign. increased	NS
Validity	N/A	Yes	N/A	MTD exceeded

Overall, it appears that the long-term administration of aripiprazole in the doses given resulted in increased tumor findings in female rats or mice. The p-values in each case are highly statistically significant. No increase in tumor incidence rates was observed among the males of any of the studies. All but one of these male studies were judged to be valid. The maximum dose in Study No. 99321 was judged to be well beyond the MTD, based on much lower average body weights of these animals compared to the controls.

Otsuka Study 011487

Table 1: Study 011487, Number of Animals Dying during Given Time Intervals, Female Mice

	Treatment Group				Total
	CTRL	LOW	MED	HIGH	
	N	N	N	N	N
Week 0-52	4	4	6	7	21
53-78	10	11	12	12	45
79-91	10	9	16	12	47
92-103	11	12	11	12	46
104-104	25	24	15	17	81
Total	60	60	60	60	240

Table 2: Study 011487, Dose-Mortality Trend Tests* for Female Mice

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	3.02	0.0821
	Depart from Trend	2.83	0.2430
	Homogeneity	5.85	0.1191
Kruskal-Wallis	Dose-Mortality Trend	2.88	0.0898
	Depart from Trend	1.94	0.3785
	Homogeneity	4.82	0.1854

* The results are produced by: Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2:1, by Donald G. Thomas, National Cancer Institute.

Figure 1: Study 011487, Kaplan Meier Survival Curves in Female Mice

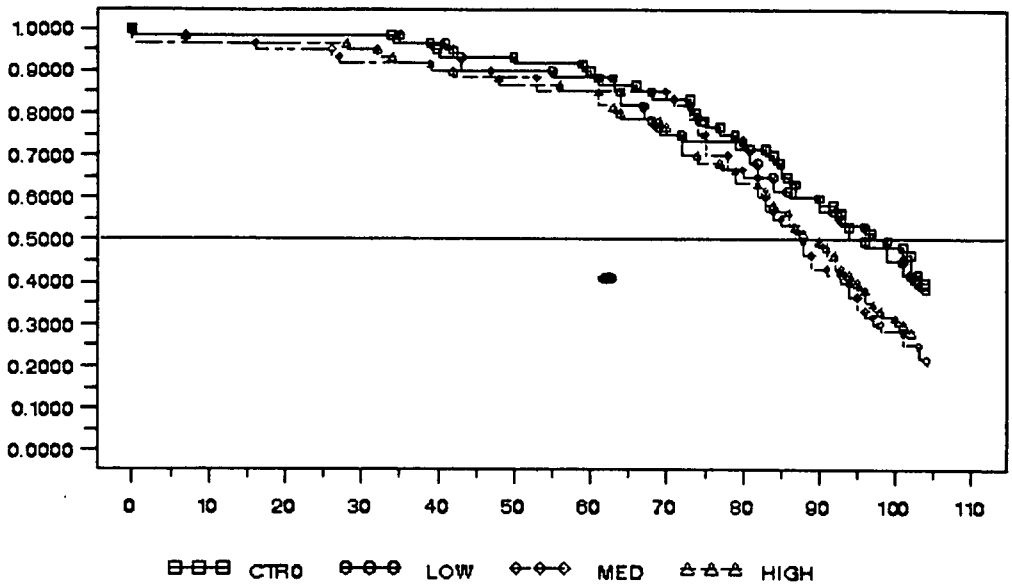

Table 3: Study 011487, Test for Dose-Dependent Linear Trend in Tumors, Female Mice

Organ Code	Organ Name	Tumor Code	Tumor Name	CTRL	LOW	MED	HIGH	pValue (Exact)	pValue (Asymp)	Natural Tumor # in control group	Natural Rate (in ctrl group)	Tumor type
01	Heart	0180	Malignant schwannoma (Hea	0	0	1	0	0.5957	0.6298	0	.0%	IN
03	Bone marrow(femur)	0342	Hemangioma (Bone marrow)	1	0	0	0	1.0000	0.8493	1	2%	IN
07	Thymus	0780	Malignant schwannoma (Thy	0	0	1	0	0.5957	0.6298	0	.0%	IN
07	Thymus	0784	Histiocytic sarcoma (Thym	1	0	0	0	1.0000	0.8678	1	2%	IN
09	Lymph nodes (mesenteric)	0880	Malignant schwannoma (Lym	0	0	0	1	0.2609	0.0698	0	.0%	IN
13	Spleen	1342	Hemangioma (Spleen)	0	2	5	1	0.5631	0.5784	0	.0%	MX
13	Spleen	1372	Hemangiosarcoma (Spleen)	1	0	0	0	1.0000	0.8160	1	2%	FA
13	Spleen	1380	Malignant schwannoma (Spl	0	0	1	1	0.2387	0.1763	0	.0%	IN

18	Lung	1835	Adenoma (Lung)	12	5	12	7	0.6500	0.6572	12	20%	MX
18	Lung	1865	Adenocarcinoma (Lung)	6	7	12	6	0.4467	0.4559	6	10%	MX
18	Lung	1880	Malignant schwannoma (Lun	0	0	1	0	0.5957	0.6298	0	0%	IN
18	Lung	1884	Histiocytic sarcoma (Lung	1	0	0	0	1.0000	0.8678	1	2%	IN
28	Esophagus	2880	Malignant schwannoma (Eso	0	0	0	1	0.2553	0.0668	0	0%	IN
29	Stomach (non-glandular po	2960	Squamous cell carcinoma (	0	1	0	0	0.6914	0.7419	0	0%	IN
30	Stomach (glandular portio	3076	Leiomyosarcoma (Stomach(g	0	0	1	0	0.5000	0.6083	0	0%	IN
31	Small intestine	3176	Leiomyosarcoma (Small int	0	0	1	0	0.5000	0.6083	0	0%	IN
32	Large intestine	3246	Leiomyoma (Large intestin	0	0	0	1	0.2099	0.0413	0	0%	IN
32	Large intestine	3276	Leiomyosarcoma (Large int	0	0	1	0	0.5000	0.6083	0	0%	IN
34	Liver	3435	Hepatocellular adenoma (L	1	1	0	1	0.4846	0.4392	1	2%	IN
34	Liver	3442	Hemangioma (Liver)	2	3	3	2	0.5607	0.5865	2	3%	MX
34	Liver	3467	Cholangiocarcinoma (Liver	0	0	0	1	0.2276	0.0503	0	0%	FA
34	Liver	3472	Hemangiosarcoma (Liver)	1	0	0	0	1.0000	0.8197	1	2%	IN
34	Liver	3476	Leiomyosarcoma (Liver)	0	0	1	0	0.5000	0.6083	0	0%	IN
34	Liver	3484	Histiocytic sarcoma (Live	1	1	0	0	0.9343	0.8764	1	2%	IN
36	Gallbladder	3635	Adenoma (Gallbladder)	0	0	1	1	0.1207	0.1067	0	0%	IN
37	Pancreas	3736	Islet cell adenoma (Pancr	0	0	2	0	0.4603	0.5753	0	0%	IN
37	Pancreas	3750	Schwannoma (Pancreas)	0	0	0	1	0.2099	0.0413	0	0%	IN
37	Pancreas	3776	Leiomyosarcoma (Pancreas)	0	0	1	0	0.5000	0.6083	0	0%	IN
38	Kidney	3835	Adenoma (Kidney)	1	1	0	0	0.9262	0.8653	1	2%	IN
38	Kidney	3880	Malignant schwannoma (Kid	0	0	1	0	0.5957	0.6298	0	0%	IN
41	Urinary bladder	4146	Leiomyoma (Urinary bladde	0	2	1	1	0.3341	0.3989	0	0%	IN
52	Ovary	5235	Luteoma (Ovary)	1	0	0	0	1.0000	0.8197	1	2%	IN
52	Ovary	5236	Adenoma (Ovary)	2	1	2	1	0.5354	0.5852	2	3%	IN
52	Ovary	5242	Hemangioma (Ovary)	1	3	1	0	0.9187	0.9160	1	2%	MX
52	Ovary	5246	Leiomyoma (Ovary)	0	1	0	0	0.7609	0.7825	0	0%	IN
52	Ovary	5264	Malignant granulosa-theca	0	0	1	0	0.4937	0.5987	0	0%	FA
52	Ovary	5276	Leiomyosarcoma (Ovary)	0	0	1	0	0.5000	0.6083	0	0%	IN

54	Uterus	5431	Endometrial stromal polyp	3	5	3	5	0.1945	0.1951	3	5%	IN
54	Uterus	5442	Hemangioma (Uterus)	2	2	0	0	0.9840	0.9510	2	3%	MX
54	Uterus	5446	Leiomyoma (Uterus)	0	0	1	1	0.2387	0.1763	0	.0%	IN
54	Uterus	5465	Adenocarcinoma (Uterus)	0	0	2	1	0.2164	0.2462	0	.0%	MX
54	Uterus	5472	Hemangiosarcoma (Uterus)	0	1	0	0	0.6914	0.7419	0	.0%	IN
54	Uterus	5474	Endometrial stromal sarco	0	0	0	1	0.3333	0.1065	0	.0%	IN
54	Uterus	5476	Leiomyosarcoma (Uterus)	1	0	0	0	1.0000	0.8197	1	2%	IN
54	Uterus	5484	Histiocytic sarcoma (Uter	0	1	0	0	0.6914	0.7419	0	.0%	IN
59	Pituitary	5935	Anterior adenoma (Pituita	2	4	8	14	0.0001	0.0000	2	3%	MX
59	Pituitary	5936	Adenoma in intermediate p	1	0	1	1	0.3182	0.3273	1	2%	MX
60	Thyroid	6035	Follicular adenoma (Thyro	1	0	0	0	1.0000	0.8197	1	2%	IN
60	Thyroid	6036	C-cell adenoma (Thyroid)	0	0	0	1	0.2609	0.0674	0	.0%	IN
62	Adrenal	6236	Subcapsular cell adenoma	0	2	0	0	0.7222	0.7967	0	.0%	IN
62	Adrenal	6239	Pheochromocytoma (Adrenal	0	0	2	0	0.4804	0.5937	0	.0%	IN
64	Cerebrum	6433	Glioma (Cerebrum)	0	0	0	1	0.2435	0.0588	0	.0%	FA
64	Cerebrum	6436	Meningioma (Cerebrum)	0	0	1	0	0.3951	0.5475	0	.0%	IN
68	Spinal cord (thoracic)	6780	Malignant schwannoma (Spi	0	0	0	1	0.2276	0.0503	0	.0%	FA
72	Bone (sternum)	7280	Malignant schwannoma (Bon	0	0	1	0	0.5957	0.6298	0	.0%	IN
74	Bone (vertebra)	7242	Hemangioma (Bone)	0	0	1	0	0.3951	0.5475	0	.0%	IN
81	Harderian gland	8135	Adenoma (Harderian gland)	4	2	1	2	0.6763	0.6887	4	7%	IN
86	Skin	8631	Papilloma (Skin)	1	0	0	0	1.0000	0.8197	1	2%	IN
86	Skin	8635	Sebaceous gland adenoma (	0	0	1	0	0.3951	0.5475	0	.0%	IN
86	Skin	8640	Fibroma (Skin)	1	0	0	0	1.0000	0.8303	1	2%	FA
86	Skin	8642	Hemangioma (Skin)	0	0	0	1	0.2553	0.0668	0	.0%	IN
86	Skin	8650	Schwannoma (Skin)	0	0	1	1	0.1715	0.1505	0	.0%	MX
86	Skin	8654	Histiocytoma (Skin)	0	0	1	0	0.5333	0.6207	0	.0%	IN
86	Skin	8660	Squamous cell carcinoma (	0	0	0	1	0.2412	0.0583	0	.0%	FA
86	Skin	8661	Basal cell carcinoma (Ski	0	1	0	0	0.6907	0.7359	0	.0%	FA
86	Skin	8670	Fibrosarcoma (Skin)	0	1	0	0	0.7872	0.8036	0	.0%	IN
86	Skin	8678	Osteosarcoma (Skin)	0	0	1	0	0.5076	0.5952	0	.0%	FA
86	Skin	8680	Malignant schwannoma (Ski	0	0	1	1	0.2165	0.1746	0	.0%	IN
86	Skin	8684	Histiocytic sarcoma (Skin	0	0	2	0	0.4603	0.5753	0	.0%	IN

95	Mammary gland	9535	Adenoma (Mammary gland)	0	0	0	2	0.0696	0.0147	0	0%	IN
95	Mammary gland	9565	Adenocarcinoma (Mammary g	1	5	13	19	0.0000	0.0000	1	2%	MX
95	Mammary gland	9566	Adenoacanthoma (Mammary g	0	2	15	10	0.0019	0.0011	0	0%	MX
95	Mammary gland	9568	Carcinosarcoma (Mammary g	1	0	1	1	0.3441	0.3376	1	2%	IN
99	General	9988	Myelogenic leukemia (Gene	1	0	0	0	1.0000	0.8437	1	2%	FA
99	General	9989	Malignant lymphoma (Gener	15	17	10	12	0.6388	0.6467	15	25%	MX

Table 4: Study 011487, Number of Animals Dying during Given Time Intervals, Male Mice

	Treatment Group				Total
	CTRL	LOW	MED	HIGH	
	N	N	N	N	N
Week 0-52	8	7	5	6	26
53-78	13	9	12	4	38
79-91	9	12	9	9	39
92-103	9	16	10	11	46
104-104	21	16	24	30	91
Total	60	60	60	60	240

Table 5: Study 011487, Dose-Mortality Trend Tests* for Male Mice

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	6.06	0.0138
	Depart from Trend	0.72	0.6978
	Homogeneity	6.78	0.0793
Kruskal-Wallis	Dose-Mortality Trend	6.04	0.0140
	Depart from Trend	0.20	0.9026
	Homogeneity	6.24	0.1003

* The results are produced by: Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2:1, by Donald G. Thomas, National Cancer Institute.

Figure 2: Study 011487, Kaplan Meier Survival Curves in Male Mice

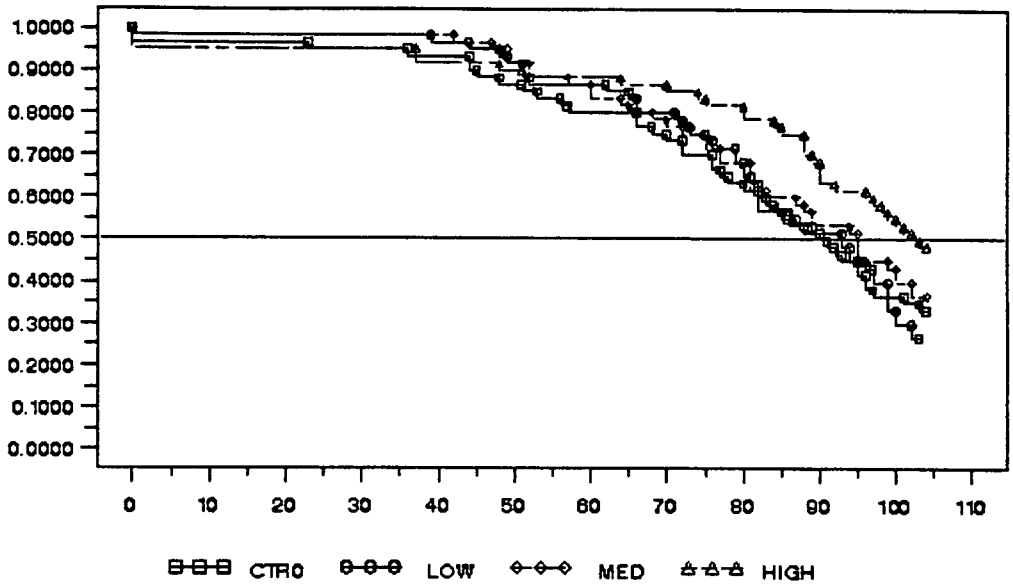

Table 6: Study 011487, Test for Dose-Dependent Linear Trend in Tumors, Male Mice

Organ Code	Organ Name	Tumor Code	Tumor Name	CTRL	LOW	MED	HIGH	pValue (Exact)	pValue (Asymp)	Natural Tumor # in control group	Natural Rate (in ctrl group)	Tumor type
01	Heart	0184	Histiocytic sarcoma (Hear	1	0	0	0	1.0000	0.8246	1	2%	IN
03	Bone marrow(femur)	0342	Hemangioma (Bone marrow)	0	0	0	1	0.3297	0.1043	0	.0%	IN
09	Lymph nodes (mesenteric)	0842	Hemangioma (Lymph nodes)	0	1	0	0	0.7692	0.8170	0	.0%	IN
13	Spleen	1342	Hemangioma (Spleen)	1	1	2	2	0.2600	0.2716	1	2%	IN
13	Spleen	1356	Mesotheliom a (Spleen)	0	0	0	1	0.3082	0.0919	0	.0%	FA
13	Spleen	1372	Hemangiosar coma (Spleen)	1	0	1	0	0.7811	0.8155	1	2%	IN
18	Lung	1835	Adenoma (Lung)	11	10	10	16	0.1381	0.1370	11	18%	MX
18	Lung	1865	Adenocarcin oma (Lung)	16	13	12	15	0.6389	0.6438	16	27%	MX
23	Tongue	2331	Panilloma	0	0	1	0	0.5934	0.6641	0	.0%	IN

			(Tongue)									
31	Small intestine	3165	Adenocarcinoma (Small int	0	0	0	2	0.1062	0.0305	0	.0%	IN
34	Liver	3435	Hepatocellular adenoma (L	9	16	11	11	0.6863	0.6905	9	15%	MX
34	Liver	3442	Hemangioma (Liver)	2	4	8	4	0.5899	0.6003	2	3%	MX
34	Liver	3465	Hepatocellular carcinoma	9	13	10	12	0.3713	0.3765	9	15%	MX
34	Liver	3466	Hepatoblastoma (Liver)	0	1	0	0	0.7758	0.8011	0	.0%	FA
34	Liver	3472	Hemangiosarcoma (Liver)	1	0	4	0	0.8451	0.8420	1	2%	MX
34	Liver	3484	Histiocytic sarcoma (Live	1	0	1	0	0.7402	0.7702	1	2%	MX
36	Gallbladder	3635	Adenoma (Gallbladder)	0	0	1	1	0.2809	0.2513	0	.0%	IN
37	Pancreas	3756	Mesothelioma (Pancreas)	0	0	0	1	0.3082	0.0919	0	.0%	FA
37	Pancreas	3772	Hemangiosarcoma (Pancreas	1	0	0	0	1.0000	0.8737	1	2%	IN
37	Pancreas	3784	Histiocytic sarcoma (Panc	0	0	1	0	0.4565	0.5919	0	.0%	IN
38	Kidney	3835	Adenoma (Kidney)	0	0	1	1	0.2821	0.2488	0	.0%	IN
38	Kidney	3842	Hemangioma (Kidney)	0	0	1	0	0.5934	0.6641	0	.0%	IN
43	Testis	4337	Interstitial cell tumor (	1	0	0	1	0.5531	0.4340	1	2%	IN
43	Testis	4342	Hemangioma (Testis)	1	1	0	0	0.9652	0.8792	1	2%	IN
46	Seminal vesicle	4635	Adenoma (Seminal vesicle)	2	0	0	0	1.0000	0.9384	2	3%	IN
47	Coagulating gland	4735	Adenoma (Coagulating glan	0	0	0	1	0.2391	0.0556	0	.0%	IN
47	Coagulating gland	4756	Mesothelioma (Coagulating	0	0	0	1	0.3082	0.0919	0	.0%	FA
48	Prostate	4856	Mesothelioma (Prostate)	0	0	0	1	0.3082	0.0919	0	.0%	FA
48	Prostate	4872	Hemangiosarcoma (Prostate	1	0	0	0	1.0000	0.8737	1	2%	IN
60	Thyroid	6035	Follicular adenoma (Thyro	1	0	0	1	0.4844	0.3663	1	2%	IN
62	Adrenal	6239	Pheochromocytoma (Adrenal	0	1	0	0	0.8043	0.7745	0	.0%	IN
64	Cerebrum	6433	Glioma	0	1	0	0	0.7692	0.8170	0	.0%	IN

			(Cerebrum)									
64	Cerebrum	6436	Meningioma (Cerebrum)	0	0	1	0	0.5249	0.6227	0	0%	FA
72	Bone (sternum)	7272	Hemangiosarcoma (Bone)	0	0	1	0	0.5121	0.6112	0	0%	FA
74	Bone (vertebra)	7278	Osteosarcoma (Bone)	1	0	0	1	0.4399	0.3284	1	2%	FA
81	Harderian gland	8135	Adenoma (Harderian gland)	8	5	7	5	0.7935	0.7972	8	13%	IN
86	Skin	8631	Papilloma (Skin)	1	0	0	0	1.0000	0.8737	1	2%	IN
86	Skin	8640	Fibroma (Skin)	1	0	0	0	1.0000	0.8737	1	2%	IN
86	Skin	8642	Hemangioma (Skin)	0	0	1	0	0.5934	0.6641	0	0%	IN
86	Skin	8650	Schwannoma (Skin)	0	0	1	2	0.0666	0.0458	0	0%	IN
86	Skin	8672	Hemangiosarcoma (Skin)	0	0	1	0	0.5739	0.6514	0	0%	FA
86	Skin	8676	Leiomyosarcoma (Skin)	0	0	0	2	0.0984	0.0264	0	0%	FA
86	Skin	8680	Malignant schwannoma (Ski	0	1	0	0	0.7784	0.7953	0	0%	FA
86	Skin	8684	Histiocytic sarcoma (Skin	0	1	1	1	0.4148	0.4604	0	0%	IN
99	General	9988	Myelogenic leukemia (Gene	0	0	0	2	0.0630	0.0120	0	0%	FA
99	General	9989	Malignant lymphoma (Gener	7	9	10	6	0.8272	0.8290	7	12%	MX

Table 7: Study 011932, Number of Animals Dying during Given Time Intervals, Female Mice

	Treatment Group		Total
	CTRL1	LOW	
	N	N	N
Week 0-52	1	6	7
53-78	12	12	24
79-91	12	16	28
92-100	10	11	21
101-101	25	15	40
Total	60	60	120

Table 8: Study 011932, Dose-Mortality Trend Tests* for Female Mice

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	4.25	0.0391
Kruskal-Wallis	Dose-Mortality Trend	4.70	0.0302

* The results are produced by: Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2:1, by Donald G. Thomas, National Cancer Institute.

Figure 3: Study 011932, Kaplan Meier Survival Curves in Female Mice

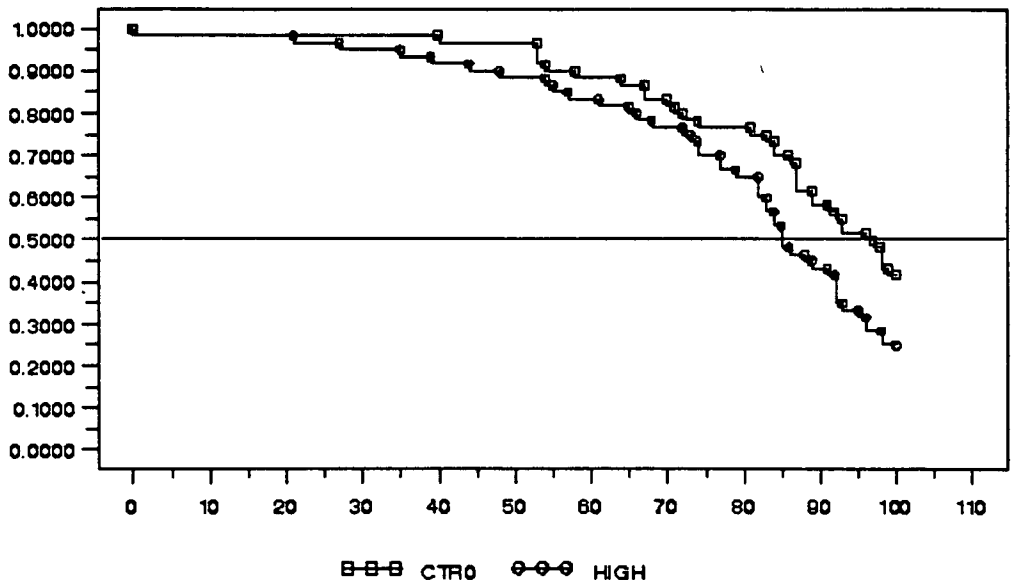

Table 9: Study 011932, Test for Dose-Dependent Linear Trend in Tumors, Female Mice

Organ Code	Organ Name	Tumor Code	Tumor Name	CTRL1	LOW	pValue (Exact)	pValue (Asymp)	Natural Tumor # in control group	Natural Rate (in ctrl group)	Tumor type
13	Spleen	1342	Hemangioma (Spleen)	1	0	1.0000	0.8604	1	2%	IN
13	Spleen	1354	Histiocytoma (Spleen)	0	1	0.5714	0.2026	0	.0%	IN
13	Spleen	1372	Hemangiosarcoma (Spleen)	2	0	1.0000	0.9059	2	3%	IN
13	Spleen	1384	Histiocytic sarcoma (Sple	0	2	0.2993	0.1033	0	.0%	IN
18	Lung	1835	Adenoma (Lung)	11	12	0.4067	0.3228	11	18%	IN
18	Lung	1865	Adenocarcinoma (Lung)	10	9	0.4906	0.3978	10	17%	MX
18	Lung	1884	Histiocytic sarcoma (Lung	0	1	0.4237	0.1287	0	.0%	FA
31	Small intestine	3176	Leiomyosarcoma (Small int	0	1	0.3889	0.1114	0	.0%	FA
34	Liver	3435	Hepatocellular adenoma (L	2	0	1.0000	0.8717	2	3%	IN
34	Liver	3442	Hemangioma (Liver)	1	2	0.5612	0.3337	1	2%	IN
34	Liver	3465	Henatocellular	2	0	1.0000	0.8717	2	3%	IN

			carcinoma							
34	Liver	3484	Histiocytic sarcoma (Live	3	1	0.8752	0.7422	3	5%	FA
36	Gallbladder	3635	Adenoma (Gallbladder)	0	1	0.5714	0.2026	0	.0%	IN
37	Pancreas	3735	Acinar cell adenoma (Panc	0	1	0.5238	0.1788	0	.0%	IN
38	Kidney	3835	Adenoma (Kidney)	0	1	0.5238	0.1788	0	.0%	IN
41	Urinary bladder	4146	Leiomyoma (Urinary bladde	0	1	0.3846	0.1092	0	.0%	IN
52	Ovary	5232	Granulosa cell tumor (Ova	2	1	0.9575	0.8395	2	3%	IN
52	Ovary	5236	Adenoma (Ovary)	1	1	0.6154	0.3649	1	2%	IN
54	Uterus	5431	Endometrial stromal polyp	8	2	0.9876	0.9654	8	13%	IN
54	Uterus	5446	Leiomyoma (Uterus)	5	1	0.9670	0.9064	5	8%	IN
54	Uterus	5465	Adenocarcinoma (Uterus)	2	0	1.0000	0.9280	2	3%	MX
54	Uterus	5484	Histiocytic sarcoma (Uter	3	0	1.0000	0.9732	3	5%	IN
59	Pituitary	5935	Anterior adenoma (Pituita	5	14	0.0044	0.0023	5	8%	MX
60	Thyroid	6035	Follicular adenoma (Thyro	2	0	1.0000	0.9543	2	3%	IN
62	Adrenal	6236	Subcapsular cell adenoma	1	0	1.0000	0.7907	1	2%	IN
62	Adrenal	6239	Pheochromocytoma (Adrenal	2	0	1.0000	0.9179	2	3%	IN
81	Harderian gland	8135	Adenoma (Harderian gland)	3	4	0.3930	0.2584	3	5%	IN
86	Skin	8631	Papilloma (Skin)	1	0	1.0000	0.8827	1	2%	IN
86	Skin	8632	Keratoacantoma (Skin)	0	1	0.3750	0.1045	0	.0%	IN
86	Skin	8636	Myxoma (Skin)	1	0	1.0000	0.8604	1	2%	IN
86	Skin	8650	Schwannoma (Skin)	0	1	0.5238	0.1788	0	.0%	IN
86	Skin	8672	Hemangiosarcoma (Skin)	1	0	1.0000	0.7882	1	2%	FA
86	Skin	8676	Leiomyosarcoma (Skin)	1	0	1.0000	0.8148	1	2%	FA
95	Mammary gland	9535	Adenoma (Mammary gland)	0	1	0.5238	0.1788	0	.0%	IN
95	Mammary gland	9542	Hemangioma (Mammary gland	0	1	0.5714	0.2026	0	.0%	IN
95	Mammary	9565	Adenocarcino	1	14	0.0000	0.0000	1	2%	MX

	gland		ma (Mammary g							
95	Mammary gland	9566	Adenoacantho ma (Mammary g	0	11	0.0000	0.0000	0	0%	MX
95	Mammary gland	9568	Carcinosarcom a (Mammary g	1	3	0.2307	0.1102	1	2%	MX
99	General	9984	Histiocytic sarcoma (Gene	0	1	0.4237	0.1287	0	0%	FA
99	General	9989	Malignant lymphoma (Gener	13	9	0.6290	0.5513	13	22%	MX

Table 10: Study 011932, Number of Animals Dying during Given Time Intervals, Male Mice

	Treatment Group		Total
	CTRL1	LOW	
	N	N	N
Week			
0-52	2	4	6
53-78	11	8	19
79-91	14	8	22
92-104	18	12	30
105-105	15	28	43
Total	60	60	120

Table 11: Study 011932, Dose-Mortality Trend Tests* for Male Mice

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	5.14	0.0234
Kruskal-Wallis	Dose-Mortality Trend	4.32	0.0376

* The results are produced by: Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2:1, by Donald G. Thomas, National Cancer Institute.

Figure 4: Study 011932, Kaplan Meier Survival Curves in Male Mice

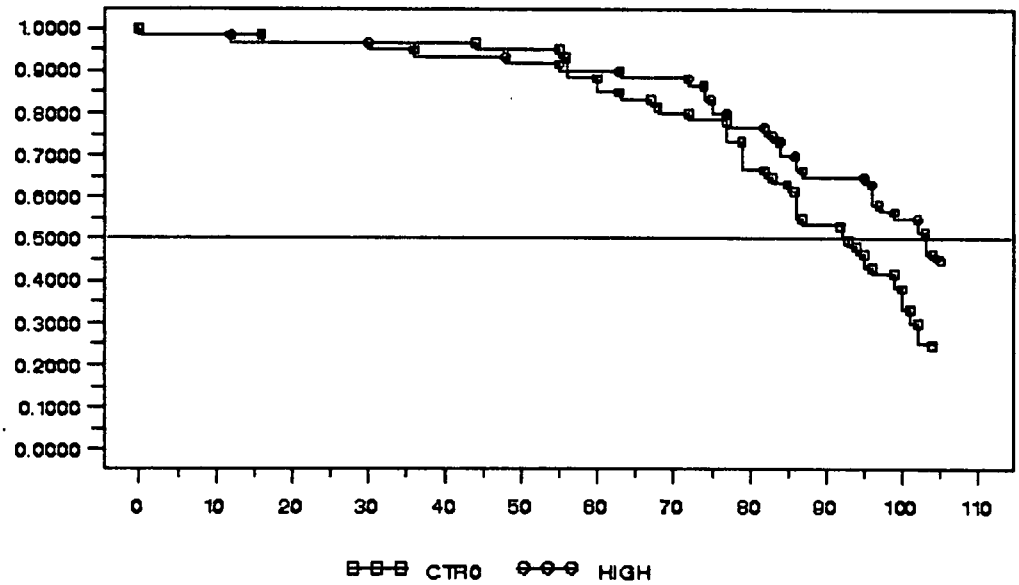

Table 12: Study 011932, Test for Dose-Dependent Linear Trend in Tumors, Male Mice

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL1	LOW	Tumor type	pValue (Exact)	pValue (Asymp)
Spleen	13	Hemangioma (Spleen)	1342	2%	1	1	IN	0.7907	0.7900
Lung	18	Adenoma (Lung)	1835	15%	9	11	IN	0.3951	0.3955
Lung	18	Adenocarcinoma (Lung)	1865	23%	14	20	MX	0.5342	0.5320
Small intestine	31	Adenoma (Small intestine)	3135	.0%	0	1	IN	0.4000	0.4191
Small intestine	31	Adenocarcinoma (Small int	3165	.0%	0	2	FA	0.2765	0.2627
Large intestine	32	Mucinous carcinoma (Large	3261	.0%	0	1	IN	0.6512	0.6244
Liver	34	Hepatocellular adenoma (L	3435	28%	17	21	IN	0.2079	0.2088
Liver	34	Hemangioma (Liver)	3442	.0%	0	2	IN	0.2742	0.2665
Liver	34	Hepatocellular carcinoma	3465	20%	12	13	MX	0.4242	0.4242
Liver	34	Hemangiosarcoma (Liver)	3472	.0%	0	1	FA	0.5102	0.5081
Gallbladder	36	Adenoma (Gallbladder)	3635	2%	1	3	IN	0.5641	0.5454
Urinary bladder	41	Papilloma (Urinary	4131	2%	1	0	IN	1.0000	0.9669

		bladde							
Testis	43	Interstitial cell tumor (	4337	2%	1	1	IN	0.6483	0.6703
Testis	43	Rete testes adenoma (Test	4339	3%	2	0	IN	1.0000	0.9966
Pituitary	59	Anterior adenoma (Pituita	5935	.0%	0	2	IN	0.2742	0.2665
Thyroid	60	Follicular adenoma (Thyro	6035	.0%	0	1	IN	0.4000	0.4191
Skeletal muscle (m. trice	78	Schwannoma (Skeletal musc	7850	2%	1	0	IN	1.0000	0.9637
Harderian gland	81	Adenoma (Harderian gland)	8135	8%	5	4	IN	0.4950	0.5035
Skin	86	Hemangioma (Skin)	8642	.0%	0	1	IN	0.4000	0.4191
Skin	86	Leiomyoma (Skin)	8646	.0%	0	1	IN	0.3636	0.3884
Skin	86	Schwannoma (Skin)	8650	2%	1	0	IN	1.0000	0.9921
Skin	86	Hemangiosarcoma (Skin)	8672	2%	1	0	IN	1.0000	0.9669
Skin	86	Histiocytic sarcoma (Skin	8684	2%	1	0	IN	1.0000	0.9689
General	99	Histiocytic sarcoma (Gene	9984	3%	2	0	FA	1.0000	0.9918
General	99	Myelogenic leukemia (Gene	9988	2%	1	0	FA	1.0000	0.9873
General	99	Malignant lymphoma (Gener	9989	8%	5	4	MX	0.8114	0.8114

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Executive CAC
Date of Meeting: 7/16/02
Mouse/Rat Carcinogenicity Studies

Committee: Joseph Contrera, Ph.D., HFD-901, Acting Chair
Jim Farrelly Ph.D., HFD-530, Alternate Member
Abby Jacobs, Ph.D., HFD-540, Alternate Member
Barry Rosloff, Ph.D., Supervisory Pharmacologist
Lois Freed, Ph.D.HFD-120, Presenting Reviewer

Author of Draft: Lois M. Freed, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA #21-436
Drug Name: aripiprazole
Sponsor: Otsuka Pharmaceuticals

Mouse Carcinogenicity Studies: two 2-yr dietary carcinogenicity studies were conducted in CD-1 mice. Study 1 was conducted at doses of 0, 1, 3, and 10 mg/kg. No dose-limiting toxicities were observed. No drug-related tumors were detected in male mice. In female mice, there were significant increases in anterior pituitary adenomas and mammary gland tumors [adenocarcinoma, adenoacanthoma] at 3 and 10 mg/kg. Study 2 was conducted at doses of 0 and 30 mg/kg. Body weight was reduced in drug-treated males [10%] relative to control males. Mortality rate was significantly increased in drug-treated females. No drug-related tumor findings were detected in male mice. In female mice, there were significant increases in anterior pituitary adenoma and mammary gland tumors [adenocarcinoma, adenoacanthoma] in drug-treated females. The sponsor attributed the neoplastic findings to increases in serum prolactin [not measured in the carcinogenicity studies]; a direct drug-effect on DNA synthesis in the pituitary was also suggested as a possible mechanism underlying the increase in pituitary adenomas.

Rat Carcinogenicity Studies: two 2-yr dietary carcinogenicity studies were conducted in rats. Study 1 was conducted in Fischer 344 rats at doses of 0, 1, 3, and 10 mg/kg. No dose-limiting toxicities were observed. No drug-related tumors were detected in male rats. In female rats, there was a significant increase in mammary gland fibroadenomas at the HD. Study 2 was conducted in Sprague-Dawley rats at doses of 0, 0, 10, 20, 40, and 60 mg/kg. Dose-related decreases in body weight [compared to controls] were observed in both males and females. No drug-related tumor findings were detected in male rats. In female rats, there was a significant increase in adrenocortical tumors [carcinoma, combined adenoma and carcinoma]. No mechanism was proposed by the sponsor for the adrenocortical tumors.

Executive CAC Recommendations and Conclusions: the ExeCAC concluded that the assessment of carcinogenic potential was adequate in both mice and rats based on body wt effects in male mice, male rats, and female rats and on an increase in mortality in female mice at the highest doses tested. Aripiprazole was negative for neoplasms in male mice and rats. In female mice, pituitary adenomas and mammary gland tumors [adenocarcinoma, adenoacanthoma] at 3, 10, and 30 mg/kg were considered drug-related. In female rats, the increase in mammary gland fibroadenomas at 10 mg/kg in Study 1 and the increase in adrenocortical tumors [carcinoma, combined adenoma/carcinoma] at 60 mg/kg in Study 2 were considered drug-related.

The Committee recommended that the sponsor be asked to provide evidence for an association between

mammary gland adenoacanthomas and hyperprolactinemia.

Joseph Contrera, Ph.D.
Acting Chair, Executive CAC

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Joe Contrera
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