CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

Rat Carcinogenicity Study

NDA/Serial Number:	21- 641
Drug Name:	Rasagiline Mesylate
Indication:	Parkinson's Disease
Applicant:	Teva
Date:	Originally Submitted: 8/01/2003 Supplemental tissue evaluation submitted 11/04/2004; Final datasets submitted 05/24/05
Biometrics Division:	Division of Biometrics I, HFD-710
Statistical Reviewer:	Tristan Massie, Ph.D.
Concurring Reviewers:	Roswitha Kelly, M.S., Pre-Clinical Coordinator James Hung, Ph.D., Acting Deputy Director
Medical Division:	Neuropharmacological Drug Products, HFD-120
Pharm/Tox Team:	Paul Roney, Ph.D. Lois Freed, Ph.D. Team Leader
Project Manager:	Theresa Wheelous

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1. Executive Summary

1.1. Conclusions and Recommendations

Occasionally in carcinogenicity studies the complete set of tissues from terminally sacrificed animals are only examined for the control and high dose groups. A supplemental evaluation of the low and middle dose groups was performed for this rat study because the high dose groups exhibited significantly lower average body weight compared to the controls and there were no statistically significant tumor trends. Before the supplemental evaluation the test for trend in Ovarian B-Granulosa Theca Cell tumors in female rats was nearly significant. After the supplemental evaluation this trend was statistically significant. This was the only significant change in conclusions that resulted from the supplemental evaluation. However, this trend in Ovarian B-Granulosa Theca cell tumors was not significant when the high dose was excluded. Aside from the low dose vs. placebo comparison of the incidence of Parathyroid B-Adenomas in males which was cited in the original review of the rat study no other tumor findings reached statistical significance.

The occurrence of 1 melanoma in the male high dose group, although not statistically significant, is notable because of the concerns about melanoma in humans. There were no other melanomas reported in any other group.

1.2. Brief Overview of Carcinogenicity Study

In the rat study Rasagiline Mesylate was administered daily by gavage to .CD®(SD)IGS BR rats for at least 104 weeks at target dose levels (expressed in terms of base) of 0.3, 1.0, and 3.0 mg/kg/day for males (Groups 3-5, respectively) and 0.5, 2.0, 5.0, and 17.0 mg/kg/day for females (Groups 3-6, respectively). Control rats (Groups 1 and 2; 0 mg/kg/day) received the vehicle (distilled water). All doses were given at a constant volume of 10 mL/kg/day. Each main study group had 65 males and 65 females.

1.3. Statistical Issues and Findings

The high dose groups exhibited much lower average body weight relative to the controls so the sponsor was advised to go back and examine the low and middle dose groups more thoroughly. Average body weight was also statistically significantly lower in the male medium dose group (1 mg/kg) and the female medium high dose group (5 mg/kg) than in the controls. Only the male low and the female low and medium groups did not have more than 10% lower average body weight than the controls at week 52. However, the male medium and female medium high groups had greater average body weight than the high groups.

There was no dose mortality trend apparent in males or females. The trend in females in incidence of B-Granulosa Theca Cell Tumors in the Ovary was statistically significant when the high dose was included but not otherwise. There were no other significant tests

for trend in the females either excluding or including the high dose group. There were no significant tests for trend in males either excluding or including the high dose group. There were no significant pairwise comparisons in females but in males the low dose had a statistically significant increase compared to the combined control groups in B-Adenomas in the Parathyroid.

When the sponsor initially submitted this data after the supplemental examination of the middle and low dose groups, we found that there were some inconsistencies between the study report and the data set in the number of tissues examined. In particular, it appeared that fewer male low and middle dose group animals were at risk at terminal sacrifice than what was expected based on the mortality analysis. The lower numbers of animals at risk inflated the tumor incidence rates of several tumor/tissue combinations and resulted in statistical significance for M-Lymphomas in Hemato Neoplasia in females and M-Leukemia in Hemato Neoplasia in males when the high dose groups were excluded. In addition, the male medium dose appeared to have statistically significant increases compared to the combined control groups in B-Adenoma, Hepatocellular tumors in the Liver and M-Leukemias in Hemato Neoplasia. In all of these cases of statistical significance there were at most 2 tumors in a dose group. Thus, it is not surprising that the statistical significance of these tumors disappeared when the numbers of animals at risk in the low and middle dose groups at terminal sacrifice were changed to their proper, larger values.

In summary, in females, only the trend (including the high dose group) in Ovarian B-Granulosa/Theca Cell Tumors was statistically significant. When the high dose was excluded this trend was not significant. In males, only the pairwise comparison of the incidence of B-Adenomas in the Parathyroid between the low dose group and the combined control groups was statistically significant.

The only significant change in conclusions that resulted from the supplemental evaluation was that the increase in Ovarian B-Granulosa Theca Cell tumors went from borderline significant to significant.

2. Introduction

2.1. Overview

In addition to the two year rat study reviewed here the sponsor conducted a two year mouse study. The mouse study was previously reviewed with the original submission. It was deemed adequate. For the results of the mouse study and the original results of the rat study before the supplemental examination please see the original statistical review of carcinogenicity dated February 9, 2004.

Although in the original analysis of the rat study there were no statistically significant tumor trends for the drug groups relative to the controls there was concern because the high dose groups exhibited significantly lower average body weight (~20% difference) compared to the control groups suggesting that the MTD was exceeded. In the initial

pathology evaluation all tissues from animals that died prior to study termination were examined regardless of the animal's dose. All tissues from terminally sacrificed animals were examined for control and high dose animals. However, in the terminally sacrificed low and mid dose groups (group 3 (0.3 mg/kg) and 4 (1.0 mg/kg) of males, and groups 3 (0.5 mg/kg), 4 (2 mg/kg), and 5 (5 mg/kg) of females) only tissues containing grossly visible lesions were evaluated. Since the lower dose animals were not all thoroughly examined the following statement was included in the approvable letter.

For the 2-year carcinogenicity study in rats, you need to conduct microscopic analysis of a full battery of tissues in the low and mid-dose groups. This additional analysis is needed because the high dose, although not associated with an increase in any tumor type, was associated with an excessive decrease in body weight (relative to controls). That is, the high dose exceeded a maximally tolerated dose, defined as a >10% decrease in body weight relative to controls. This request has previously been provided to you in the minutes of the Executive Carcinogenicity Assessment Committee meeting held on June 8, 2004.

2.2. Data Sources

The rat data which was revised based on the supplemental evaluation is located at the following address:
\\Cdsesub1\n21641\N_000\2004-11-04\pharmtox\datasets\6751-109

We found inconsistencies between records in the submitted TUMOR data set, between the TUMOR data set and the sponsor's report, and between the TUMOR and the MICRO data files. For example, the number of mid-dose animals at risk at the time of terminal sacrifice and the number of animals having a particular tissue examined varied greatly even after the supplemental evaluation. Further, we found in the TUMOR data set animals which had one record indicating a specific tumor in a particular organ and another record indicating that this organ was not even examined. We raised these issues with the sponsor. Initially, they stated that their analyses utilized the TUMOR dataset for tumor incidences but went to the MICRO data set to determine which animals were examined for each particular tissue and, thus, in their opinion, there was no need to correct the organ examination data in the TUMOR file. However, since their datasets did not conform to the agency standards for the submission of electronic carcinogenicity data and since our analysis program relies strictly on the format of the TUMOR data file specified in the guidance we needed a complete and correct TUMOR.xpt file from the sponsor. After another teleconference with the sponsor they submitted a revised TUMOR data set and asserted that it was accurate. This data set is located at the following address:

\\Cdsesub1\n21641\N_000\2005-05-24\pharmtox\datasets\6751-109

The original rat data submitted before the examination of the terminally sacrificed animals in the low and middle dose groups is located at the following address:
\\Cdsesub1\n21641\N_000\2003-09-05\pharmtox\datasets\6751-109.

3. Statistical Evaluation

3.1. Rat Study 6751-109

Statistical Methods

The sponsor used the Cochran-Armitage test to test for trends in tumor incidence and Fisher's exact test for pairwise comparisons. These tests do not adjust for intercurrent mortality. This reviewer used the prevalence method for incidental tumors and the death rate method for fatal tumors as described by Peto (1980) which do adjust for intercurrent mortality. This reviewer combined the two control groups for the analysis and used the dose values as the scores in the trend test. The sponsor only analyzed the trend tests with the high dose group included but this reviewer also considered trend tests without the high dose group since the high dose exceeded the MTD. The standard FDA significance levels for two (one rat and one mouse) two year carcinogenicity studies, which adjust for the multiplicity of testing, are 0.025 for trend tests for rare tumors and 0.005 for common tumors; for pair-wise comparisons the FDA significance levels are 0.05 for rare tumors and 0.01 for common tumors. Rare tumors are those which occur in 1 % or less of the control group.

3.1.1. Sponsor's Results

Tissues from a total of 105 animals were selected for the re-examination of the low and mid dose groups. This corresponds to the number of middle and low dose group animals that underwent terminal sacrifice. The numbers of animals evaluated per group in this supplemental evaluation are shown in Table 1.

Table 1 Number of Animals Evaluated in Middle Dose Groups for Supplemental Evaluation

Sex	Group	Dose (mg/kg)	N examined
Males	Group 3 (Low)	0.3	24
	Group 4 (Medium)	1	22
Females	Group 3 (Low)	0.5	23
	Group 4 (Medium)	2	16
	Group 5 (Medium High)	5	20

All efforts were made to perform this supplemental evaluation in a manner as consistent as possible with the initial evaluation. However, the pathologist who performed the initial evaluation was no longer available so a different pathologist performed the supplemental evaluation.

In the view of the sponsor the results of this supplemental evaluation served to confirm the findings of the original evaluation regarding effects related to test article administration and no additional test article related effects were observed.

3.1.2. Reviewer's Results

Female Rats

The 2 mg/kg (medium low) and 5 mg/kg (medium high) female groups had 5% and 11% lower average weight than the combined controls, respectively, at week 52. The high dose, 17 mg/kg, had a 19% lower weight than the controls at week 52. At week 78 the weight differential relative to the controls was 4, 16, and 22 percent for the medium, medium high, and high dose groups, respectively. Thus, both the high and the medium high doses exceeded the 10% threshold of excessively lower body weight relative to the controls but the medium high group was closer to the threshold.

The test for a dose-mortality trend among the female groups (excluding the high dose) was not significant ($p>0.155$). Note that as indicated in the original review the test for a dose mortality trend was not significant when the high dose was included either ($p=0.5796$). More than 25 animals were surviving in each group at week 80 thus there were adequate numbers for length of exposure and for animals at risk.

Table 2 Female Rats: Tests for Dose Mortality Relationship (Excluding High Dose group)

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	2.6957	0.441	3.1794	0.3648
Dose-Mortality Trend	1.2142	0.2705	2.0197	0.1553
Homogeneity	3.9099	0.4183	5.1991	0.2675

After including the data from the supplementary examinations there was a statistically significant trend in females in B-Granulosa/Theca Cell tumors in the Ovary. However, this tumor trend is not statistically significant if the high dose is excluded. The pairwise comparison between the high dose and combined controls was also not significant.

The complete table of tumor incidences and tests for tumor trend both excluding and including the high dose is shown below in Table 3.

Table 3 Female Rats: Tumor Incidence and Tests for Trends

Organ Code	Organ Name	Tumor Code	Tumor Name	DOSE1 Control 1	DOSE2 Control 2	DOSE3 0.5 mg/kg	DOSE4 2 mg/kg	DOSE5 5 mg/kg	DOSE6 17 mg/kg	Groups 1-5 Trend P-Value (Exact/ Asymptotic)	Groups 1-6 Trend P-Value (Exact/ Asymptotic)
AC	ADRENAL, CORTEX	248	B-ADENOMA	1	1	2	1	0	0	0.862/ 0.892	0.941/ 0.907
AC	ADRENAL, CORTEX	286	M-CARCINOMA	2	0	0	0	1	0	0.480/ 0.463	0.700/ 0.764
AM	ADRENAL,	249	B-	2	2	3	1	1	1	0.762/	0.782/

	MEDULLA		PHEOCHROMOCYTOMA							0.795	0.795
AM	ADRENAL, MEDULLA	481	M-MALIGNANT PHEOCHROMOCYTOMA	0	0	1	0	0	0	0.560/ 0.762	0.639/ 0.747
BR	BRAIN W/STEM	294	M-ASTROCYTOMA	1	0	0	2	1	1	0.208/ 0.216	0.310/ 0.376
CV	UTERUS, CERVIX	173	B-FIBROMA	1	0	0	0	0	0	1.000/ 0.879	1.000/ 0.779
CV	UTERUS, CERVIX	268	M-NEUROFIBROSARCOMA	1	0	0	0	0	0	1.000/ 0.847	1.000/ 0.777
CV	UTERUS, CERVIX	325	B-LEIOMYOMA	0	0	0	0	0	1	NA	0.150/ 0.014
HN	HEMATO NEOPLASIA	2	M-LYMPHOMA	0	0	1	1	1	1	0.162/ 0.205	0.202/ 0.268
HN	HEMATO NEOPLASIA	264	M-SARCOMA, HISTOCYTIC	0	1	1	1	1	2	0.304/ 0.355	0.142/ 0.150
KD	KIDNEY	300	M-LIPOSARCOMA	0	2	0	0	0	0	1.000/ 0.895	1.000/ 0.839
KD	KIDNEY	380	B-LIPOMA	0	1	1	1	1	0	0.298/ 0.348	0.691/ 0.790
LI	LIVER	280	M-CARCINOMA, HEPATOCELLULAR	0	1	0	0	0	1	1.000/ 0.848	0.351/ 0.198
LI	LIVER	385	B-CHOLANGIOMA	0	0	1	0	0	0	0.578/ 0.775	0.667/ 0.761
LI	LIVER	409	B-ADENOMA, HEPATOCELLULAR	1	0	0	0	0	0	1.000/ 0.841	1.000/ 0.773
LU	LUNG	400	M-LEIOMYOSARCOMA	0	0	0	0	0	1	NA	0.210/ 0.036
MF0	MAMMARY,CRANIAL	145	B-FIBROADENOMA	20	12	13	9	14	12	0.653/ 0.664	0.715/ 0.721
MF0	MAMMARY,CRANIAL	221	M-ADENOCARCINOMA	0	7	4	0	0	1	0.998/ 0.990	0.932/ 0.925
MF0	MAMMARY,CRANIAL	225	B-ADENOMA	0	0	0	1	0	0	0.471/ 0.545	0.513/ 0.624
MF0	MAMMARY,CRANIAL	461	M-FIBROSARCOMA	0	1	0	0	0	0	1.000/ 0.874	1.000/ 0.776
MF1	MAMMARY,CAUDAL	132	B-ADENOMA	1	2	1	2	3	1	0.162/ 0.167	0.496/ 0.537
MF1	MAMMARY,CAUDAL	195	M-ADENOCARCINOMA	5	4	6	6	1	0	0.923/ 0.922	0.999/ 0.994
MF1	MAMMARY,CAUDAL	206	B-FIBROADENOMA	15	22	19	14	13	5	0.883/ 0.886	1.000/ 1.000
MF1	MAMMARY,CAUDAL	383	B-FIBROMA	0	0	0	1	0	0	0.365/ 0.457	0.500/ 0.683
MF1	MAMMARY,CAUDAL	393	M-SARCOMA, NOS	0	0	0	1	0	0	0.365/ 0.457	0.500/ 0.683
MF1	MAMMARY,CAUDAL	407	M-NEUROFIBROSARCOMA	0	0	0	2	0	0	0.334/ 0.361	0.589/ 0.733
OV	OVARY	320	B-GRANULOSA/THECA CELL TUMOR	0	0	0	0	1	2	0.191/ 0.050	0.018/ 0.006
OV	OVARY	420	B-ADENOMA, INTERSTITIAL GLD	0	1	0	0	0	0	1.000/ 0.850	1.000/ 0.785
OV	OVARY	441	M-SERTOLI CELL TUMOR	0	1	0	0	0	0	1.000/ 0.841	1.000/ 0.773
PA	PANCREAS	301	M-CARCINOMA, ISLET CELL	1	0	0	0	0	1	1.000/ 0.840	0.303/ 0.157
PA	PANCREAS	353	B-ADENOMA, ISLET CELL	2	0	0	0	1	0	0.474/ 0.455	0.698/ 0.763
PA	PANCREAS	424	B-ADENOMA, ACINAR CELL	0	1	1	0	0	0	0.820/ 0.854	0.883/ 0.835
PC	CAVITY, ABDOM	102	M-NEUROFIBROSARCOMA	0	0	0	0	0	1	NA	0.667/ 0.268
PI	PITUITARY	429	M-CARCINOMA	0	0	0	1	0	0	0.368/	0.486/

										0.484	0.673
PI	PITUITARY	86	B-ADENOMA	57	57	59	51	58	51	0.234/ 0.239	0.803/ 0.805
PT	PARATHYROID	422	B-ADENOMA	0	0	1	0	0	0	0.628/ 0.785	0.688/ 0.750
SQ	SUBCUTANEOUS TIS	150	M-SARCOMA, NOS	0	2	0	0	0	0	1.000/ 0.892	1.000/ 0.871
SQ	SUBCUTANEOUS TIS	217	M-MALIG FIBROUS HISTIOCYTOMA	1	0	0	0	0	0	1.000/ 0.892	1.000/ 0.892
SQ	SUBCUTANEOUS TIS	304	M-HEMANGIOSARCOMA	0	0	1	0	0	0	1.000/ 0.921	1.000/ 0.921
SQ	SUBCUTANEOUS TIS	329	B-FIBROMA	0	0	0	1	0	1	0.333/ 0.240	0.167/ 0.146
SQ	SUBCUTANEOUS TIS	330	M-FIBROSARCOMA	0	0	0	1	0	0	0.333/ 0.240	0.333/ 0.240
SS	SKIN, OTHER	363	M-NEUROFIBROSARCOMA	2	0	2	1	0	0	0.981/ 0.980	0.996/ 0.969
SS	SKIN, OTHER	382	B-KERATOACANTHOMA	0	0	0	1	0	0	0.714/ 0.685	0.795/ 0.772
SS	SKIN, OTHER	421	B-SQUAMOUS CELL PAPILLOMA	0	1	0	0	1	0	0.520/ 0.492	0.719/ 0.773
SS	SKIN, OTHER	426	M-SQUAMOUS CELL CARCINOMA	0	0	0	2	0	0	0.580/ 0.602	0.733/ 0.778
SS	SKIN, OTHER	446	B-BASAL CELL ADENOMA	0	0	0	1	0	0	0.517/ 0.600	0.606/ 0.704
TH	THYMUS	387	M-THYMOMA	0	0	1	1	0	0	0.426/ 0.601	0.626/ 0.770
TY	THYROID	246	B-"C" CELL ADENOMA	5	6	4	6	3	2	0.724/ 0.742	0.927/ 0.922
TY	THYROID	297	B-FOLLICULAR CELL ADENOMA	0	2	0	0	1	0	0.480/ 0.463	0.700/ 0.764
TY	THYROID	299	M-FOLLICULAR CELL CARCINOMA	1	3	0	2	1	1	0.543/ 0.600	0.630/ 0.674
TY	THYROID	443	M-"C" CELL CARCINOMA	0	0	1	0	2	1	0.048/ 0.037	0.162/ 0.197
UT	UTERUS	214	B-ENDOMETRIAL STROMAL POLYP	6	4	0	2	3	5	0.626/ 0.656	0.252/ 0.260
UT	UTERUS	392	B-LEIOMYOMA	0	1	0	1	0	1	0.597/ 0.687	0.313/ 0.307
VA	VAGINA	331	M-NEUROFIBROSARCOMA	1	1	0	0	0	0	1.000/ 0.897	1.000/ 0.854

Male Rats

The 0.3 mg/kg (low), 1 mg/kg (medium), and 3 mg/kg (high) male groups had respectively 5%, 14%, and 22% lower average weight than the controls at week 52. At week 78 the average body weight was 3%, 13%, and 22 % lower for the low, medium, and high dose groups, respectively, relative to the combined controls. Thus, both the high and the medium doses exceeded the 10% threshold of excessively lower weight relative to the controls but the medium dose group was closer to the threshold than the high dose group.

The test for a dose-mortality trend among the male groups (excluding the high dose) was not significant ($p \geq 0.6598$, Table 4). Note that as indicated in the original review this test was also not significant when the high dose was included ($p=0.541$). More than 25 animals were surviving in each group at week 80 providing adequate numbers for length of exposure and for animals at risk.

Table 4 Male Rats: Tests for Dose Mortality Relationship (Excluding High Dose Group)

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	1.2216	0.5429	1.4996	0.4725
Dose-Mortality Trend	0.1937	0.6598	0.1095	0.7407
Homogeneity	1.4153	0.702	1.6091	0.6573

There were no statistically significant trends in tumor incidence in the males. However, the low dose had a statistically significant increase compared to the combined control groups in B-Adenomas in the Parathyroid (exact p=0.0037). The medium dose had a statistically significant increase in B-Follicular Cell Adenomas in the Thyroid compared to control group 1 (exact p=0.008) but not to the combined control groups (exact p=0.039 > 0.01).

Table 5 shows all tumors and all tests for trend both excluding and including the high dose group (3 mg/kg).

Table 5 Male Rats: Tumor Incidence and Tests for Trends

Organ Code	Organ Name	Tumor Code	Tumor Name	DOSE1 Control 1	DOSE2 Control 2	DOSE3 0.3 mg/kg	DOSE4 1 mg/kg	DOSE5 3 mg/kg	Groups 1-4 Trend P-Value (Exact/ Asymptotic)	Groups 1-5 Trend P-Value (Exact/ Asymptotic)
AC	ADRENAL, CORTEX	256	B-ADENOMA	1	1	0	0	2	1.000/ 0.976	0.137/ 0.130
AC	ADRENAL, CORTEX	259	M-CARCINOMA	1	1	0	0	1	1.000/ 0.979	0.491/ 0.518
AM	ADRENAL, MEDULLA	156	B-PHEOCHROMOCYTOMA	10	8	7	11	3	0.331/ 0.418	0.967/ 0.968
AM	ADRENAL, MEDULLA	297	M-MALIGNANT PHEOCHROMOCYTOMA	5	4	2	0	2	0.998/ 0.997	0.873/ 0.894
BR	BRAIN W/STEM	14	M-OLIGODENDROGLIOMA	0	0	0	1	0	0.251/ 0.335	0.399/ 0.624
BR	BRAIN W/STEM	174	M-ASTROCYTOMA	2	0	0	0	1	1.000/ 0.979	0.507/ 0.532
BR	BRAIN W/STEM	322	B-GRANULAR CELL TUMOR	0	1	0	0	0	1.000/ 0.981	1.000/ 0.884
DU	DUODENUM	450	M-CARCINOMA	0	1	0	0	0	1.000/ 0.981	1.000/ 0.891
HC	HEAD, CORONAL	192	M-NEUROFIBROSARCOMA	0	0	1	0	0	0.200/ 0.985	0.429/ 0.796
HC	HEAD, CORONAL	266	M-CARCINOMA, SQUAMOUS CELL	0	1	0	0	0	NA	1.000/ 0.856
HN	HEMATO NEOPLASIA	316	M-SARCOMA, HISTOCYTIC	3	2	4	2	0	0.652/ 0.764	0.970/ 0.967
HN	HEMATO NEOPLASIA	418	M-LEUKEMIA, LARGE GRANULAR L	0	1	0	2	1	0.170/ 0.256	0.257/ 0.338
HT	HEART	360	M-	0	0	0	1	1	0.248/	0.122/

			NEUROFIBROSARCOMA						0.340	0.135
HT	HEART	451	M-ATRIOCAVAL MESOTHELIOMA	0	1	0	0	0	1.000/ 0.980	1.000/ 0.886
JE	JEJUNUM	436	M-CARCINOMA	1	0	0	0	0	1.000/ 0.981	1.000/ 0.892
KD	KIDNEY	185	M-LIPOSARCOMA	1	0	0	0	0	1.000/ 0.979	1.000/ 0.886
KD	KIDNEY	402	M-CARCINOMA, TUBULAR CELL	0	1	0	0	0	1.000/ 0.980	1.000/ 0.884
KD	KIDNEY	405	B-LIPOMA	0	0	2	0	0	0.510/ 0.838	0.665/ 0.836
LC	CORD, LUMBAR	354	M-ASTROCYTOMA	0	0	0	1	0	0.236/ 0.327	0.368/ 0.605
LI	LIVER	335	M-CARCINOMA, HEPATOCELLULAR	0	2	3	2	0	0.307/ 0.455	0.811/ 0.862
LI	LIVER	433	B-ADENOMA, HEPATOCELLULAR	1	0	0	2	0	0.166/ 0.255	0.599/ 0.737
LI	LIVER	487	B-CHOLANGIOMA	0	0	0	1	0	0.261/ 0.354	0.420/ 0.641
MM	MAMMARY, MALE	143	B-FIBROADENOMA	0	1	0	0	0	1.000/ 1.000	1.000/ 1.000
MM	MAMMARY, MALE	300	B-FIBROMA	2	1	3	1	0	0.267/ 0.476	0.738/ 0.869
MM	MAMMARY, MALE	482	B-LIPOMA	0	0	1	0	0	0.667/ 0.939	0.750/ 0.839
MS	LN, MESENTERIC	118	M-HEMANGIOSARCOMA	0	1	0	1	0	0.389/ 0.568	0.597/ 0.761
MS	LN, MESENTERIC	310	B-HEMANGIOMA	0	0	0	0	1	NA	0.115/ 0.024
PA	PANCREAS	206	B-ADENOMA, ISLET CELL	5	3	3	4	2	0.526/ 0.644	0.709/ 0.755
PA	PANCREAS	396	M-SARCOMA, NOS	0	1	0	0	0	1.000/ 0.980	1.000/ 0.884
PA	PANCREAS	444	M-CARCINOMA, ISLET CELL	0	1	0	2	0	0.166/ 0.255	0.599/ 0.737
PA	PANCREAS	481	M-CARCINOMA, ACINAR CELL	1	0	0	0	0	1.000/ 0.982	1.000/ 0.884
PA	PANCREAS	503	B-ADENOMA, ACINAR CELL	0	0	2	0	0	0.535/ 0.849	0.714/ 0.858
PI	PITUITARY	138	M-ASTROCYTOMA	1	1	0	0	1	1.000/ 0.974	0.521/ 0.521
PI	PITUITARY	60	B-ADENOMA	42	51	46	34	33	0.974/ 0.978	0.984/ 0.983
PR	PROSTATE	85	M-CARCINOMA	0	1	0	0	0	1.000/ 0.978	1.000/ 0.885
PT	PARATHYROID	149	B-ADENOMA	0	0	5	1	0	0.272/ 0.460	0.804/ 0.868
SP	SPLEEN	181	M-HEMANGIOSARCOMA	1	0	0	0	0	1.000/ 0.976	1.000/ 0.885
SQ	SUBCUTANEOUS TIS	313	B-FIBROMA	1	1	0	1	1	0.625/ 0.740	0.458/ 0.454
SQ	SUBCUTANEOUS TIS	431	B-LIPOMA	1	0	0	0	1	1.000/ 0.993	0.600/ 0.508
SQ	SUBCUTANEOUS TIS	467	M-NEUROFIBROSARCOMA	0	0	1	0	0	0.750/ 0.949	0.833/ 0.877
SS	SKIN, OTHER	136	B-SQUAMOUS CELL PAPILLOMA	5	3	1	1	1	0.986/ 0.991	0.981/ 0.979
SS	SKIN, OTHER	148	B-FIBROMA	0	0	3	1	1	0.401/ 0.597	0.525/ 0.626
SS	SKIN, OTHER	200	B-KERATOACANTHOMA	2	3	3	1	3	0.930/ 0.959	0.728/ 0.766
SS	SKIN, OTHER	253	M-SQUAMOUS CELL	2	1	0	1	1	0.746/	0.600/

			CARCINOMA						0.877	0.670
SS	SKIN, OTHER	263	B-LIPOMA	1	0	0	0	0	1.000/ 0.970	1.000/ 0.886
SS	SKIN, OTHER	311	M-MELANOMA	0	0	0	0	1	NA	0.188/ 0.068
SS	SKIN, OTHER	381	M-NEUROFIBROSARCOMA	1	0	1	1	1	0.494/ 0.680	0.383/ 0.465
SS	SKIN, OTHER	465	B-ADENOMA, SEBACEOUS	0	0	0	0	2	NA	0.079/ 0.031
SS	SKIN, OTHER	468	M-FIBROSARCOMA	0	0	1	0	0	0.633/ 0.928	0.738/ 0.866
TE	TESTIS	291	B-SEMINOMA	1	0	0	0	0	1.000/ 0.973	1.000/ 0.888
TE	TESTIS	299	B-INTERSTITIAL CELL TUMOR	1	3	0	0	3	1.000/ 0.987	0.130/ 0.150
TY	THYROID	139	M-FOLLICULAR CELL CARCINOMA	1	0	2	0	0	0.677/ 0.889	0.835/ 0.896
TY	THYROID	220	B-FOLLICULAR CELL ADENOMA	0	4	3	7	1	0.023/ 0.033	0.572/ 0.629
TY	THYROID	270	B-"C" CELL ADENOMA	4	3	6	6	6	0.201/ 0.274	0.137/ 0.151
TY	THYROID	387	M-"C" CELL CARCINOMA	0	1	2	0	1	0.714/ 0.903	0.468/ 0.558

Findings related to inconsistency of sponsor's study report and 11/04/2004 Tumor.xpt data file

For the sake of having a complete account of the events that transpired in the review of this rat study this section documents the statistically significant findings that were found based on the 11/04/2004 TUMOR dataset. However, as detailed below, several of these findings are not significant based on the 05/24/2005 TUMOR data set that superseded the 11/04/2004 data set.

In the original data submission, before the sponsor went back and examined the low and middle dose group animals that were terminally sacrificed, an animal had a record only if either a tumor was observed in a particular tissue or if a particular tissue was not examined for that animal. When a tissue was properly examined but did not show any tumor, no record was made of this finding. Once the sponsor re-examined the low and middle dose terminally sacrificed animals, they apparently did not remove from the TUMOR data set the records which indicated that a tissue had previously not been examined, but simply added any new findings. Therefore, inconsistencies arose for terminally sacrificed animals that had tumors found in the supplemental examination but whose tissues had not been originally examined. For example, in the 09/05/2003 TUMOR data set animal C01580 (a terminally sacrificed male middle dose animal) had a single record associated with the adrenal medulla and this record indicated that the adrenal medulla was not examined. However, in the 11/04/2004 TUMOR data set animal C01580 had two contradictory records associated with the adrenal medulla organ. The first record indicated that the adrenal medulla was not examined, while the second one suggested that the adrenal medulla was examined and a B-Pheochromocytoma tumor was found there. Similarly, some animals showed two records for certain tissues, each indicating that the tissue was not examined. Thus, it seemed that the sponsor had not

checked the 11/04/2004 TUMOR data set for inconsistencies after adding the findings from the supplemental examination. We could not be certain of this though.

Another issue was that the 11/04/2004 TUMOR and MICRO data sets did not always agree on how many terminally sacrificed low and middle dose group animals were examined for certain tissues. For example, the TUMOR data set suggested that the thyroid gland was examined in only 6 mid-dose males that were terminally sacrificed. However, 23 mid-dose males were killed at terminal sacrifice and the MICRO dataset suggested that the thyroid gland was examined in all 23 of these animals. A similar problem occurred for other tissues. The result of these discrepancies was that in the reviewer's analyses there were statistically significant tumor findings based on the TUMOR file that were not significant based on the sponsor's report which relied on the MICRO file. For example, consider the parathyroid. There were 5 benign adenomas in the low group and 1 in the medium group. Table 6 shows the incidence of these tumors categorized by the time the animal died and the group the animal belonged to. The first row for a given time interval gives the number of animals that died in that interval with an incidental (non-fatal) b-adenoma in the parathyroid. The second row gives the number of animals that died in that time interval but did not have a b-adenoma in the parathyroid. According to the table there is only 1 animal at risk in the 1 mg group at terminal sacrifice which implies that the 22 other sacrificed male middle dose animals did not have their parathyroids examined. Having 0 out of 1 animals in the middle dose group without a tumor does not necessarily preclude the existence of a trend and thus the statistic for this time interval is driven by the large incidence in the 0.3 mg group. If there were only tumors at terminal sacrifice the p-value would be (p=.0393 based on this time interval alone) but since there was also a tumor in the 1 mg dose group between weeks 79 and 91 and none in the other groups the overall p-value is smaller (p=0.012). Since there weren't any of these tumors in the control groups the appropriate significance level for the trend test is 0.025 and the result is significant. However, according to the sponsor's most recent submission of this data actually 18 male 1 mg group animals had their parathyroid tissues examined at terminal sacrifice and only 5 did not. Since, in this case, none of these 18 middle dose animals had this tumor a trend is no longer supported. The p-value for the terminal sacrifice table alone would be 0.493 and the overall result which also includes the tumor that occurred between weeks 79 and 91 is no longer statistically significant (p=0.2721).

Table 6 Incidence of Parathyroid B-Adenomas in Males by Time Interval

Time Interval	Table Row#	DOSE1 Control 1	DOSE2 Control 2	DOSE3 0.3 mg/kg	DOSE4 1 mg/kg
79-91	1	0	0	0	1
79-91	2	11	15	6	13
FINALKILL105-106	1	0	0	5	0
FINALKILL105-106	2	20	19	16	1*
Total		0	0	5	1

* 1 based on 11/04/2004 TUMOR.xpt data file
18 based on 05/24/2005 TUMOR.xpt data file

For the same reason, namely lower and apparently incorrect numbers at risk at terminal sacrifice in the middle and low dose groups, several other tumors were found to be statistically significant based on the 11/04/2004 data. These are listed in Table 7.

Table 7 Tumors Originally Thought To Be Significant On The Basis Of 11/04/04 TUMOR.xpt Data

	TREND EXCLUDING HIGH DOSE	LOW VS. CONTROLS	MIDDLE VS. CONTROLS
Males	Hemato Neoplasia M-Leukemias	Parathyroid B-Adenomas	1) Hemato Neoplasia M-Leukemias ; 2) Liver B-Adenoma, Hepatocellular
Females	Hemato Neoplasia M-Lymphomas		

The sponsor stated that the tissue examination data in the 11/04/2004 MICRO data set was correct and that in their analyses they used the TUMOR data set for the incidence of tumors but the number of tissues examined was determined from the MICRO data set. However, because of the inconsistency of the tissue examination information between the MICRO and TUMOR data sets and since our carcinogenicity software program relies on the TUMOR.xpt file only (see: Guidance for Industry: Providing Regulatory Submissions in Electronic Format -NDA) we requested the sponsor to validate the data sets and correct any errors or inconsistencies. Only the low dose vs. combined controls comparison of the Parathyroid B-Adenomas remains statistically significant for the corrected TUMOR.xpt data set, submitted on 05/24/2005. Note that the trend in Ovarian B-Granulosa Theca cell tumors in female rats including the high dose group was also statistically significant based on the final 05/24/2005 data.

4. Conclusions

The high dose groups exhibited large weight differences relative to the controls so the sponsor was advised to go back and examine the low and middle dose groups more thoroughly. Average weight was also statistically significantly less in the male medium dose group (1 mg/kg) and the female medium high dose group (5 mg/kg) than in the controls. Only the male low and the female low and medium dose groups did not have more than 10% lower average body weight than the controls at week 52. However, the male medium dose group and the female medium high dose groups had higher average body weight than the high dose groups and their weight difference relative to the controls was closer to the 10% threshold.

There was no dose mortality trend apparent in males or females. The only statistically significant test for trend in tumor incidence was for Ovarian B-Granulosa/Theca Cell Tumors. However, this was not statistically significant when the high dose was excluded, nor was the high dose vs. combined control comparison statistically significant. In fact, there were no significant pairwise comparisons in females but in males the low dose had a statistically significant increase compared to the combined control groups in B-Adenomas in the Parathyroid.

When the sponsor initially submitted this data, after the supplemental examination of the middle and low dose groups, we found that there were some inconsistencies between the study report and the data set in the number of tissues examined. In particular, it appeared that for certain tissues fewer male low and middle dose group animals were at risk at terminal sacrifice than what was expected based on the mortality analysis. This resulted in the apparent statistical significance of several tumors. In all of these cases of statistical significance there were at most 2 tumors in a dose group and thus, it is not surprising that the statistical significance of these tumors disappeared when the numbers of animals at risk in the low and middle dose groups at terminal sacrifice were changed to their proper, larger values.

In summary, in females, only the trend (including the high dose group) in Ovarian B-Granulosa/Theca Cell Tumors was statistically significant. When the high dose group was excluded, the trend did not reach statistical significance. In males, only the pairwise comparison of the incidence of B-Adenomas in the Parathyroid between the low dose group and the combined control groups was statistically significant. The only significant change in conclusions that resulted from the supplemental evaluation of the terminally sacrificed low and middle dose group animals was that the trend in Ovarian B-Granulosa Theca Cell tumors went from borderline significant to significant.

The occurrence of 1 melanoma in the male high dose group is also notable although it was not statistically significant. There were no other melanomas reported in any other group.

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Tristan Massie
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Roswitha Kelly
7/21/05 09:50:05 AM
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James Hung
7/24/05 11:40:24 AM
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-641
Drug Name:	Agilect ® Rasagiline Mesylate
Indication(s):	Parkinson's Disease
Applicant:	TEVA Neuroscience, Inc.
Date(s):	Submitted September 5, 2003
Review Priority:	Standard
Biometrics Division:	Division I (HFD-710)
Statistical Reviewer:	Sharon Yan, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader
	James Hung, Ph.D., Acting Deputy Director
	Kooros Mahjoob, Ph.D., Acting Director
	Charles Anello, Sc. D., Deputy Director (HFD-700)
Medical Division:	Neuropharmacological Drug Products (HFD-120)
Clinical Team:	Leonard Kapcala, M.D., Clinical Reviewer
	Lisa Jones, M.D., Safety Reviewer
	John Feeney, M.D., Team Leader
	Russell Katz, M.D., Director
Project Manager:	Teresa Wheelous, R.Ph., (PM)

Table of Contents

1. EXECUTIVE SUMMARY

This NDA submitted by TEVA Neuroscience provided clinical support for the use of rasagiline 1 mg and 2 mg as a mono-therapy and rasagiline 0.5 mg and 1 mg as adjunctive therapy for the treatment of Parkinson's disease. The application contained information of 3 pivotal, randomized, double-blind, placebo-controlled studies.

1.1 Conclusions and Recommendations

The studies TEMPO, LARGO, and PRESTO have demonstrated that rasagiline at dosages of 1 mg and 2 mg is superior to placebo as mono-therapy with respect to the measure of total UPDRS score, and rasagiline at dosages of 0.5 mg and 1 mg is superior to placebo as adjunctive therapy as measured by total daily "Off" time.

Numerically, rasagiline 1 mg appeared to be as effective as rasagiline 2 mg when used as mono-therapy, as shown in Study TEMPO. Rasagiline 0.5 mg was numerically less effective than rasagiline 1 mg but could be the lowest effective dose when used as adjunctive therapy, as shown in Study PRESTO.

1.2 Brief Overview of Clinical Studies

The clinical program of rasagiline consisted of 3 pivotal studies: TEMPO for mono-therapy, and LARGO and PRESTO for adjunctive therapy. A summary of the studies is presented in Table 1.

Table 1 Summary of Pivotal Studies with Mean (SD) Changes in the Primary Efficacy Endpoint

Study/ Protocol #	Indication	Duration	Primary Endpoint	Treatment Group Mean (SD)				
				0.5 mg	1 mg	2 mg	Entacap	Placebo
TEMPO (232) (North America)	Mono	26 weeks	Change in UPDRS III	N/A	0.06 p=.0001	0.72 p=.0001	N/A	3.91
LARGO (122) (EU, Israel, Argentina)	Adjunct	18 weeks	Change in daily "Off" time (hour)	N/A	-1.17 p=.0001	N/A	-1.19 p=.0001	-.35
PRESTO (North America)	Adjunct	26 weeks	Change in daily "Off" time (hour)	-1.38 p=.0199	-1.85 p=.0001	N/A	N/A	-.88

Primary efficacy data for the use of rasagiline as monotherapy in Parkinson's disease (PD) were derived from the 6-month placebo-controlled phase of study TEMPO. The study consisted of a double-blind, randomized, placebo-controlled, parallel group design for 6 months, followed by a 6-months active treatment phase. The study was conducted in US and Canada. A total of 404 subjects were randomized, of whom 266 received rasagiline (1 mg: 134; 2 mg: 132), and 138 received placebo. The primary efficacy endpoint of the study was the change from baseline to treatment in UPDRS subtotal of section III scores. Significant benefit of rasagiline treatment with respect to this endpoint was shown in the study.

Efficacy data for the use of rasagiline as adjunct therapy to Levodopa (LD) were derived from two studies: LARGO and PRESTO. Both studies were of a double-blind, randomized, placebo-controlled, parallel group design. Rasagiline at 1 mg dose was studied in LARGO, and rasagiline at doses of 0.5 mg and 1 mg was studied in PRESTO. LARGO also included an active comparator of entacopone. The duration of double-blind treatment phase was 18 weeks for LARGO and 26 weeks for PRESTO. A total of 687 subjects were randomized in LARGO, of whom 231 received rasagiline 1 mg, 229 received placebo, and 227 received entacapone 200 mg with each dose of LD. In PRESTO, a total of 472 subjects were randomized, of whom 149 received rasagiline 1 mg, 164 received rasagiline 0.5 mg, and 159 received placebo.

The protocol-defined primary efficacy endpoint for LARGO and PRESTO was the change from baseline in the mean total daily "Off" time from home diary. In both studies, rasagiline was shown to be more effective than placebo with statistical significance with respect to the primary efficacy endpoint.

1.3 Statistical Issues and Findings

Study TEMPO was conducted in early Parkinson's disease patients who were not treated with Levodopa (LD) at the enrollment. The primary efficacy parameter was the change from baseline in total UPDRS score. After 6 months of treatment with rasagiline as mono-therapy, the mean UPDRS score remained quite similar to baseline value for the two rasagiline groups, while increased by about 4 points for the placebo-treated patients. It appears that rasagiline 1 mg is as effective as rasagiline 2 mg.

When used as adjunctive therapy, patients who were treated with rasagiline showed a decrease in the total daily "Off" time by at least one hour at the end of the treatment phase, while patients who were treated with placebo remained at the same level as baseline in their total daily "Off" time. It was also found in both adjunctive therapy studies that while rasagiline-treated patients had decrease in the total daily "Off" time, their times spent in "On without dyskinesia" were increased.

It was first brought to my attention by medical office Dr. Leonard Kapcala that Study LARGO was upsized after sample reassessment when 1/3 of patients completed the study. It was planned to enroll 450 subjects (150 in each group), but a total of 687 subjects were actually randomized. The protocol was not amended to reflect the change.

This reviewer has examined the data of the first 450 subjects (originally projected sample size). The treatment difference between rasagiline 1 mg and placebo carried a p-value of 0.0005 for the first 450 subjects. Therefore, the treatment difference would be significant even if the sample size was not increased.

2. INTRODUCTION

2.1 Overview

This NDA submission consisted of 3 pivotal studies for the treatment of Parkinson's disease: TEMPO for mono-therapy; LARGO and PRESTO for adjunctive therapy. All three studies were of randomized, double-blind, placebo-controlled, and parallel group design.

In the mono-therapy study of TEMPO, rasagiline 1 mg and 2 mg were used to compare with the treatment of placebo. For the adjunctive therapy, rasagiline 1 mg was used in LARGO, and rasagiline 0.5 mg and 1 mg were used in PRESTO. An active comparator of entacopone was also included in LARGO.

The primary efficacy endpoint for the mono-therapy TEMPO was the change from baseline in the total UPDRS. For the two adjunctive therapy studies, the primary efficacy endpoint was the change from baseline in the total daily "Off" time. All three studies showed significance treatment effect with respect to their corresponding primary efficacy endpoints.

2.2 Data Sources

The path to the CDER Electronic Document Room (EDR) is:
http:\\Cdsesub1\n21641\N_000\2003-09-05\clinstat

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Monotherapy - Study TEMPO (Protocol 232)

3.1.1.1 Study Objectives

The objectives of this study were to assess the efficacy, tolerability and safety of two doses of rasagiline in early PD patients who were not receiving or did not require LD/carbidopa therapy.

3.1.1.2 Study Design

This was a North American, multicenter (32 centers: 28 US and 4 Canadian centers), randomized, double-blind, parallel group, phase III clinical study conducted to early PD patients. The study consisted of a 26-week, placebo-controlled treatment phase followed by a 26-week active-treatment phase.

Patients were randomized in equal numbers to one of two (1 or 2 mg/day) dosages of rasagiline or to placebo. A one-week titration period was followed by a 25-week maintenance period during the placebo-controlled phase.

The second phase of the study was a 26-week active-treatment phase in which investigators and patients remained blinded to treatment assignment. Patients were transferred to the active-treatment phase if additional therapy was required before completing the 26-week placbo-controlled phase.

To be included in the study, patients were required to have idiopathic PD with a severity of <= 3 in USA or < 3 in Canada on the Modified Hoehn and Yahr scale. For at least six weeks prior to baseline, patients could not be treated with LD or dopamine agonists.

3.1.1.3 Efficacy Measures and Statistical Analysis Methods

Primary Efficacy Endpoint and Analysis

The efficacy evaluation was based on the 26-week placebo-controlled phase. The primary efficacy endpoint for the placebo-controlled phase was the change in subtotal of UPDRS section III scores (ADL, Motor, and Mentation) from baseline to the termination visit. UPDRS was measured at Weeks 0 (baseline), 4, 8, 14, 20, and 26 (termination). Patients that needed LD therapy before the 26-week visit and any others who terminated prematurely from the study had their last observation carried forward (LOCF). Missing items in the UPDRS scale were replaced according to the LOCF rule.

The baseline adjusted analysis of covariance was to be used for comparing the adjusted mean differences between the changes observed in each of the active drug groups versus placebo (two contrasts) incorporating terms for treatment and center. Baseline UPDRS was to be included in the model as a covariate. A treatment-by-center interaction term was to be included in the model if it was significance ($p < .05$).

Secondary Efficacy Endpoints and Analyses

The individual sub-scales of the UPDRS scores, namely, mental, motor and ADL as well as Hoehn and Yahr stage and Schwab and England ADL were to be analyzed in the same way as total UPDRS. Time to need for LD therapy and proportion of patients who did not need LD therapy at the end of 6-month placebo-controlled phase were also included as secondary efficacy parameters. No adjustment for multiple testing was proposed.

3.1.1.4 Patient Disposition

Four hundred and seventy-three (473) patients were screened. Of these, 404 (84%) patients enrolled and were randomly allocated to three treatment groups: 1 or 2 mg rasagiline or placebo (Table 2).

Table 2 Distribution of Patients by Country

TVP-1012/232 Placebo-Controlled Phase	1 mg		2 mg		PLACEBO		All	
	N	%	N	%	N	%	N	%
CANADA	18	13.4	14	10.6	15	10.9	47	11.6
USA	116	86.6	118	89.4	123	89.1	357	88.4
All	134	100.0	132	100.0	138	100.0	404	100.0

Table 3 summarizes the termination reasons by treatment group and the need for LD therapy. One hundred and eleven (82.8%) patients on 1 mg rasagiline, 105 (79.5%) patients on 2 mg rasagiline, and 112 (81.2%) patients on placebo completed the 6-month, placebo-controlled phase of the study without needing LD therapy. Patients, who fail to complete the placebo-controlled phase due to a need for LD and continued into the active-treatment phase, were not considered as early withdrawals.

Table 3 Termination Reasons by the Need for Additional Anti-PD Therapy

TVP-1012/232 Placebo-Controlled Phase		1 mg		2 mg		PLACEBO		All	
		N	%	N	%	N	%	N	%
Need for Additional Therapy	Termination Reason								
No	Normal Completion	111	93.3	105	95.5	112	97.4	328	95.3
	Adverse Experience	5	4.2	1	0.9	1	0.9	7	2.0
	Failed to Return	1	0.8	.	.	.	.	1	0.3
	Subject Request	2	1.7	2	1.8	2	1.7	6	1.7
	Unsatisfactory Response	.	.	1	0.9	.	.	1	0.3
	Other	.	.	1	0.9	.	.	1	0.3
	All	119	88.8	110	83.3	115	83.3	344	85.1
Yes	Termination Reason								
	Normal Completion	14	93.3	19	86.4	21	91.3	54	90.0
	Adverse Experience	.	.	1	4.5	.	.	1	1.7
	Subject Request	.	.	.	.	1	4.3	1	1.7
	Unsatisfactory Response	.	.	1	4.5	1	4.3	2	3.3
	Protocol Violation	.	.	1	4.5	.	.	1	1.7
	Other	1	6.7	.	.	.	.	1	1.7
	All	15	11.2	22	16.7	23	16.7	60	14.9
All	Termination Reason								
	Normal Completion	125	93.3	124	93.9	133	96.4	382	94.6
	AE	5	3.7	2	1.5	1	0.7	8	2.0
	Failed to Return	1	0.7	.	.	.	.	1	0.2
	Subject Request	2	1.5	2	1.5	3	2.2	7	1.7
	Unsatisfactory Response	.	.	2	1.5	1	0.7	3	0.7
	Protocol Violation	.	.	1	0.8	.	.	1	0.2
	Other	1	0.7	1	0.8	.	.	2	0.5
	All	134	100.0	132	100.0	138	100.0	404	100.0

*assessed as a need for LD

3.1.1.5 Demographic and Baseline Characteristics

Summary statistics of baseline demographic characteristics is provided in Table 4. The sponsor reported that a great majority of subjects were Caucasians (95%). There were no statistically significant differences between the treatment groups in demographic characteristics.

Table 4 Patient Demographic Characteristics by Treatment Group

Characteristic	Rasagiline 1 mg (n=134)	Rasagiline 2 mg (n=132)	Placebo (n=138)
Sex (n, %)			
Male	90 (67.2)	74 (56.1)	93 (67.4)
Female	44 (32.8)	58 (43.9)	45 (32.6)
Age (years)			
Mean (SD)	61.6 (10.3)	60.4 (11.4)	60.5 (10.8)
Min	33	32	32
Max	92	79	92

Symptoms at the time of PD diagnosis for all patients are presented in Table 5 by treatment group. Most patients had defined symptoms and signs of the disease such as tremor, rigidity and bradykinesia. Less than one sixth of the patients exhibited postural disturbances at the time of diagnosis. No statistically significant differences between treatment groups were reported.

Table 5 Symptoms at the Time of PD Diagnosis for All Patients by Treatment Group

Symptoms at Diagnosis	Rasagiline 1 mg (n=134)		Rasagiline 2 mg (n=132)		Placebo (n=138)	
	N	%	N	%	N	%
Tremor	114	85.1	116	87.9	111	80.4
Rigidity	86	64.2	96	72.7	91	65.9
Bradykinesia	82	61.2	85	64.4	102	73.9
Posture	15	11.2	20	15.2	18	13.0

On average, mean disease duration in all treatment groups was one year at study entry: 0.94 year for the placebo, 0.93 year for the 1 mg rasagiline and 1.16 year for the 2 mg group (ranged from few days to 10.6 years). Disease durations for all treatment groups were similar.

Baseline disease characteristics are displayed in Table 6. No statistical significant differences (ANOVA) between groups were reported, except for UPDRS mental scale (p=0.0123).

Table 6 Patient Disease Characteristics at Baseline by Treatment Group

	Rasagilien 1 mg (n=134) Mean (SD)	Rasagiline 2 mg (n=132) Mean (SD)	Placebo (n=138) Mean (SD)
Total UPDRS	24.69 (11.25)	25.89 (9.54)	24.54 (11.61)
UPDRS Mental	0.94 (1.11)	1.20 (1.27)	0.79 (1.08)
UPDRS ADL	5.90 (3.35)	6.73 (3.22)	6.16 (3.53)
UPDRS Motor	17.85 (8.89)	17.95 (7.52)	17.59 (8.84)
S/E ADL Subject	92.31 (5.87)	90.68 (7.04)	91.81 (5.95)
S/E ADL Rater	92.16 (5.67)	90.23 (6.17)	91.20 (6.32)
H/Y Stage	1.85 (0.48)	1.88 (0.48)	1.86 (0.50)
QOL Score	28.30 (15.16)	30.19 (16.79)	26.95 (15.67)
Timed Motor Score	12.78 (3.91)	13.02 (3.25)	13.52 (6.24)
BECK Total Score	2.39 (2.47)	3.05 (3.22)	2.54 (2.79)
Mini Mental Status	29.1 (1.5)	29.1 (1.3)	29.2 (1.2)

3.1.1.6 Efficacy Results

The efficacy results present in this section are from reviewer's analyses. The results obtained by this reviewer are mostly identical to the ones reported by the sponsor with some minor differences. All analyses were applied to ITT subject population using LOCF for missing values.

3.1.1.6.1 Primary Efficacy Endpoint - Change from Baseline in Total UPDRS Score

Total UPDRS scores and the change from baseline are shown by week in Table 7. The LOCF imputation scheme was implemented to account for early discontinuation and any interim missing data.

Table 7 Mean Total UPDRS Scores and Change from Baseline by Treatment Group [Source: Reviewer's Analysis]

	Rasagiline 1 mg (n=134)			Rasagiline 2 mg (n=132)			Placebo (n=138)	
	Mean	Mean Change	p-value	Mean	Mean Change	p-value	Mean	Mean Change
Baseline	24.69			25.87			24.54	
Week 4	23.57	-1.12	0.1394	24.01	-1.68	0.0066	23.83	-0.42
Week 8	23.16	-1.53	0.0001	24.45	-1.44	0.0001	25.43	0.89
Week 14	23.21	-1.48	0.0001	24.48	-1.24	0.0001	25.66	1.12
Week 20	23.92	-0.77	0.0001	24.87	-1.02	0.0001	26.82	2.28
Week 26 (Primary Endpoint)	**24.75**	**0.06**	**0.0001**	**26.61**	**0.72**	**0.0001**	**28.44**	**3.91**

A decrease from baseline in total UPDRS was observed in all treatment groups at Week 4, which disappeared in the next visit in the placebo group. Starting from Week 8, there was a steady

increase in UPDRS in the placebo group, from an increase of 0.89 point at Week 8 to an increase of 3.91 at the at Week 26 termination. For the two rasagiline treatment groups, there were decreases in UPDRS from Week 4 through Week 20, but such decreases in UPDRS turned to an increase of 0.06 and 0.72 point for 1 mg and 2 mg groups, respectively, at the Week 26.

The principal statistical analysis compared the mean change from baseline in total UPDRS for each of the active-treatment groups to placebo (two contrasts) using ANCOVA adjusted for baseline UPDRS, treatment, center and treatment-by-center interaction.

Following 26 weeks of treatment, the change from baseline UPDRS differed significantly between either of the active-treatment groups and the placebo ($p<0.0001$ for both contrasts using Hochberg's Step-up Bonferroni procedure for multiple comparisons). The Least Square estimate of the treatment difference in UPDRS between 1 mg and placebo was -4.20 points (95% CI [-5.65, -2.75]), and the difference between 2 mg and placebo was -3.56 points (95% CI [-5.03, -2.09]).

3.1.1.6.2 Secondary Endpoints

Secondary efficacy variables listed in the Statistical Analysis Plan (SAP) included individual sub-scales of the UPDRS scores, namely, mental, motor and ADL as well as Hoehn and Yahr stage, Schwab and England ADL, and time to need for LD therapy. Except for time to need for LD therapy, which was to be analyzed by Cox's proportional hazard model, all other secondary efficacy variables were analyzed in the same way as total UPDRS. The sponsor did not propose any methods for the adjustment of multiple testing in order to control for the type I error. Therefore, the results of analyses of secondary efficacy variables are considered exploratory, and the p-values included in the following table are nominal p-values and should be interpreted cautiously.

Table 8 Summary of Secondary Efficacy Results by Treatment Group [Source: Reviewer's Analysis]

	Rasagiline 1 mg (n=134) Mean (SD)	Rasagiline 2 mg (n=132) Mean (SD)	Placebo (n=138) Mean (SD)
Mental Score			
Baseline	0.94 (1.11)	1.20 (1.27)	0.79 (1.08)
Change	0.15 (1.50)	-0.04 (1.25)	0.34 (1.06)
Nominal p-value	0.1771	0.0503	
ADL Score			
Baseline	5.90 (3.35)	6.73 (3.22)	6.16 (3.53)
Change	0.21 (2.57)	-0.06 (2.39)	1.18 (2.48)
Nominal p-value	0.0001	0.0001	
Motor Score			
Baseline	17.85 (8.89)	17.95 (7.52)	17.59 (8.84)
Change	-0.29 (4.92)	0.82 (4.46)	2.38 (6.29)
Nominal p-value	0.0001	0.0050	

The mean UPDRS mental at baseline was higher in the 2 mg group compared to the 1 mg and placebo groups. The differences between the treatment groups in the change of mental score were small at the Week 26 termination and did not reach statistical significance (Table 8).

Following 26-week treatment period, patients on both doses of rasagiline maintained mean ADL and mean Motor scores similar to baseline, while patients on placebo experienced an increase of 1.18 point in their mean ADL score and an increase of 2.38 points in their mean Motor score (Table 8).

Since few patients needed LD therapy during the placebo-controlled phase, time to need for LD therapy and proportion of patient who needed LD therapy were not analyzed.

3.1.2 Adjunctive Therapy - Study LARGO (Protocol 122)

3.1.2.1 Objectives

The objectives of the study were to evaluate the efficacy, tolerability and safety of rasagiline mesylate versus placebo in PD subjects with motor fluctuations on levodopa/peripheral dopa decarboxylase inhibitor (DDI, i.e. carbidopa or benserazide) therapy.

3.1.2.2 Study Design

This was a multicenter, double-blind, double-dummy, randomized, placebo and entacapone-controlled study that was conducted in 3 parallel groups of PD subjects in Europe, Argentina and Israel. It was designed to assess the efficacy and safety of rasagiline mesylate as an adjunctive therapy to levodopa/DDI. On entering the study, subjects were being treated chronically with levodopa/DDI therapy and were experiencing motor fluctuations.

The double-blind treatment phase consisted of an 18-week period divided into an initial 6-week levodopa dose adjustment phase and a subsequent 12-week levodopa dose maintenance phase.

Following a screening visit to ensure study eligibility, subjects entered a 2 to 4 week placebo "run-in" phase during which a subject's individual levodopa/DDI dosage regimen was optimized. After being optimized, the dosage regimen had to remain stable for at least 2 weeks before the subject underwent randomization at visit 0 (baseline).

Subjects were randomized based on a 1:1:1 assignment ratio into one of the following treatment groups:

1) Rasagiline mesylate 1 mg once daily
2) Placebo
3) Entacapone 200 mg with each levodopa dose

The levodopa dosage could be decreased for the first 6 weeks of the study period at the discretion of the investigator but had to remain constant for the last 12 weeks.

Post-randomization visits were conducted at the end of week 3/visit 1, week 6/visit 2, week 10/visit 3, week 14/visit 4 and week 18/visit 5.

The primary study objective and a number of other endpoints were assessed from data recorded by subjects in the "24-hour" diary in which subjects rated themselves as "ON without dyskinesia or without troublesome dyskinesia", "ON with troublesome dyskinesias", "OFF", or "asleep". Subjects were instructed on how to complete the diary at the screening visit and thereafter completed it during the 3 consecutive days immediately prior to baseline, and during the 3 consecutive days immediately prior to visits 2, 3, 4, and 5.

3.1.2.3 Efficacy Measures and Statistical Analysis Methods

Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint for this trial was the change from baseline to treatment in the mean total daily "OFF" time.

The mean total daily "Off" time during treatment was based on averaging measurements from Week 6 through Week 18 (12 daily diaries). Baseline measurement for an individual subject was the mean value of total daily "Off" time recorded in 3 diaries completed before randomization.

The principal statistical analysis of the primary endpoint was an Analysis of Covariance (ANCOVA) comparing the adjusted means of the changes observed in the rasagiline 1mg/day treatment group to placebo by performing a single degree of freedom comparison (contrast) in a model that includes the 3 treatment groups. The model includes the effects of treatment group, center and baseline mean total daily "OFF" time as a covariate. The treatment-by-center interaction was to be included in the model if it is found to be statistically significant ($p<.10$).

Secondary Endpoints and Analyses

Three secondary endpoints were pre-defined for this study. The hierarchical approach at an alpha level of 5% for each secondary endpoint was to be used to protect from an inflation of Type-I error. The three secondary endpoints, given in the hierarchical order of the statistical analysis, are:

1. Global Improvement by Examiner

   This scale is part of the Clinical Global Evaluation (CGE) questionnaire. The range of the Global Improvement by examiner scale is from: -3 = "Very much improved", through 0 = "No change", to 3 = "Very much worse".

2. Change from baseline to last observed value in UPDRS ADL (Activities of Daily Living) during "OFF" state.

   The UPDRS ADL during "OFF" state score is the sum of 13 items (each item ranges from 0 to 4).

3. Change from baseline to last observed value in UPDRS Motor during "ON" state.

   The UPDRS motor score is the sum of 27 items (each item ranges from 0 to 4).

The Global Improvement scale by examiner was to be analyzed using baseline adjusted analysis of covariance, comparing the adjusted means of the changes observed in the rasagiline group versus placebo. Terms for treatment and center were to be included in the model. The treatment-by-center interaction was to be included in the model if it was found to be statistically significant ($p<.10$).

For UPDRS ADL and Motor subscores, baseline-adjusted analysis of covariance was to be used for comparing the adjusted means of the changes observed in the rasagiline group versus placebo, incorporating terms for treatment and center, with baseline scores included in the model as a covariate.

For the purpose of score calculation, missing items in each visit were to be replaced by the mean of the non-missing items, provided that the number of non-missing items was greater than or equal to 10 for ADL score and 20 for motor score. Otherwise, the UPDRS sub-score for that visit was to be assigned a missing value.

Centers with low number of subjects with post-randomization data (<5) were to be combined together, as predefined in the SAP, in order to allow estimation of the treatment-by-center interaction.

3.1.2.4 Patient Disposition

A total of 802 subjects with idiopathic Parkinson's Disease were screened for study eligibility, and 687 subjects underwent randomization. A total of 231 subjects entered the rasagiline treatment group, 227 subjects entered the entacapone treatment group, and 229 subjects entered the placebo treatment group.

Eighty-eight subjects withdrew from the study prematurely, and 599 subjects completed study. The most common reasons for prematurely withdrawing from the study were subject withdrawal of consent and the experiencing of AEs, each with an overall incidence of 4.9%. The following table presents a summary of subject disposition by treatment groups.

Table 9 Disposition of Patients by Treatment Group

TVP-1012/122 (LARGO)	Rasagiline 1 mg		Entacapone		Placebo		All	
	N	%	N	%	N	%	N	%
Completion According to Protocol	208	90.0	197	86.8	194	84.7	599	87.2
Adverse Experience	7	3.0	16	7.0	11	4.8	34	4.9
Failed to Return	1	0.4	1	0.4	.	.	2	0.3
Subject Withdrew Consent	12	5.2	7	3.1	15	6.6	34	4.9
Investigator's Decision	1	0.4	1	0.4	4	1.7	6	0.9
Sponsor's Decision	.	.	1	0.4	.	.	1	0.1
Initiation of Any Prohibited Treatment	.	.	1	0.4	.	.	1	0.1
Death	2	0.9	3	1.3	4	1.7	9	1.3
Other	.	.	.	.	1	0.4	1	0.1
All	231	100.0	227	100.0	229	100.0	687	100.0

Cross-reference: Individual data listing of Termination Reasons and Exposure to Study Drug in Appendix 16.2.2

3.1.2.5 Demographic and Baseline Characteristics

Demographic characteristics of subjects are presented in Table 10. A great majority of subjects from all treatment groups were Caucasians. Males accounted for 57% to 67% of the subjects. The mean age for the 3 treatment groups was between 63 and 65 years.

On entry into the study, subjects had a mean PD duration of approximately 9 years (Table 11). All subjects were on chronic levodopa treatment with a mean levodopa treatment duration of approximately 7.6 years. All subjects were experiencing motor fluctuations – all treatment groups had a mean fluctuation duration of approximately 3.3 years. Overall, 351 (51%) patients entered the study with dyskinesia. There were no statistically significant differences between the treatment groups in any of the above disease characteristics at baseline.

Table 10 Demographic Characteristics of Patient (ITT) by Treatment Group

Characteristic	Rasagiline 1 mg	Entacapone	Placebo
Race (n, %)			
Caucasian	227 (98.3)	225 (99.1)	226 (98.7)
Other	4 (1.7)	2 (0.9)	9 (1.3)
Sex (n, %)			
Male	154 (66.7)	139 (61.2)	132 (57.6)
Female	77 (33.3)	88 (38.8)	97 (42.4)
Age (years)			
Mean (SD)	63.9 (9.0)	63.0 (9.4)	64.8 (8.8)
Median	64.3	64.2	65.4

Table 11 Baseline Disease Characteristics of Patient (ITT) by Treatment Group

Characteristic	Rasagiline 1 mg (n=231)	Entacapone (n=227)	Placebo (n=229)
PD Duration (years)			
Mean (SD)	8.7 (4.9)	9.2 (4.7)	8.8 (4.8)
Median	7.9	8.9	7.7
Levodopa Treatment Duration (years)			
Mean (SD)	7.5 (4.6)	7.6 (4.5)	7.6 (4.7)
Median	6.9	6.9	6.8
Fluctuation Duration (years)			
Mean (SD)	3.3 (3.2)	3.2 (2.7)	3.3 (2.8)
Median	2.4	2.5	2.5
Dyskinesia Duration (years)			
Mean (SD)	3.9 (3.5)	3.2 (2.7)	3.3 (2.8)
Median	2.9	2.5	2.5
Daily Waking Time (hours)			
Mean	16.07 (1.66)	16.02 (1.66)	16.05 (1.89)
Median	16.17	16.00	16.17
Daily "Off" Time (hours)			
Mean (SD)	5.58 (2.37)	5.60 (2.59)	5.55 (2.44)
Median	5.17	5.50	5.17
LD Total Daily Dose (mg)			
Mean (SD)	721.9 (333.6)	705.9 (320.6)	696.9 (295.4)
Median	700	625	625

3.1.2.6 Efficacy Results

The results presented in this section are from the reviewer's analyses, which are mostly identical to the ones from the sponsor's analyses with some additional analyses as indicated. All analyses were applied to ITT subject population using LOCF for missing values.

3.1.2.6.1 Primary Efficacy Endpoint - Change from Baseline in Total Daily "Off" Time

The primary endpoint for this trial was the change from baseline to treatment in the mean total daily "OFF" time.

At the baseline, the mean total daily "Off" time was about 5.5 hours for all treatment groups. Although all treatment groups had a decrease in the mean total daily "Off" time during the treatment period, the analysis showed that subjects in both rasagiline and entacapone groups had significantly larger improvement in the total daily "Off" time than subjects in the placebo group. The analysis of covariance showed a significant treatment effect of a reduction of 0.78 hour for

rasagiline over placebo (p = 0.0001, 95% CI: -1.18 to –0.39). The following table presents a summary of mean total daily "Off" time.

Table 12 Mean (SD) Total Daily "Off" Time and Change from Baseline by Treatment Group [Source: Reviewer's Analysis]

	Rasagline 1 mg (n=222)	Entacapone (n=218)	Placebo (n=218)
Baseline	5.58 (2.38)	5.58 (2.56)	5.54 (2.45)
Treatment	4.41 (2.65)	4.39 (2.53)	5.19 (2.85)
Change	-1.17 (2.16)	-1.19 (2.19)	-.35 (2.46)
p-value	.0001	.0001	

The total daily time of "On without dyskinesia" was also examined in order to verify that the decrease in the total daily "Off" time from the rasagiline treatment group was truly of treatment effect. The change from baseline in the mean total daily times of "On without dyskinesia" were 0.89 hour for the rasagiline 1 mg and entacapone groups and 0.05 hour for the placebo group. Therefore, the decrease in the "Off" time observed in the rasagiline 1 mg group was mostly transformed into an increase in the time of "On without dyskinesia".

3.1.2.6.2 Secondary Efficacy Endpoints

Since significant treatment difference was found in the primary efficacy endpoint, secondary endpoints are tested based on the hierarchical order of the following as planned.

1. Global Improvement by the Examiner
2. Change from Baseline to Termination in UPDRS ADL During "OFF" state
3. Change From Baseline to Termination in UPDRS Motor During "ON" State

The Global Improvement by Examiner was analyzed by ANCOVA model first, as specified in the Statistical Analysis Plan. The score is of categorical variable in nature, and a p-value of 0.0237 from the Wilk-Shapiro test indicated that the normal assumption was violated. Since there was no alternative method planned, this reviewer choose to use Cochran-Mental-Haenszel (CMH) test, which in the reviewer's opinion an appropriate test, for the comparison of the treatment groups. It was found from the CMH test that rasagiline group had a statistically significant larger improvement than the placebo group with a p-value of less than 0.001. The results are presented in Table 13.

Significant treatment differences between rasagiline group and placebo group were also found in ADL score at "Off" state and Motor score at "On" state.

At baseline, the mean ADL scores at "Off" state were 18.95, 19.04, and 18.71 for rasagiline, Entacapone, and placebo groups, respectively. During the treatment, a mean improvement of 2.61, 2.28, and 0.89 point was observed in the rasagiline, entacopone, and placebo groups,

respectively. The comparison of rasagiline versus placebo had a p-value of .0001, and the comparison of Entacapone versus placebo carried a p-value of .0015.

For the UPDRS Motor score at "On" state, a mean improvement of -3.87 and -3.51 points were observed in the rasagiline and entacopone groups, respectively, compared to a mean improvement of -.82 point in the placebo group. The treatment differences were statistically significant with a p-value of .0001 for the comparison of rasagiline versus placebo and a p-value of .0009 for the comparison of Entacapone versus placebo.

Table 13 Summary of Secondary Efficacy Results by Treatment Group [Source: Reviewer's Analysis]

	Rasagiline 1 mg (n=222)	Entacapone (n=220)	Placebo (n=218)
CGE (p-value)	-.93 <0.001	-.79 <0.001	-.44
ADL at "Off"			
Baseline	18.95	19.04	18.71
Last Visit	16.34	16.76	17.82
Change	-2.61	-2.28	-.89
p-value	.0001	.0012	
Motor at "On"			
Baseline	23.78	23.00	23.54
Last Visit	19.91	19.49	22.72
Change	-3.87	-3.51	-.82
p-value	.0001	.0006	

3.1.3 Adjunctive Therapy - Study PRESTO (Protocol 133)

3.1.3.1 Study Objectives

The objectives of the study were to evaluate the efficacy, tolerability and safety of two dosages of rasagiline (0.5 or 1 mg/day) compared to placebo in PD subjects with motor fluctuations on levodopa therapy.

3.1.3.2 Study Design

This was a multi-center, double-blind, randomized, placebo-controlled study that was conducted in 3 parallel groups of PD subjects in North America. It was designed to assess the efficacy and safety of rasagiline as adjunct therapy to levodopa/DDI. On entering the study subjects were being treated chronically with levodopa/DDI therapy and were experiencing motor fluctuations.

The double-blind treatment phase consisted of a 26-week period divided into an initial 6-week levodopa dose adjustment phase and a subsequent 20-week levodopa dose maintenance phase. Following a screening visit, subjects were randomly assigned in a 1:1:1 ratio to one of the 3

treatment groups: 0.5 mg /day rasagiline, 1 mg/day rasagiline and placebo. In case of intolerability the levodopa dosage could be decreased for the first 6 weeks of the study period at the discretion of the investigator but had to remain constant for the last 20 weeks.

Post-randomization visits were conducted at the end of weeks 3, 6, 10, 14, 20 and 26 weeks for efficacy and/or safety evaluations.

3.1.3.3 Efficacy Measures and Statistical Analysis Methods

Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint for this trial was the change from baseline to treatment in the mean total daily "Off" time.

The total daily "Off" time was measured through 3 subject daily diaries prior to randomization (baseline measurement), and 9 subject daily diaries during treatment: 3 diaries prior to week 6, 3 diaries prior to week 14, and 3 diaries prior to week 26 (termination visit).

The principal statistical analysis of the primary endpoint was an Analysis of Covariance (ANCOVA) adjusting for baseline mean total daily "Off" time. The adjusted means of the changes observed in each of the active drug groups (two contrasts) were to be compared with placebo. The model was to include the fixed effects of treatment group, center and baseline mean total daily "Off" time. The treatment-by-center interaction will be included in the model if it is found to be statistically significant (i.e., if $p< 0.10$).

The Hochberg's Step-up modification to Bonferroni method will be used to protect from inflation in type I error due to multiple comparisons.

Secondary Efficacy Endpoints and Analyses

Each statistically significant effective dose, as determined by the principal analysis of the primary endpoint, was to be further tested for additional four secondary end-points. These secondary endpoints, given in the hierarchical order of the statistical analysis, are:

1. Global Improvement by Examiner.
   This scale is part of the Clinical Global Evaluation (CGE) questionnaire. The range of the Global Improvement by examiner scale is from: -3 = "Very much improved", through 0 = "No change", to 3 = "Very much worse".

2. Change from baseline to last observed value in UPDRS ADL (Activities of Daily Living) during "OFF" state.
   The UPDRS ADL during "OFF" state score is the sum of 13 items (each item ranges from 0 to 4).

3. Change from baseline to last observed value in UPDRS Motor during "ON" state.

The UPDRS motor score is the sum of 27 items (each item ranges from 0 to 4).

4. Change from Baseline in Quality of Life (QOL) Scale (PD- QUALIF).
   The quality of life scale includes 32 items, 23 of them are positive questions and 9 are negative. The negative questions will be inverted and the PD- QUALIF score will be calculated as the sum of all items. Each item ranges from 0 to 4 points, hence the total PD-QUALIF score ranges from 0 to 128 points.

The hierarchical approach at an alpha level of 5% for each effective dose was to be used to protect from an inflation of Type-I error.

For each of the secondary efficacy endpoints, an ANCOVA model was to be used to compare each of the active drug groups (two contrasts) versus placebo. The model was to include treatment group and center. For analyses of UPDRS ADL score, UPDRS Motor score, and PD-QUALIF, the corresponding baseline value was also to be included as a covariate. The treatment-by-center interaction was to be included in the model if it was found to be statistically significant (i.e., if $p < 0.10$).

For the purpose of score calculation, missing items in each visit were replaced by the mean of the non-missing items.

3.1.3.4 Patient Disposition

A total of 606 subjects with idiopathic Parkinson's Disease were screened for study eligibility and 472 subjects underwent randomization: 164 subjects entered the 0.5 mg/day rasagiline treatment group, 149 subjects entered the 1 mg/ day rasagiline treatment group, and 159 subjects entered the placebo treatment group. Subjects were enrolled at 57 study sites in the United States (49 sites) and Canada (8 sites).

A total of 58 subjects withdrew prematurely. The most common reason for prematurely withdrawing from the study was the experiencing of AEs with an overall incidence of 7% (Table 14). The 0.5 mg/day rasagiline treatment group had the largest withdrawal due to AEs (9%). This was followed by the 1 mg/ day rasagiline treatment group (6%) and then by the placebo treatment group (5%).

Table 14 Disposition of Patients by Treatment Group

TVP-1012/133 (PRESTO)	0.5 mg		1 mg		Placebo		All	
	N	%	N	%	N	%	N	%
Completion According to Protocol	142	86.6	132	88.6	140	88.1	414	87.7
Adverse Experiences	15	9.1	9	6.0	8	5.0	32	6.8
Lost to follow-up	0	0	0	0	0	0	0	0
Subject Withdrew Consent	3	1.8	3	2.0	3	1.9	9	1.9
Investigator's Decision	1	0.6	2	1.3	.	.	3	0.6
Sponsor's Decision	0	0	0	0	0	0	0	0
Initiation of exclusionary treatment	0	0	0	0	0	0	0	0
Pregnancy	0	0	0	0	0	0	0	0
Death	1	0.6	1	0.7	.	.	2	0.4
Other	.	.	1	0.7	1	0.6	2	0.4
Worsening of PD	2	1.2	1	0.7	7	4.4	10	2.1
All	164	100.0	149	100.0	159	100.0	472	100.0

Cross-reference: Individual data listing of Termination Reasons and Exposure to Study Drug in Appendix 16.2.2.1

3.1.3.5 Demographic and Baseline Characteristics

Patient's demographic and baseline characteristics are summarized in Table 15. The treatment groups are similar in characteristics of race, gender and age.

Table 15 Demographic Characteristics of Patients (ITT) by Treatment Group

Characteristic	0.5 mg (n=164)	1.0 mg 2.0 (n=149)	Placebo (n=159)
Race (n, %)			
White	150 (91.5)	136 (91.3)	145 (91.2)
Other	14 (8.5)	13 (8.7)	14 (8.8)
Sex (n, %)			
Male	102 (62.2)	99 (66.4)	104 (65.4)
Female	62 (37.8)	50 (33.6)	55 (34.6)
Age (years)			
Mean (SD)	62.6 (9.5)	62.9 (8.9)	64.5 (9.9)
Median	62.8	63.1	65.3

Summary statistics of baseline disease characteristics is presented in Table 16. No statistically significant differences between the treatment groups in baseline disease characteristics were reported.

Table 16 Baseline Disease Characteristics of Patients by Treatment Group

Characteristic	0.5 mg	1.0 mg	Placebo
PD Duration (years)			
Mean (SD)	9.32 (5.6)	8.83 (5.4)	9.68 (4.9)
Median	8.1	7.9	9.3
Levodopa Treatment Duration (years)			
Mean (SD)	8.28 (7.0)	7.87 (5.4)	8.53 (4.7)
Median	5.5	6.9	8.1
Fluctuation Duration (years)			
Mean (SD)	4.43 (4.4)	3.71 (3.1)	4.24 (3.3)
Median	3.1	2.8	3.4
Dyskinesia Duration (years)	4.57 (4.1)	3.67 (3.8)	4.44 (3.4)
Mean (SD)	3.5	2.7	3.4
Median			
Daily Waking Time (hours)			
Mean	16.58 (1.58)	16.66 (1.39)	16.69 (1.52)
Median	16.50	16.67	16.50
Daily "Off" Time (hours)			
Mean (SD)	6.05 (2.04)	6.27 (2.55)	5.97 (2.21)
Median	5.83	5.67	5.83
LD Total Daily Dose (mg)			
Mean (SD)	749.7 (379.0)	814.7 (470.5)	821.3 (485.1)
Median	700.0	700.0	700.0

3.1.3.6 Efficacy Results

The efficacy results present in this section are from reviewer's analyses. Except for the additional analyses performed by this reviewer as indicated, the results obtained by this reviewer are mostly identical to the ones reported by the sponsor with minor differences.

All analyses were performed to ITT patient population, with LOCF applied to missing values.

3.1.3.6.1 Primary Efficacy Endpoint - Change from Baseline in Total Daily "Off" Time

The principal analysis for the primary efficacy parameter, change from baseline to treatment in the total daily "Off" time, was an ANCOVA model with factors of treatment and center, and covariate of baseline total daily "Off" time.

At the baseline, the mean total daily "OFF" time was about 6 hours for all treatment groups. During the treatment period, a mean decrease of "Off" time was observed in all three treatment groups: 1.38 hours for the 0.5 mg rasagiline group, 1.85 hours for the 1.0 mg rasagiline group, and 0.88 hour for the placebo group. The improvement observed in both rasagiline treatment

groups were statistically significantly larger than the improvement observed in the placebo group, resulting a significant treatment difference between 0.5 mg and placebo of 0.49 hour (p=0.0199; 95% CI [.08, .91]) and a significant treatment difference between 1 mg and placebo of 0.94 hour (p=.0001; 95% CI [.51, 1.36]). The following table summarizes the results.

Table 17 Mean Total Daily "Off" Time and Change from Baseline by Treatment Group [Source: Reviewer's Analysis]

	Rasagline 0.5 mg (n=157)	Rasagiline 1 mg (n=142)	Placebo (n=152)
Baseline	6.01 (2.01)	6.25 (2.52)	5.98 (2.23)
Treatment	4.41 (2.65)	4.39 (2.53)	5.19 (2.85)
Change	-1.38 (1.96)	-1.85 (2.03)	-0.88 (1.98)
p-value	.0199	.0001	

The total daily time of "On without dyskinesia" was also examined in order to verify that the decrease in the total daily "Off" time from the rasagiline treatment group was truly of treatment effect. The change from baseline in the mean total daily times of "On without dyskinesia" were 1.13 hour for the rasagiline 0.5 mg group, 1.32 hour group for the rasagiline 1 mg, and 0.51 hour for the placebo group. Therefore, the decreases in the "Off" time observed in the rasagiline 0.5 mg and 1 mg groups were mostly transformed into an increase in the time of "On without dyskinesia".

3.1.3.6.2 Secondary Efficacy Endpoints

Since treatment effects were found in both 0.5 mg rasagiline and 1.0 mg rasagiline groups, secondary efficacy endpoints were analyzed. There were 4 secondary efficacy endpoints, to be tested by the hierarchical order as described in Section 3.1.3.3.

The Global Improvement by Examiner was first analyzed by using an ANOVA model. Even though the scores were of categorical values in nature, the data did not seem to deviate from the normal assumption significantly (p=.2771, Wilk-Shapiro test). However, this reviewer chose to apply CMH test to confirm the results obtained from the ANOVA model.

It was found that the means of the Global Improvement by Examiner were -0.40 for 0.5 mg rasagiline group, -0.66 for 1.0 mg rasagiline group, and -0.02 for the placebo group. A mean value between -1 and 0 in the score, as observed in all treatment groups, indicates a situation between "No Change" and "Minimally improved". The analysis from the ANOVA model showed that both doses of rasagiline treatment were significantly better than the placebo, with a p-value of .0027 from the comparison of 0.5 mg rasagiline group versus placebo group and a p-value of .0001 from the comparison of 1.0 mg rasagiline group versus placebo group. The p-values from the CMH test were .004 and .001 for the corresponding two comparisons (without multiple testing adjustment), respectively. Results are presented in Table 18.

At the baseline, the mean ADL scores were about 15.5 for all treatment groups. During the treatment period, the mean ADL scores decreased by 0.60 and 0.68 for 0.5 mg rasagiline group and 1.0 mg rasagiline group, respectively, and increased by 0.68 for the placebo group. The difference between each of the rasagiline groups and placebo group carried a p-value of .0069 for 0.5 mg rasagiline versus placebo and a p-value of 0.0034 for 1.0 mg rasagiline versus placebo (Table 18).

The mean motor scores were similar across the treatment groups at the baseline. During the treatment period, a decrease in mean motor scores was observed in the two rasagiline groups, while an increase was observed in the placebo group. The differences in the change of mean motor scores were found to be statistically significant for both comparisons of rasagiline 0.5 mg group versus placebo group (p=0.0010) and rasagilien 1.0 mg group versus placebo group (p=0.0008) (Table 18).

Treatment difference for PD-QUALIF was found not statistically significant (Table 18).

Table 18 Summary of Secondary Efficacy Results by Treatment Group [Source: Reviewer's Analysis]

	0.5 mg	1.0 mg	Placebo
CGE (p-value)	-0.40	-0.66	-0.02
	.0027	.0001	
ADL at "Off"			
Baseline	15.75	15.54	15.54
Last Visit	15.16	14.86	16.22
Change	-.60	-.68	.68
p-value	.0069	.0034	
Motor at "On"			
Baseline	21.45	20.87	20.81
Last Visit	20.09	19.57	22.02
Change	-1.43	-1.30	1.21
p-value	.0010	.0008	
PD-QUALIF			
Baseline	51.15	50.94	51.76
Last Visit	51.95	52.40	54.86
Change	.80	1.46	3.10
p-value	.0651	.2229	

3.2 Evaluation of Safety

Readers should refer to Safety Review by Dr. Lisa Jones for Evaluation of Safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The following table presents the efficacy results by gender and age. Over 90% of the patients were Caucasians, and therefore, results by race were not performed. The p-values presented in the table are nominal p-values, which should be interpreted cautiously.

The efficacy results appear to be consistent across gender and age groups. However, in Study PRESTO the treatment difference between rasagiline 0.5 mg and placebo among female subjects was only 0.16 hour (9.6 minutes), compared to the difference of 0.63 hour (37.8 minutes) among the male subjects.

Table 19 Summary of Efficacy Results by Demographic Characteristics and Study [Source: Reviewer's Analysis]

Study/ Protocol #	Primary Endpoint	Variable	Treatment Group Mean (SD)				
			0.5 mg	1 mg	2 mg	Entacap	Placebo
TEMPO (232)	Change in total UPDRS	Gender					
		Male (n=257)		0.27 (p=.002)	0.93 (p=.006)		3.68
		Female (n=147)		-0.36 (p<.001)	0.46 (p=.006)		4.37
		Age					
		< 65 (226)		0.07 (p=.002)	0.11 (p=.003)		3.76
		>= 65 (178)		0.05 (p<.001)	1.46 (p=.006)		4.11
LARGO (122)	Change in daily "Off"	Gender					
		Male (n=414)		-1.26 (p=.025)		-1.27 (p=.024)	-0.58
		Female (n=244)		-0.97 (p=.021)		-1.06 p=.003)	-0.02
		Age					
		< 65 (312)		-0.94 (p=.236)		-1.31 (p=.017)	-0.56
		> =65 (n=346)		-1.37 (p<.001)		-1.08 (p=.002)	-0.18
PRESTO (133)	Change in daily "Off"	Gender					
		Male (n=295)	-1.49 (p=.020)	-1.86 (p<.001)			-0.86
		Female (n=156)	-1.12 (p=.658)	-1.92 (p=.129)			-0.96
		Age					
		< 65 (n=237)	-1.35 (p=.127)	-1.49 (p=.030)			-0.86
		>= 65 (n=214)	-1.42 (p=.188)	-2.33 (p<.001)			-0.90

4.2 Other Special/Subgroup Populations

No other special/subgroup analyses were performed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The effectiveness of rasagiline used as mono-therapy was demonstrated by a single study TEMPO. The study used doses of 1 mg and 2 mg. The effectiveness was shown in both dosages, with rasagiline 1 mg shown to be as effective as 2 mg with respect to the primary efficacy endpoint.

The effectiveness of rasagiline used as adjunctive therapy was demonstrated in two studies: LARGO, and PRESTO. Rasagiline 0.5 mg was used in PRESTO only and rasagiline 1 mg was used in both studies. The two studies used same primary efficacy endpoint. Rasagiline 0.5 mg was shown to be effective in PRESTO, and rasagiline 1 mg was shown to be effective in both studies.

5.2 Conclusions and Recommendations

The three studies submitted in this NDA have provided substantial evidence that rasagiline is efficacious and superior to placebo in the treatment of Parkinson's disease with respect to their primary efficacy endpoints: rasagiline at dosage of 1 mg and 2 mg are efficacious and superior to placebo when used as mono-therapy, rasagiline at dosage of 0.5 mg and 1 mg is efficacious and superior to placebo when used as adjunctive therapy to LD therapy.

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CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

Carcinogenicity Studies

NDA/Serial Number:	21- 641
Drug Name:	Rasagiline Mesylate
Indication:	Parkinson's Disease
Applicant:	Teva
Date:	Submitted: 9/05/2003
Biometrics Division:	Division of Biometrics I, HFD-710
Statistical Reviewer:	Tristan Massie, Ph.D.
Concurring Reviewers:	Roswitha Kelly, M.S., Pre-Clinical Coordinator Kooros Mahjoob, Ph.D., Deputy Director
Medical Division:	Neuropharmacological Drug Products, HFD-120
Pharmacologist:	Paul Roney, Ph.D.
Pharm/Tox Team Leader:	Lois Freed, Ph.D.
Project Manager:	Theresa Wheelous

Keywords: Carcinogenicity, Survival Analysis, Trend Test

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Statistical Review and Evaluation

1. Executive Summary

1.1. Conclusions and Recommendations

The 2-year rat study, which utilized a control group and 0.3, 1.0, and 3.0 mg/kg/day dose groups for males and a control group and 0.5, 2.0, 5.0 and 17.0 mg/kg/day dose groups for females, found no strictly significant drug-related increases in tumor incidence in males or females. Note that in the females the trend for the B-Granulosa/Theca Cell Tumor in the Ovary was nearly significant (p=0.0281). However, the pair-wise comparison is the more appropriate method, since not all animals in the low and intermediate dose groups were examined, and the increase from 0 in the controls to 2 in the high dose did not reach statistical significance (p=0.1077). Therefore, strictly speaking, there were no drug-related increases in tumor incidence in the males or females. Enough rats lived long enough for a tumor challenge, but the high dose groups exhibited large weight suppression compared to the control groups for both males and females. Therefore, it appears that the MTD was exceeded and that the design of the study was not adequate.

The 2-year mouse study utilized a control group and 1, 15, and 45 mg/kg/day dose groups for males and females. In the mouse study there were several tumors that were significant at the 0.05 level in males and females, but excluding combinations only the pair-wise comparison between the control group and the high dose group for the adenoma of the Harderian gland in the males was significant using the FDA significance levels. The trend in alveolar/bronchiolar carcinoma was borderline significant. Pair-wise comparisons of the high dose group and vehicle were also significant in the males for the combination of adenomas and carcinomas of the Harderian gland and for the combination of alveolar/bronchiolar adenomas and carcinomas of the lung with mainstem bronchi.
In the females, there were no significant trends or pair-wise comparisons in tumor incidences based on the FDA significance criteria, although the combination of the alveolar bronchiolar adenomas and carcinomas of the lung with mainstem bronchi was very close to significance for both the trend test and the pair-wise comparison of the high dose and control. Also in the female study, enough animals survived long enough for a tumor challenge, but the high dose may not have reached the MTD since the high dose group did not have lower survival or mean weight than the control group. Therefore, the female study may have been insufficient.

1.2. Brief Overview of Carcinogenicity Studies

This submission contains two carcinogenicity studies: one in the rat and one in the mouse.

In the rat study Rasagiline Mesylate was administered daily by gavage to
- CD®(SD)IGS BR rats for at least 104 weeks at target dose levels (expressed in terms of base) of 0.3, 1.0, and 3.0 mg/kg/day for males (Groups 3-5, respectively) and 0.5, 2.0, 5.0, and 17.0 mg/kg/day for females (Groups 3-6, respectively). Control rats (Groups 1 and 2; 0 mg/kg/day) received the vehicle (distilled water). All doses were given at a constant volume of 10 mL/kg/day. Each main study group had 65 males and 65 females.

In the mouse study Rasagiline Mesylate was administered daily by oral gavage to
- CD-1® (ICR)BR albino mice for at least 104 weeks at target dose levels (expressed in terms of base) of 1, 15, and 45 mg/kg/day (Groups 2-4, respectively). Control mice(Group 1; 0 mg/kg/day) received the vehicle (distilled water). All doses were given at a constant volume of 5 mL/kg/day. Each main study group had 55 males and 55 females.

1.3. Statistical Issues and Findings

The test for a dose related trend in tumor incidences is normally preferred over the pair-wise comparison of the high dose group and the control group because it is more powerful, except in cases of nonlinearity. In some cases though, not all relevant tissues were examined for all animals in the low-dose and mid-dose groups. In such cases, the results of the trend test are only approximately correct, so the pair-wise comparison of the high dose group and the control group is preferred. Although all pair-wise comparisons of the high dose group and the control group are not presented in this review they were all examined and the significant ones are mentioned.

In the rat study there was no significant difference between the survival of the drug groups and the controls in the males or females. In the male rats there were no significant drug-related increases in tumor incidence. In the females the trend for the B-Granulosa/Theca Cell Tumor in the Ovary was very nearly significant ($p=0.0281$) compared to the relevant FDA significance level of 0.0250. However, the pair-wise comparison is the more appropriate method, since not all animals in the low and intermediate dose groups were examined, and the increase from 0 in the controls to 2 in the high dose did not reach statistical significance ($p=0.1077$). Therefore, strictly speaking, there were no significant drug-related increases in tumor incidence in the male or female rats. Enough rats lived long enough for an adequate exposure. However, each of the high dose groups (3.0 mg/kg/day for males, 17.0 mg/kg/day for females) had

significantly lower average weight (> 20% difference at 1 year) than the corresponding control group, so the maximum tolerated dose was likely exceeded. Therefore, the rat study appears to have been inadequate for both males and females.

In the mouse study there were important differences between the males and females. In the males there was a marginally significant time adjusted trend in survival (Gehan p=0.0685 and Cox p=0.0977), although the middle dose group had higher survival than the control group for much of the time. The pair-wise comparison between the survival of the high dose group and the control was also nearly significant (Gehan p=0.0533 and Cox p=0.077). It should be noted that gavage accidents were microscopically determined for four 45 mg/kg/day males (A72669, A72672, A72694, and A72703) found dead during Weeks 8 through 21. This may have influenced the Gehan results since the Gehan test weighs early differences more than later ones. In the female mice the differences between the survival of the dose groups and the control group were less noteworthy.

The sponsor reported that at doses of 15 and 45 mg/kg/day for males and 45 mg/kg/day for females an apparent increase in two tumors common to the mouse was observed. These were the bronchiolar/alveolar adenoma/carcinoma in both sexes and the adenoma/carcinoma of the Harderian gland in the males. However, as seen in the following table, if we do not consider combinations of tumors then only the pair-wise comparison for the adenoma of the Harderian gland in the males met the FDA criteria for significance. The trend in alveolar/bronchiolar carcinoma of the lung w/ mainstem bronchi was borderline significant in the males. When we look at combinations we see that for the males the trend in alveolar/bronchiolar adenoma or carcinoma was significant. Pair-wise comparisons of the high dose group and vehicle were significant in the males for the combination of adenomas and carcinomas of the Harderian gland and for the combination of alveolar/bronchiolar adenomas and carcinomas of the lung with mainstem bronchi.

In the females, there were no significant trends or pair-wise comparisons in tumor incidences based on the FDA significance criteria, although the combination of the alveolar bronchiolar adenomas and carcinomas of the lung with mainstem bronchi was very close to significance for both the trend test and the pair-wise comparison of the high dose and control.

For the males the design is considered adequate since there was at least one significant drug related increase in tumor incidence. However, for the females, since there was no significant weight difference between the high dose and vehicle in the first year, no difference in survival, and no strictly significant differences in tumor incidence, the study may have been inadequate for this gender.

Table 1 Notable Differences in Tumor Incidences in Mice

							Trend		High vs. Control	
	Organ Name	Tumor Name	Control	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)	P-Value (Exact Method)	P-Value (Asymptotic Method)
Females	LUNG W/ MAINSTEM BRONCHI	ALVEOLAR BRONCHIOLAR ADENOMA	12	8	11	17	0.0119	0.0096	0.0511	0.0333
	LUNG W/ MAINSTEM BRONCHI	ALVEOLAR / BRONCHIOLAR CARCINO	2	5	8 *	5	0.2075	0.2100	0.1645	0.0876
	LUNG W/ MAINSTEM BRONCHI	A./B. ADENOMA or A./B. CARCINOMA	13	12	19	20	0.0071	0.0058	0.0175	0.0109
	HARDERIAN GLAND	ADENOMA	2	0	0	3	N/A	N/A	0.3543	0.2095
	HARDERIAN GLAND	CARCINOMA	0	0	0	1	N/A	N/A	0.4000	0.1147
	HARDERIAN GLAND	ADENOMA or CARCINOMA	2	0	0	4	N/A	N/A	0.1990	0.1048
Males	LUNG W/ MAINSTEM BRONCHI	ALVEOLAR BRONCHIOLAR ADENOMA	10	6	17	13	0.0304	0.0257	0.1309	0.0897
	LUNG W/ MAINSTEM BRONCHI	ALVEOLAR / BRONCHIOLAR CARCINO	6	6	9	13	0.0065	0.0050	0.0267	0.0151
	LUNG W/ MAINSTEM BRONCHI	A./B. ADENOMA or A./B. CARCINOMA	13	11	23	24	0.0007	0.0005	0.0074	0.0045
	HARDERIAN GLAND	ADENOMA	3	8	11	9	0.0231	0.0219	0.0071	0.0029
	HARDERIAN GLAND	CARCINOMA	0	1	0	0	0.7402	0.7845	N/A	N/A
	HARDERIAN GLAND	ADENOMA or CARCINOMA	3	9	11	9	0.0347	0.0340	0.0071	0.0029

N/A = not applicable because low and mid-dose groups were not completely examined

* Pair-wise comparison between medium dose (15) and control for alveolar bronchiolar carcinoma in females is nearly significant (Asymptotic p=0.02 and Exact p=0.04) compared to the 0.01 significance level for common tumors.

2. Introduction

2.1. Overview

This submission contains two carcinogenicity studies: one in the rat and one in the mouse.

In the rat study Rasagiline Mesylate was administered daily by gavage to CD®(SD)IGS BR rats for at least 104 weeks at target dose levels (expressed in terms

of base) of 0.3, 1.0, and 3.0 mg/kg/day for males (Groups 3-5, respectively) and 0.5, 2.0, 5.0, and 17.0 mg/kg/day for females (Groups 3-6, respectively). Control rats (Groups 1 and 2; 0 mg/kg/day) received the vehicle (distilled water). All doses were given at a constant volume of 10 mL/kg/day. Each main study group had 65 males and 65 females. In the neoplastic analyses, when the low- and mid-dose group animals did not have complete histopathological examinations, they were excluded from the statistical analyses and only the control versus high-dose group comparisons were made.

In the mouse study Rasagiline mesylate was administered daily by oral gavage to CD-1® (ICR)BR albino mice for at least 104 weeks at target dose levels (expressed in terms of base) of 1, 15, and 45 mg/kg/day (Groups 2-4, respectively). Control mice(Group 1; 0 mg/kg/day) received the vehicle (distilled water). All doses were given at a constant volume of 5 mL/kg/day. Each main study group had 55 males and 55 females. In the neoplastic analyses, when the low-dose and mid-dose group animals did not have complete histopathological examinations, they were excluded from the statistical analyses and only the control versus high-dose group comparisons were made.

2.2. Data Sources

The rat data including the tumor dataset, tumor.xpt, is located at the following address: \\Cdsesub1\n21641\N_000\2003-09-05\pharmtox\datasets\6751-109.

The mouse data including the tumor dataset, tumor.xpt, is located at the following address: \\Cdsesub1\n21641\N_000\2003-09-05\pharmtox\datasets\6751-104.

3. Statistical Evaluation

3.1. Rat Study 6751-109

This study assessed the carcinogenic potential of Rasagiline mesylate (TVP-1012) N-propargyl-1(R)-aminoindan mesylate, a selective monoamine oxidase-B inhibitor. Rasagiline mesylate (TVP-1012) was administered daily by gavage to .CD®(SD)IGS BR rats for at least 104 weeks at target dose levels (expressed in terms of base) of 0.3, 1.0, and 3.0 mg/kg/day for males (Groups 3-5, respectively) and 0.5, 2.0, 5.0, and 17.0 mg/kg/day for females (Groups 3-6, respectively). Control rats (Groups 1 and 2; 0 mg/kg/day) received the vehicle (distilled water). All doses were given at a constant volume of 10 mL/kg/day. Each main study group had 65 males and 65 females. Rats were housed individually and food and water was available ad libitum. The upper dose in the female is in excess of 25 fold the exposure measure (human AUC) for the highest dose in phase II clinical trials. The highest dose in the male is below this level, being limited by excessive reduction in body weight gain noted in chronic toxicity studies. Females also expressed reduction in body weight gain at the high dose, but to a lesser extent. For the females, a high intermediate dose of 5.0 mg/kg was added as a backup, in case the body weight reduction at 17.0 mg/kg compromised the health and life expectancy of the females. The low dose of 0.5 mg/kg was set as a low multiple of the highest dose used in phase II clinical studies (4 mg/day or 0.08 mg/kg for a human of 50 kg weight). The

current intended clinical human dose for treatment of PD stands at 1 mg/day. Relative exposures of rats to humans have therefore increased to 6, 23, and 84 multiples for male rats at 0.3, 1.0, and 3.0 mg/kg/day rasagiline and to 6, 32, 96, and 399 multiples for female rats at 0.5, 2.0, 5.0, and 17.0 mg/kg/day for rasagiline, respectively. In the nonneoplastic and neoplastic analyses, since the low- and mid-dose group animals did not have complete histopathological examinations, they were excluded from the statistical analyses and only the control versus high-dose group comparisons were made.

3.1.1. Statistical Methods

The sponsor analyzed unadjusted survival data by the National Cancer Institute (NCI) lifetable package. The test included Graphical (Kaplan-Meier product-limit estimation curves); Cox Tarone binary regression methods for trend and heterogeneity; and Gehan-Breslow nonparametric methods for trend and heterogeneity. Nonneoplastic lesions were analyzed by the Cochran-Armitage test for trend and the Fisher-Irwin exact test for heterogeneity.

Neoplastic lesions: Incidental tumors were analyzed by Dinse-Lagakos logistic prevalence methods for trend and heterogeneity. Rapidly lethal and palpable tumors are analyzed in the same manner as survival. Ordinal dose levels (e.g., 0, 1, 2, 3, . . .) were used in all the analyses. Continuity correction was used for all asymptotic tests. In the nonneoplastic and neoplastic analyses, since the low- and mid-dose group animals did not have complete histopathological examinations, they were excluded from the statistical analyses and only the control versus high-dose group comparisons were made.

This reviewer analyzed the rat study data using the internal software Carcin developed by Drs. Ted Guo and Feng Zhou. Differences with the sponsor should be minor but p-values and conclusions may be affected by the use of different statistical methodology if results were close to the levels of significance. Codes 0, 1, 2, 3, etc. were used for the dose groups in the rat study rather than the actual dose values because the Carcin program would not run successfully with the actual dose values. Trends in tumors were computed to present the tumor incidences for all groups and they can serve as an approximation to the trends had all tissues been microscopically examined. All pair-wise comparisons between high-dose and combined controls were also examined since the low- and mid-dose group animals did not have complete histopathological examinations.
The FDA significance levels for trends are 0.025 for rare tumors and 0.005 for common tumors; for pair-wise comparisons the FDA significance levels are 0.05 for rare tumors and 0.01 for common tumors. Rare tumors are those which occur in 1 % or less of the control group.

3.1.2. Sponsor's Results

Survival rates at the end of Week 104 were 32, 31, 39, 35, and 37% for males (0, 0, 0.3, 1.0 and 3.0 mg/kg/day groups, respectively) and 34, 34, 35, 25, 31, and 34% for females (0, 0, 0.5, 2.0, 5.0, and 17.0 mg/kg/day groups, respectively). There was no significant trend or group difference in survival in any of the male treated groups versus either of the control groups. In the females, there was a slightly significant higher mortality in Group 4

(2.0 mg/kg/day) females compared to Group 2 (but not compared to Group 1) by the Gehan-Breslow test(but not by the Cox-Tarone test). The difference between the two methods can be explained in terms of some earlier deaths in this group compared to Group 2. In any case, there was no significant trend because the dose-response in this case is non-monotonic. The difference in Group 4 is attributable to background variation in survival.

All rats that were found dead or sacrificed *in extremis* during the study were weighed and subjected to a gross postmortem examination. Neoplasms were those commonly seen in this strain of rat and were not higher in the drug-treated groups. Statistical pair-wise analysis only showed significant reductions in the incidences of several neoplasms in the high-dose groups. These included significant decreases in the incidences of pheochromocytomas of the adrenal medulla in the 3.0 mg/kg/day males, pituitary adenomas in the 3.0 mg/kg/day males, combined incidences of thyroid follicular cell adenomas and carcinomas in the 17.0 mg/kg/day females, and mammary gland fibroadenomas and adenocarcinomas in the caudal mammary gland of the 17.0 mg/kg/day females.

There were no significant differences between the body weight gains or body weights of the two control groups. Mean body weight gains and weights of the drug-treated groups, except the 0.5 mg/kg/day females, were significantly lower compared to both control groups in a dose-related manner. As seen in the following table, mean body weights were lower than both control groups at major study intervals of Weeks 14, 28, and 52 for the 0.3 mg/kg/day males and Weeks 14, 28, 52, and 78 for the 1.0 and 3.0 mg/kg/day males. Mean body weights were lower than both control groups at major study intervals of Week 14 for the 2.0 mg/kg/day females; Weeks 14, 28, 52, and 78 for the 5.0 mg/kg/day females; and Weeks 14, 28, 52, 78, and 105 for the 17.0 mg/kg/day females.

Table 2 Male Rats: Summary of Mean Body Weights

Male Rats: Summary of Mean Body Weights

Males	Group 1 0 mg/kg	Group 2 0 mg/kg	Group 3 0.3 mg/kg	Group 4 1 mg/kg	Group 5 3 mg/kg
Mean body weights in grams (% difference compared to Group 1 control)					
Week 1	235	233 (-1%)	233 (-1%)	228 (-3%)	232 (-1%)
Week 14	570	560 (-2%)	538 (-6%) *#	511 (-10%) *#	463 (-19%) *#
Week 28	688	674 (-2%)	641 (-7%) *#	590 (-14%) *#	542 (-21%) *#
Week 52	779	766 (-2%)	734 (-6%) *#	662 (-15%) *#	606 (-22%) *#
Week 78	819	784 (-4%)	775 (-5%)	696 (-15%) *#	625 (-24%) *#
Week 105	741	676 (-9%)	698 (-6%)	715 (-4%)	667 (-10%)

* Mean value significantly different from control Group 1 at $p < 0.05$.
# Mean value significantly different from control Group 2 at $p < 0.05$.

Table 3 Female Rats: Summary of Mean Body Weights

Female Rats: Summary of Mean Body Weights

Females	Group 1 0 mg/kg	Group 2 0 mg/kg	Group 3 0.5 mg/kg	Group 4 2 mg/kg	Group 5 5 mg/kg	Group 6 17 mg/kg
Mean body weights in grams (% difference compared to Group 1 control)						
Week 1	173	171 (-1%)	169 (-2%)	171 (-1%)	169 (-2%)	168 (-3%)
Week 14	301	303 (1%)	296 (-2%)	286 (-5%) *#	273 (-9%) *#	254 (-16%) *#
Week 28	350	346 (-1%)	339 (-3%)	338 (-3%)	322 (-8%) *#	301 (-14%) *#
Week 52	425	415 (-2%)	411 (-3%)	400 (-6%)	372 (-12%) *#	340 (-20%) *#
Week 78	484	488 (1%)	468 (-3%)	466 (-4%)	406 (-16%) *#	381 (-21%) *#
Week 105	505	475 (-6%)	447 (-11%)	480 (-5%)	438 (-13%)	365 (-28%) *#

* Mean value significantly different from control Group 1 at $p < 0.05$.
\# Mean value significantly different from control Group 2 at $p < 0.05$.

3.1.3. Reviewer's Comments

There were some slight discrepancies between the reviewer's and sponsor's results due to differences in the analysis methods. For example, in the mortality analysis, the reviewer used the Cox log rank test and the Kruskal-Wallis test, while the sponsor used the Tarone method. This reviewer combined the two control groups for the analysis.

There were no significant dose-mortality trends in the rats. In the males there were no significant drug-related increases in tumor incidence. In the females the trend for the B-Granulosa/Theca Cell Tumor in the Ovary was very nearly significant (p=0.0281) compared to the relevant FDA significance level of 0.0250. However, the pair-wise comparison is the more appropriate method, since not all animals in the low and intermediate dose groups were examined, and the increase from 0 in the controls to 2 in the high dose did not reach statistical significance (p=0.1077). Therefore, strictly speaking, there were no significant drug-related increases in tumor incidence in the male or female rats.

Table 4, Table 5, and Figure 1 show that there was no significant difference between the mortality of the dose groups and the control groups in the female rats. Table 6 summarizes the tumor incidences in the female rats by dose group. There were no strictly significant trends or pair-wise comparisons.

Table 7, Table 8, and Figure 2 show that there was no significant difference between the mortality of the dose groups and the combined control group in the male rats. Table 9 summarizes the tumor incidences in the male rats by dose group. There were no significant trends or pair-wise comparisons.

Table 4 Female Rat: Analysis of Mortality (dose groups coded 0, 0 and 1, 2, 3, 4)

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR1	0-52	65	1	64	98.5	1.5
	53-78	64	16	48	73.8	26.2
	79-91	48	15	33	50.8	49.2
	92-104	33	11	22	33.8	66.2
	FINALKILL105-105	22	22	0		
CTR2	0-52	65	3	62	95.4	4.6
	53-78	62	10	52	80.0	20.0
	79-91	52	14	38	58.5	41.5
	92-104	38	16	22	33.8	66.2
	FINALKILL105-105	22	22	0		
LOW	0-52	65	2	63	96.9	3.1
	53-78	63	13	50	76.9	23.1
	79-91	50	14	36	55.4	44.6
	92-104	36	13	23	35.4	64.6
	FINALKILL105-105	23	23	0		
MED	0-52	65	4	61	93.8	6.2
	53-78	61	20	41	63.1	36.9
	79-91	41	12	29	44.6	55.4
	92-104	29	13	16	24.6	75.4
	FINALKILL105-105	16	16	0		
MEDHI	0-52	65	3	62	95.4	4.6
	53-78	62	18	44	67.7	32.3
	79-91	44	13	31	47.7	52.3
	92-104	31	11	20	30.8	69.2
	FINALKILL105-105	20	20	0		
HIGH	0-52	65	7	58	89.2	10.8
	53-78	58	7	51	78.5	21.5
	79-91	51	12	39	60.0	40.0
	92-104	39	17	22	33.8	66.2
	FINALKILL105-105	22	22	0		

Table 5 Female Rat: Dose-Mortality Trend Test (dose groups coded 0, 0, 1, 2, 3, 4)

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	4.1949	0.3803	5.5209	0.2379
Dose-Mortality Trend	0.1912	0.6619	0.3069	0.5796
Homogeneity	4.3861	0.4953	5.8278	0.3233

Figure 1 Female Rat: Survival (dose groups coded 0, 0, and 1-4)

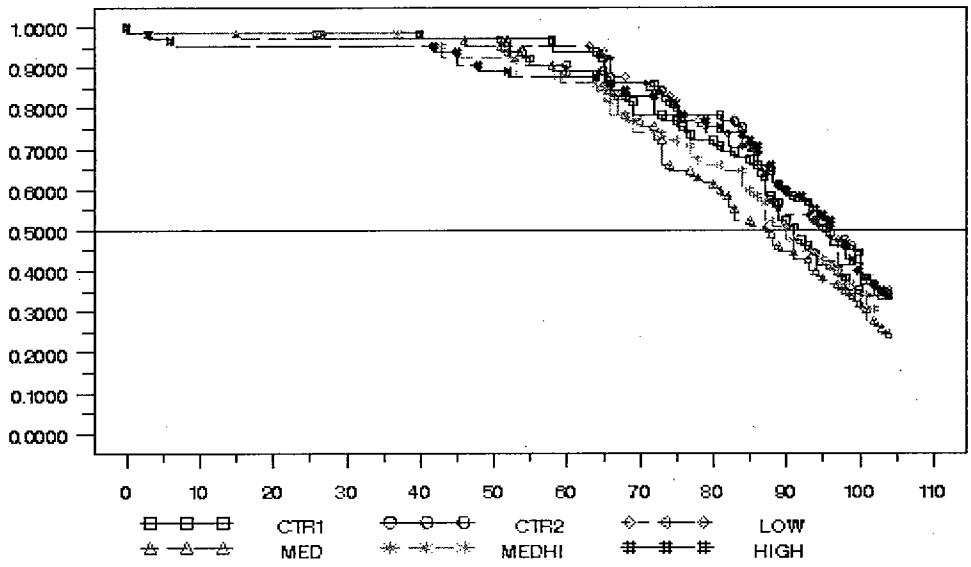

Table 6 Female Rat: Tumor Incidences (using dose groups coded 0, 0 and 1, 2, 3, 4)

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW	MED	MEDHI	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
AC	ADRENAL, CORTEX	248	B-ADENOMA	1	1	2	1	0	0	0.9224	0.9203
AC	ADRENAL, CORTEX	286	M-CARCINOMA	2	0	0	0	1	0	0.7553	0.7724
AM	ADRENAL, MEDULLA	249	B-PHEOCHROMOCYTOMA	2	2	1	1	1	1	0.7551	0.7634
BR	BRAIN W/STEM	294	M-ASTROCYTOMA	1	0	0	2	1	1	0.2212	0.2168
CV	UTERUS, CERVIX	173	B-FIBROMA	1	0	0	0	0	0	1.0000	0.9426
CV	UTERUS, CERVIX	268	M-NEUROFIBROSARCOMA	1	0	0	0	0	0	1.0000	0.9010
CV	UTERUS, CERVIX	325	B-LEIOMYOMA	0	0	0	0	0	1	0.1500	0.0955
HN	HEMATO NEOPLASIA	2	M-LYMPHOMA	0	0	1	1	1	1	0.1600	0.1525
HN	HEMATO NEOPLASIA	264	M-SARCOMA, HISTOCYTIC	0	1	1	1	1	2	0.1402	0.1366
KD	KIDNEY	300	M-LIPOSARCOMA	0	2	0	0	0	0	1.0000	0.9523
KD	KIDNEY	380	B-LIPOMA	0	1	0	1	0	0	0.6846	0.7482
LI	LIVER	280	M-CARCINOMA, HEPATOCELLULAR	0	1	0	0	0	1	0.4853	0.4645
LI	LIVER	385	B-CHOLANGIOMA	0	0	1	0	0	0	0.6667	0.7863
LI	LIVER	409	B-ADENOMA,	1	0	0	0	0	0	1.0000	0.8555

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW	MED	MEDHI	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
			HEPATOCELLULAR								
LU	LUNG	400	M-LEIOMYOSARCOMA	0	0	0	0	0	1	0.2099	0.1262
MF0	MAMMARY,CRANIAL	145	B-FIBROADENOMA	20	12	12	9	12	12	0.7671	0.7680
MF0	MAMMARY,CRANIAL	221	M-ADENOCARCINOMA	0	7	4	0	0	1	0.9822	0.9777
MF0	MAMMARY,CRANIAL	225	B-ADENOMA	0	0	0	1	0	0	0.5132	0.5197
MF0	MAMMARY,CRANIAL	461	M-FIBROSARCOMA	0	1	0	0	0	0	1.0000	0.9397
MF1	MAMMARY,CAUDAL	132	B-ADENOMA	1	2	1	2	3	1	0.3518	0.3561
MF1	MAMMARY,CAUDAL	195	M-ADENOCARCINOMA	5	4	5	6	1	0	0.9783	0.9754
MF1	MAMMARY,CAUDAL	206	B-FIBROADENOMA	15	22	17	11	13	5	0.9949	0.9945
MF1	MAMMARY,CAUDAL	383	B-FIBROMA	0	0	0	1	0	0	0.5000	0.5545
MF1	MAMMARY,CAUDAL	393	M-SARCOMA, NOS	0	0	0	1	0	0	0.5000	0.5545
MF1	MAMMARY,CAUDAL	407	M-NEUROFIBROSARCOMA	0	0	0	2	0	0	0.5032	0.4863
OV	OVARY	320	B-GRANULOSA/THECA CELL TUMOR	0	0	0	0	1	2	0.0281	0.0179
OV	OVARY	420	B-ADENOMA, INTERSTITIAL GLD	0	1	0	0	0	0	1.0000	0.9273
OV	OVARY	441	M-SERTOLI CELL TUMOR	0	1	0	0	0	0	1.0000	0.8587
PA	PANCREAS	301	M-CARCINOMA, ISLET CELL	1	0	0	0	0	1	0.4359	0.3969
PA	PANCREAS	353	B-ADENOMA, ISLET CELL	2	0	0	0	0	0	1.0000	0.9196
PA	PANCREAS	424	B-ADENOMA, ACINAR CELL	0	1	0	0	0	0	1.0000	0.9250
PC	CAVITY, ABDOM	102	M-NEUROFIBROSARCOMA	0	0	0	0	0	1	0.6667	0.6382
PI	PITUITARY	429	M-CARCINOMA	0	0	0	1	0	0	0.4677	0.5383
PI	PITUITARY	86	B-ADENOMA	57	57	56	50	56	51	0.5527	0.5540
SQ	SUBCUTANEOUS TIS	150	M-SARCOMA, NOS	0	2	0	0	0	0	1.0000	0.9240
SQ	SUBCUTANEOUS TIS	217	M-MALIG FIBROUS HISTIOCYTOMA	1	0	0	0	0	0	1.0000	0.8920
SQ	SUBCUTANEOUS TIS	304	M-HEMANGIOSARCOMA	0	0	1	0	0	0	1.0000	0.9615
SQ	SUBCUTANEOUS TIS	329	B-FIBROMA	0	0	0	1	0	1	0.1667	0.1458
SQ	SUBCUTANEOUS TIS	330	M-FIBROSARCOMA	0	0	0	1	0	0	0.3333	0.3618
SS	SKIN, OTHER	363	M-NEUROFIBROSARCOMA	2	0	2	1	0	0	0.9946	0.9947
SS	SKIN, OTHER	382	B-KERATOACANTHOMA	0	0	0	1	0	0	0.7949	0.7551
SS	SKIN, OTHER	421	B-SQUAMOUS CELL PAPILLOMA	0	1	0	0	1	0	0.8274	0.8355
SS	SKIN, OTHER	426	M-SQUAMOUS CELL CARCINOMA	0	0	0	2	0	0	0.6322	0.6316
SS	SKIN, OTHER	446	B-BASAL CELL ADENOMA	0	0	0	1	0	0	0.6056	0.6331
TH	THYMUS	387	M-THYMOMA	0	0	1	1	0	0	0.6899	0.5548
TY	THYROID	246	B-"C" CELL ADENOMA	5	6	3	3	1	2	0.9373	0.9348
TY	THYROID	297	B-FOLLICULAR CELL ADENOMA	0	2	0	0	1	0	0.7058	0.7215
TY	THYROID	299	M-FOLLICULAR CELL CARCINOMA	1	3	0	1	1	1	0.6870	0.7017
TY	THYROID	443	M-"C" CELL CARCINOMA	0	0	0	0	1	1	0.1144	0.0760
UT	UTERUS	214	B-ENDOMETRIAL STROMAL POLYP	6	4	0	2	3	5	0.4886	0.4940
UT	UTERUS	392	B-LEIOMYOMA	0	1	0	1	0	1	0.3592	0.3800

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW	MED	MEDHI	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
VA	VAGINA	331	M-NEUROFIBROSARCOMA	1	1	0	0	0	0	1.0000	0.9515

Table 7 Male Rat: Analysis of Mortality (using dose groups coded 0, 0, and 1, 2, 3)

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR1	0-52	65	2	63	96.9	3.1
	53-78	63	18	45	69.2	30.8
	79-91	45	13	32	49.2	50.8
	92-104	32	12	20	30.8	69.2
	FINALKILL105-106	20	20	0		
CTR2	0-52	65	1	64	98.5	1.5
	53-78	64	13	51	78.5	21.5
	79-91	51	17	34	52.3	47.7
	92-104	34	14	20	30.8	69.2
	FINALKILL105-106	20	20	0		
LOW	0-52	65	2	63	96.9	3.1
	53-78	63	13	50	76.9	23.1
	79-91	50	9	41	63.1	36.9
	92-104	41	16	25	38.5	61.5
	FINALKILL105-106	25	25	0		
MED	0-52	65	2	63	96.9	3.1
	53-78	63	12	51	78.5	21.5
	79-91	51	16	35	53.8	46.2
	92-104	35	12	23	35.4	64.6
	FINALKILL105-106	23	23	0		
HIGH	0-52	65	7	58	89.2	10.8
	53-78	58	19	39	60.0	40.0
	79-91	39	7	32	49.2	50.8
	92-104	32	8	24	36.9	63.1
	FINALKILL105-106	24	24	0		

Table 8 Male Rat: Dose-Mortality Trend Test (using dose groups coded 0, 0, and 1-3)

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	1.4606	0.6914	2.6381	0.4509
Dose-Mortality Trend	0.0105	0.9184	0.3734	0.5412
Homogeneity	1.4711	0.8318	3.0115	0.5559

Figure 2 Male Rat: Survival (using dose groups coded 0, 0, and 1-3)

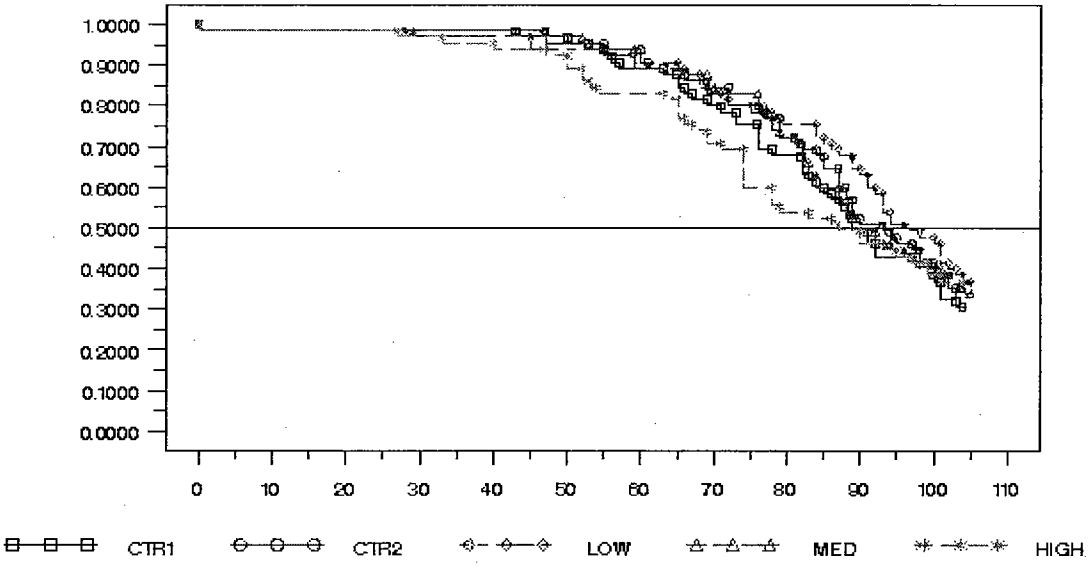

Table 9 Male Rat: Tumor Incidences (using dose groups coded 0, 0, and 1, 2, 3)

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
AC	ADRENAL, CORTEX	256	B-ADENOMA	1	1	0	0	2	0.3205	0.3184
AC	ADRENAL, CORTEX	259	M-CARCINOMA	1	1	0	0	1	0.6817	0.6391
AM	ADRENAL, MEDULLA	156	B-PHEOCHROMOCYTOMA	10	8	4	2	3	0.9862	0.9839
AM	ADRENAL, MEDULLA	297	M-MALIGNANT PHEOCHROMOCYTOMA	5	4	2	0	2	0.9332	0.9304
BR	BRAIN W/STEM	14	M-OLIGODENDROGLIOMA	0	0	0	1	0	0.3887	0.3893
BR	BRAIN W/STEM	174	M-ASTROCYTOMA	2	0	0	0	1	0.6918	0.6638
BR	BRAIN W/STEM	322	B-GRANULAR CELL TUMOR	0	1	0	0	0	1.0000	0.8992
DU	DUODENUM	450	M-CARCINOMA	0	1	0	0	0	1.0000	0.8730
HC	HEAD, CORONAL	192	M-NEUROFIBROSARCOMA	0	0	1	0	0	0.7143	0.6487
HC	HEAD, CORONAL	266	M-CARCINOMA, SQUAMOUS CELL	0	1	0	0	0	1.0000	0.8556
HN	HEMATO	316	M-SARCOMA,	3	2	4	2	0	0.8442	0.8493

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
	NEOPLASIA		HISTOCYTIC							
HN	HEMATO NEOPLASIA	418	M-LEUKEMIA, LARGE GRANULAR L	0	1	0	2	1	0.1858	0.2210
HT	HEART	360	M-NEUROFIBROSARCOMA	0	0	0	1	1	0.1316	0.1171
HT	HEART	451	M-ATRIOCAVAL MESOTHELIOMA	0	1	0	0	0	1.0000	0.8736
JE	JEJUNUM	436	M-CARCINOMA	1	0	0	0	0	1.0000	0.8734
KD	KIDNEY	185	M-LIPOSARCOMA	1	0	0	0	0	1.0000	0.9114
KD	KIDNEY	402	M-CARCINOMA, TUBULAR CELL	0	1	0	0	0	1.0000	0.8865
KD	KIDNEY	405	B-LIPOMA	0	0	1	0	0	0.5806	0.6919
LC	CORD, LUMBAR	354	M-ASTROCYTOMA	0	0	0	1	0	0.3333	0.3559
LI	LIVER	335	M-CARCINOMA, HEPATOCELLULAR	0	2	3	2	0	0.6343	0.6482
LI	LIVER	433	B-ADENOMA, HEPATOCELLULAR	1	0	0	0	0	1.0000	0.8932
LI	LIVER	487	B-CHOLANGIOMA	0	0	0	1	0	0.3947	0.4078
MM	MAMMARY, MALE	143	B-FIBROADENOMA	0	1	0	0	0	1.0000	0.9669
MM	MAMMARY, MALE	300	B-FIBROMA	2	1	3	1	0	0.7143	0.7177
MM	MAMMARY, MALE	482	B-LIPOMA	0	0	1	0	0	0.7500	0.7845
MS	LN, MESENTERIC	118	M-HEMANGIOSARCOMA	0	1	0	1	0	0.6425	0.6808
MS	LN, MESENTERIC	310	B-HEMANGIOMA	0	0	0	0	1	0.1148	0.0828
PA	PANCREAS	206	B-ADENOMA, ISLET CELL	5	3	2	3	2	0.7185	0.7254
PA	PANCREAS	396	M-SARCOMA, NOS	0	1	0	0	0	1.0000	0.8758
PA	PANCREAS	444	M-CARCINOMA, ISLET CELL	0	1	0	0	0	1.0000	0.8730
PA	PANCREAS	481	M-CARCINOMA, ACINAR CELL	1	0	0	0	0	1.0000	0.9276
PI	PITUITARY	138	M-ASTROCYTOMA	1	1	0	0	1	0.6877	0.6954
PI	PITUITARY	60	B-ADENOMA	42	51	39	30	33	0.9629	0.9621
PR	PROSTATE	85	M-CARCINOMA	0	1	0	0	0	1.0000	0.9094
PT	PARATHYROID	149	B-ADENOMA	0	0	0	1	0	0.3962	0.3415
SP	SPLEEN	181	M-HEMANGIOSARCOMA	1	0	0	0	0	1.0000	0.9214
SQ	SUBCUTANEOUS TIS	313	B-FIBROMA	1	1	0	1	1	0.4583	0.4374
SQ	SUBCUTANEOUS TIS	431	B-LIPOMA	1	0	0	0	1	0.7333	0.7244
SQ	SUBCUTANEOUS TIS	467	M-NEUROFIBROSARCOMA	0	0	1	0	0	0.8333	0.8544
SS	SKIN, OTHER	136	B-SQUAMOUS CELL PAPILLOMA	5	3	1	1	1	0.9973	0.9963
SS	SKIN, OTHER	148	B-FIBROMA	0	0	3	1	1	0.4487	0.4473
SS	SKIN, OTHER	200	B-KERATOACANTHOMA	2	3	3	1	3	0.8602	0.8616
SS	SKIN, OTHER	253	M-SQUAMOUS CELL CARCINOMA	2	1	0	1	1	0.7809	0.7883
SS	SKIN, OTHER	263	B-LIPOMA	1	0	0	0	0	1.0000	0.9159
SS	SKIN, OTHER	311	M-MELANOMA	0	0	0	0	1	0.1875	0.1318
SS	SKIN, OTHER	381	M-NEUROFIBROSARCOMA	1	0	1	1	1	0.4378	0.4417
SS	SKIN, OTHER	465	B-ADENOMA, SEBACEOUS	0	0	0	0	2	0.0792	0.0681
SS	SKIN, OTHER	468	M-FIBROSARCOMA	0	0	1	0	0	0.7381	0.8142
TE	TESTIS	291	B-SEMINOMA	1	0	0	0	0	1.0000	0.9151
TE	TESTIS	299	B-INTERSTITIAL CELL TUMOR	1	3	0	0	3	0.3896	0.3964
TY	THYROID	139	M-FOLLICULAR CELL	1	0	1	0	0	0.8267	0.8636

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
			CARCINOMA							
TY	THYROID	220	B-FOLLICULAR CELL ADENOMA	0	4	2	5	1	0.3366	0.3413
TY	THYROID	270	B-"C" CELL ADENOMA	4	3	3	3	6	0.1149	0.1125
TY	THYROID	387	M-"C" CELL CARCINOMA	0	1	1	0	1	0.4207	0.4649

Tumor Combinations of Interest

The FDA Pharm/Tox reviewer, Dr. Paul Roney, suggested also looking at the following combinations:

i) all leukemias
ii) all malignant lymphomas.

Leukemias were only found in the male rats and there was not a drug related trend.

Table 10 Rat Study: All Leukemias

Gender	Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
Males	HN	HEMATO NEOPLASIA	418	M-LEUKEMIA, LARGE GRANULAR L	0	1	0	2	1	0.1858	0.2210

Malignant lymphomas were only found in the female rats and there was not a significant drug related trend.

Table 11 Rat Study: All Malignant Lymphomas

Gender	Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW	MED	MEDHI	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
Females	HN	HEMATO NEOPLASIA	2	M-LYMPHOMA	0	0	1	1	1	1	0.1600 *	0.1525

* The exact p-value is 0.061 if the low, medium, medium high, and high dose groups are combined.

Therefore, no increased incidences in leukemias or malignant lymphomas are apparent in the rats.

3.1.4. Validity of the Male and Female Rat Studies

As there were no statistically significant tumor increases among the male or female rats, the validity of the study needs to be assessed for each gender. Two criteria are set up for this purpose (Haseman, Chu et al., and Bart et al.):

i) Were sufficient numbers of animals exposed long enough to allow for late-developing tumors?
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. All male and female rat groups had at least 50 percent survival at week 83 so a sufficient number of animals were exposed for a sufficient length of time. In determining whether the high dose provided an adequate tumor challenge, one expects the high dose to be close to the MTD. The following criteria are employed in this assessment:

i) A dose is considered adequate if there is a detectable reduction in average body weight of up to 10 % in a dosed group relative to the controls.
ii) A dose is considered adequate if the dosed animals show a slightly increased mortality compared to the controls.
iii) A dose is considered an MTD if the dosed animals exhibit severe toxic effects attributed to the chemical. This latter evaluation is performed by the pharmacologist/toxicologist.

At the major study intervals in the first year, weeks 14, 26, and 52, the average weight of the high dose group was significantly lower (19%, 20%, and 21% for males and 16%, 14%, and 20% for females) than control group 1 (or 2) for both males and females. This suggests that the MTD was exceeded for both males and females.

In summary, reasonable numbers of animals were alive at 80 weeks but the maximum tolerated dose was exceeded. Based on this consideration, the study appears inadequate. The evaluation of possible severe toxic effects attributable to the chemical is left to the expertise of the reviewing pharmacologist.

3.2. <u>Mouse Study 6751-104</u>

In this study Rasagiline Mesylate was administered daily by oral gavage to CD-1® (ICR)BR albino mice for at least 104 weeks at target dose levels (expressed in terms of base) of 1, 15, and 45 mg/kg/day (Groups 2-4, respectively). Control mice(Group 1; 0 mg/kg/day) received the vehicle (distilled water). All doses were given at a constant volume of 5 mL/kg/day. Each main study group had 55 males and 55 females. Tap water and certified rodent diet were available ad libitum during the study period. The original maximal clinical human dose at the time of dose selection for this study was rated as 4 mg/day (= 0.08 mg/kg/day for a 50 kg patient). On the strength of further clinical data, the maximal clinical dose was reduced to 2 mg/day (= 0.04 mg/kg/day for a 50 kg patient), resulting in even higher relative exposure (AUC) of murine to human, namely 701, 105 and 3 multiples for male mice and 195, 67, and 2 multiples for female mice at 45, 15, and 1 mg/kg/day Rasgiline mesylate (TVP-1012), respectively. The current intended clinical human dose for treatment of Parkinson's disease (PD) stands at 1 mg/day. Relative exposure of murine to human has therefore further increased to 1418, 213, and 6 in males and 419, 144, and 4 in females receiving 45, 15, and 1 mg/kg/day, respectively.

In the nonneoplastic and neoplastic analyses, in the cases where the low- and mid-dose group animals did not have complete histopathological examinations, they were excluded from the statistical analyses and only the control versus high-dose group comparisons were made.

3.2.1. Statistical Methods

Survival was analyzed by life table techniques consisting of Kaplan-Meier product limit estimates, Cox-Tarone binary regression on life tables, and Gehan-Breslow nonparametric methods. Week 105 was treated as the end of study.

Neoplastic lesions. Statistical analysis was performed for the cases where the incidence in any of the treated groups, of which the animals were completely examined for histopathology, was increased or decreased by at least two occurrences over that of the control group. The incidental tumors (i.e., tumors that were not assigned to be the cause of death by the study pathologist) were analyzed by logistic regression on tumor prevalence. In the cases where no convergence was achieved for the asymptotic version of the logistic regression test because of a sparse table or the same observation time of the occurrences, the exact version of the test from LogXact-Turbo was used.

This reviewer analyzed the mouse study data using the internal software Carcin developed by Drs. Ted Guo and Feng Zhou. Differences with the sponsor should be minor but p-values and conclusions may be affected by the use of different statistical methodology if results were close to the levels of significance. Actual dose values 0, 1, 15, and 45 were used for the dose groups in the mouse study rather than codes 0, 1, 2, and 3. Trends in tumors were computed to present the tumor incidences for all groups and they can serve as an approximation to the trends had all tissues been microscopically examined. All pair-wise comparisons between high-dose and combined controls were also examined since the low- and mid-dose group animals did not always have complete histopathological examinations. The FDA significance levels for trends are 0.025 for rare tumors and 0.005 for common tumors; for pair-wise comparisons the FDA significance levels are 0.05 for rare tumors and 0.01 for common tumors. Rare tumors are those which occur in 1% or less of the control group.

3.2.2. Sponsor's Results

Survival rates at the end of Week 104 were 46, 32, 40, and 29% for males and 49, 33, 42, and 33% for females (0, 1, 15, and 45 mg/kg/day groups, respectively). The unadjusted mortality rates for the males are 32/55, 38/55, 33/55 and 41/55 for Groups 1, 2, 3, and 4 respectively. No significant positive trend in mortality was observed in this sex. There was a marginally significant increase in the male low-dose group (38/55) when compared to that of the control (p=0.0456 from Gehan-Breslow test). There was also a significant increase in the high-dose group mortality over that of the control (p=0.0428 Cox-Tarone and p=0.0255 Gehan-Breslow). The increase was more significant in the high-dose group than in the low-dose group. This is due to more early deaths in the high-dose group than

in the low-dose group. It should be noted that gavage accidents were determined for four 45 mg/kg/day males (A72669, A72672, A72694, and A72703) found dead during Weeks 8 through 21. In addition, five males in the control group (A72491, A72494, A72495, A72507, A72509), two in the 1 mg/kg/day group (A72549, A72563), and five in the 45 mg/kg/day group (A72657, A72663, A72670, A72671, A72679) died following blood collection during Week 52. There were no gross or microscopic observations to explain these events, and the cause of death for these animals microscopically is listed as "undetermined".

The female unadjusted mortality rates are 28/55, 37/55, 32/55, and 37/55 for Groups 1, 2, 3, and 4. No significant trend or group comparisons were observed in the female survival.

Neoplastic Lesions.
In the males, there were significant positive trends in the incidences of alveolar bronchiolar adenoma ($p=0.0343$), carcinoma ($p=0.0096$), and combined adenoma/carcinoma ($p=0.0002$) of the lung w/ mainstem bronchi. Based on the new Food and Drug Administration criterion (FDA, 1998) for significant trends for common tumors ($p<=0.005$), the trends in the adenoma and carcinoma alone are not significant, but the trend for the combined tumor types is. Significantly increased incidences (approximately two-fold) were observed in the high-dose groups of alveolar bronchiolar carcinoma ($p=0.0388$) and combined adenoma/carcinoma ($p=0.0046$, significant by FDA criterion), but not of adenoma, when compared to that of the control. The mid-dose group also showed a significant increase in the mid-dose hepatocellular adenoma and combined hepatocellular adenoma/carcinoma. Significant positive trends were also observed in the incidences of adenoma ($p=0.0146$) and combined adenoma/carcinoma ($p=0.0194$) of the harderian gland, which are not judged to be significant based on the FDA criterion for trend in common tumors.

In the females there was a significant positive trend in the incidences of combined alveolar bronchiolar adenoma/carcinoma of the lung w/ mainstem bronchi ($p=0.0113$), which was associated with a significant increase in the high-dose group when compared to the control ($p=0.0237$). Based on the Food and Drug Administration criterion (FDA, 1998) for the trend p-value for common tumors ($p<=0.005$), this trend is not significant. There was also a significant increase in the mid-dose group of alveolar bronchiolar carcinoma incidence ($p=0.0172$) over the control, but no significant overall trend was noted. There were no significant findings when alveolar bronchiolar adenoma was analyzed alone. In fact, there were no other significant findings at $p<=0.05$ in the female neoplastic lesions.

Mean body weights of the three male drug-treated groups of mice were essentially the same as that of the control mice throughout the majority of the study. In the group receiving 45 mg/kg/day, the mean body weights were less than that of the control group ($p<0.05$) at Weeks 2, 8, 10 through 14, 26, and 30.

Table 12 Male Mice: Summary of Mean Body Weights

Male Mice: Summary of Mean Body Weights				
	Group 1 0 mg/kg	Group 2 1 mg/kg	Group 3 15 mg/kg	Group 4 45 mg/kg
Mean body weights in grams (% difference compared to Group 1 control)				
Week 1	29.1	28.7 (-1%)	29.1 (0%)	29.0 (0%)
Week 14	38.0	37.7 (-1%)	38.0 (0%)	36.1 (-5%)*
Week 26	40.5	39.9 (-1%)	40.7 (0%)	38.5 (-5%)*
Week 54	41.1	41.5 (1%)	42.0 (2%)	40.7 (-1%)
Week 78	42.3	42.6 (1%)	42.9 (1%)	42.4 (0%)
Week 105	42.3	41.4 (-2%)	40.8 (-4%)	39.9 (-6%)

Mean body weights of the 1 and 15 mg/kg/day groups of female mice were also similar to control throughout the study. The mean body weight of the female mice receiving 45 mg/kg/day was essentially the same as that of the control group except for the periods of Weeks 3-5, 74, and 94-102 when their mean weight was less ($p<0.05$).

Table 13 Female Mice: Summary of Mean Body Weights

Female Mice: Summary of Mean Body Weights				
	Group 1 0 mg/kg	Group 2 1 mg/kg	Group 3 15 mg/kg	Group 4 45 mg/kg
Mean body weights in grams (% difference compared to Group 1 control)				
Week 1	23.7	23.5 (-1%)	24.1 (2%)	23.9 (1%)
Week 14	29.5	28.8 (-1%)	29.9 (1%)	29.1 (-4%)
Week 26	31.0	30.6 (-1%)	31.7 (2%)	30.6 (-2%)
Week 54	33.1	32.5 (-2%)	34.0 (3%)	32.2 (-3%)
Week 78	35.6	35.9 (1%)	35.8 (1%)	34.0 (-5%)
Week 105	37.8	36.0 (-5%)	37.2 (-2%)	34.7 (-8%)

3.2.3. Reviewer's Comments

There were some slight discrepancies between the reviewer's and sponsor's results due to differences in the analysis methods. For example, in the mortality analysis, the reviewer used the Cox log rank test and the Kruskal-Wallis test while the sponsor used the Tarone method. In the males there was a marginally significant time adjusted trend in survival (Kruskal-Wallis $p=0.0685$ and Cox $p=0.0977$), although the middle dose group had higher survival than the control for much of the time. The pair-wise comparison between the survival of the high dose group and the control was also nearly significant (Kruskal-Wallis $p=0.0533$ and Cox $p=0.077$). It should be noted that gavage accidents were microscopically determined for four 45 mg/kg/day males (A72669, A72672, A72694, and A72703) found dead during Weeks 8 through 21. This may have influenced the Kruskal-Wallis results since the Kruskal-Wallis test weighs early differences more than later ones. In the female mice the differences in the survival of the dose groups and the control group were less noteworthy.

The sponsor reported that at doses of 15 and 45 mg/kg/day for males and 45 mg/kg/day for females apparent increases in two tumors common to the mouse were observed. These were the bronchiolar/alveolar adenoma/carcinoma in both sexes and the

adenoma/carcinoma of the Harderian gland in the males. For the males, the trend in the alveolar bronchiolar carcinoma of the lung with mainstem bronchi was nearly significant (p=0.006) compared to the 0.005 FDA significance level for trends in common tumors. The trend in the combined alveolar bronchiolar adenoma or carcinoma of the lung with mainstem bronchi was statistically significant (p=0.0007). The pairwise comparison of the high dose group and the control group in the incidence of adenoma of the Harderian gland was significant. Pairwise comparisons of the high dose group and vehicle were also significant in the males for the combination of adenomas and carcinomas of the Harderian gland and for the combination of alveolar/bronchiolar adenomas and carcinomas of the lung with mainstem bronchi. Although there were no trends or pair-wise comparisons which were significant at the FDA significance levels for the female mice the trend and pair-wise comparison for the combination of the alveolar bronchiolar adenomas and carcinomas of the lung with mainstem bronchi were very close to significance.

Table 14, Table 15, and Figure 3 show that there were no significant differences in the mortality of the dose groups and the control group in the female mice. Table 16 summarizes the tumor incidences in the female mice by dose group.

Table 17, Table 18, and Figure 4 summarize the mortality of the dose groups and the control group in the male mice. Table 19 summarizes the tumor incidences in the male mice by dose group.

Table 14 Female Mice: Analysis of Mortality (uncoded dose groups 1, 15, 45)

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR0	53-78	55	6	49	89.1	10.9
	79-91	49	11	38	69.1	30.9
	92-104	38	11	27	49.1	50.9
	FINALKILL105-105	27	27	0		
LOW	0-52	55	2	53	96.4	3.6
	53-78	53	9	44	80.0	20.0
	79-91	44	9	35	63.6	36.4
	92-104	35	17	18	32.7	67.3
	FINALKILL105-105	18	18	0		
MED	0-52	55	3	52	94.5	5.5
	53-78	52	3	49	89.1	10.9
	79-91	49	14	35	63.6	36.4
	92-104	35	12	23	41.8	58.2
	FINALKILL105-105	23	23	0		
HIGH	0-52	55	3	52	94.5	5.5
	53-78	52	5	47	85.5	14.5
	79-91	47	15	32	58.2	41.8
	92-104	32	14	18	32.7	67.3
	FINALKILL105-105	18	18	0		

Table 15 Female Mice: Dose-Mortality Trend Test (uncoded dose groups 1, 15, 45)

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	2.5385	0.2810	2.1693	0.3380
Dose-Mortality Trend	0.9725	0.3241	0.7066	0.4006
Homogeneity	3.5110	0.3193	2.8759	0.4112

Figure 3 Female Mice: Survival (uncoded dose groups 1, 15, 45)

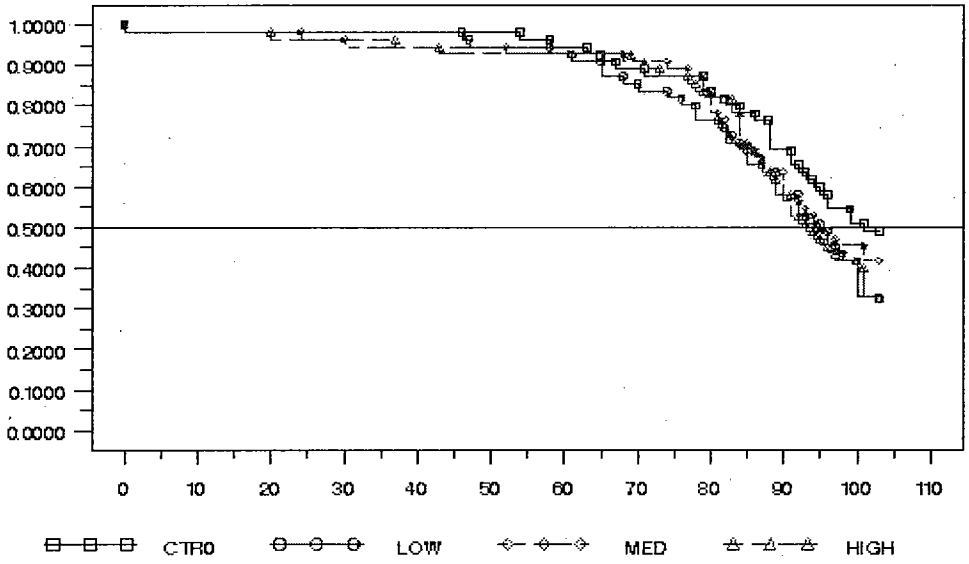

Table 16 Female Mice: Tumor Incidences (uncoded dose groups 1, 15, 45)

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
10	MANDIBULAR LYMPH NODE	1001	LYMPHOMA, MALIGNANT	0	0	0	1	0.2093	0.0370
11	ADRENAL CORTEX	1102	CARCINOMA	1	0	0	0	1.0000	0.7936
12	THYMUS	1201	LYMPHOMA, MALIGNANT	0	4	1	1	0.7260	0.7820
13	PITUITARY	1301	ADENOMA	3	0	2	0	0.8873	0.8676
13	PITUITARY	1302	CARCINOMA	0	0	1	0	0.4815	0.5176
21	SKIN	2101	FIBROSARCOMA	1	1	0	0	0.9543	0.8955
22	MAMMARY GLAND	2202	ADENOCARCINOMA	1	2	0	0	0.9258	0.8908
25	CECUM	2502	LEIOMYOSARCOMA	1	0	0	0	1.0000	0.7936
27	MESENTERIC LYMPH NODES	2701	LYMPHOMA, MALIGNANT	4	1	2	3	0.4170	0.3964
29	SPLEEN	2901	LYMPHOMA, MALIGNANT	3	1	1	1	0.8242	0.7984
29	SPLEEN	2902	HEMANGIOSARCOMA	0	0	1	1	0.1701	0.1134
31	LUNG W/ MAINSTEM BRONCHI	3101	ALVEOLAR BRONCHIOLAR ADENOMA	12	8	11	17	0.0119	0.0096
31	LUNG W/ MAINSTEM BRONCHI	3102	ALVEOLAR / BRONCHIOLAR CARCINO	2	5	8	5	0.2075	0.2100
31	LUNG W/ MAINSTEM BRONCHI	3103	SARCOMA NOS	0	1	0	0	0.7755	0.8281
31	LUNG W/ MAINSTEM BRONCHI	3104	LYMPHOMA, MALIGNANT	0	0	0	1	0.2093	0.0370
40	HARDERIAN GLAND	4001	ADENOMA	2	0	0	3	0.0802	0.0485
40	HARDERIAN GLAND	4002	CARCINOMA	0	0	0	1	0.2093	0.0370
41	BONE MARROW (F AND S)	4101	LEUKEMIA, GRANULOCYTIC	0	1	0	0	0.7391	0.7413
44	ADRENAL MEDULLA	4401	PHEOCHROMOCYTOMA	1	0	0	0	1.0000	0.7936
46	LIVER	4601	HEPATOCELLULAR ADENOMA	1	1	0	2	0.2090	0.1811
46	LIVER	4602	HEPATOCELLULAR CARCINOMA	0	1	0	0	0.7963	0.7889
46	LIVER	4603	HEMANGIOSARCOMA	1	0	0	0	1.0000	0.8413
46	LIVER	4604	HISTIOCYTIC SARCOMA	1	1	2	3	0.0606	0.0481
48	SUBCUTANEOUS TIS	4801	SQUAMOUS CELL PAPILLOMA	0	1	0	1	0.2939	0.2696
48	SUBCUTANEOUS TIS	4803	FIBROSARCOMA	1	0	0	1	0.3876	0.2501
51	SKIN, OTHER	5102	PAPILLOMA	0	1	0	0	0.7963	0.7889
52	CAVITY, ABDOM	5201	CHONDROSARCOMA	1	0	0	0	1.0000	0.7590
53	CERVIX	5301	STROMAL POLYP	1	0	0	0	1.0000	0.7936
53	CERVIX	5302	HISTIOCYTIC SARCOMA	1	1	0	0	0.9360	0.8698
53	CERVIX	5303	LEIOMYOMA	1	0	0	0	1.0000	0.7936
53	CERVIX	5304	LEIOMYOSARCOMA	0	2	0	0	0.7907	0.8649
53	CERVIX	5305	STROMAL SARCOMA	0	2	0	0	0.7768	0.8566
53	CERVIX	5306	OSTEOSARCOMA	0	0	1	0	0.4767	0.4801
54	VAGINA	5401	STROMAL POLYP	1	0	0	0	1.0000	0.7936
54	VAGINA	5402	LEIOMYOSARCOMA	0	0	1	0	0.3478	0.4475
55	OVARY	5501	CYSTADENOMA	4	0	3	0	0.9044	0.8814

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
55	OVARY	5502	GRANULOSA / THECAL CELL TUMOR	0	1	1	1	0.2389	0.2645
56	UTERUS	5601	STROMAL POLYP	1	4	2	0	0.9065	0.9190
56	UTERUS	5602	HEMANGIOSARCOMA	1	0	0	0	1.0000	0.7936
56	UTERUS	5603	HISTIOCYTIC SARCOMA	1	0	0	0	1.0000	0.8413
56	UTERUS	5604	NEUROFIBROMA	1	0	0	0	1.0000	0.8042
56	UTERUS	5605	LEIOMYOSARCOMA	0	0	1	0	0.4767	0.4801
56	UTERUS	5606	LYMPHOMA, MALIGNANT	0	0	1	0	0.4767	0.4801
56	UTERUS	5607	STROMAL SARCOMA	0	0	1	1	0.1701	0.1134
57	LN, OTHER	5701	LYMPHOMA, MALIGNANT	0	1	2	0	0.5721	0.6378
58	MUSCLE, OTHER	5801	HEMANGIOSARCOMA	1	0	0	0	1.0000	0.8042
59	VERTEBRAE	5901	OSTEOMA	0	1	0	0	0.7549	0.7953

Table 17 Male Mice: Analysis of Mortality (Dose groups coded with actual values: 0, 1, 15, 45)

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR0	0-52	55	4	51	92.7	7.3
	53-78	51	5	46	83.6	16.4
	79-91	46	9	37	67.3	32.7
	92-104	37	14	23	41.8	58.2
	FINALKILL105-105	23	23	0		
LOW	0-52	55	3	52	94.5	5.5
	53-78	52	8	44	80.0	20.0
	79-91	44	13	31	56.4	43.6
	92-104	31	14	17	30.9	69.1
	FINALKILL105-105	17	17	0		
MED	0-52	55	3	52	94.5	5.5
	53-78	52	5	47	85.5	14.5
	79-91	47	9	38	69.1	30.9
	92-104	38	16	22	40.0	60.0
	FINALKILL105-105	22	22	0		
HIGH	0-52	55	9	46	83.6	16.4
	53-78	46	10	36	65.5	34.5
	79-91	36	6	30	54.5	45.5
	92-104	30	16	14	25.5	74.5
	FINALKILL105-105	14	14	0		

Table 18 Male Mice: Dose-Mortality Trend Test (uncoded dose groups 1, 15, 45)

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test				
Depart from Trend	2.6864	0.2610	3.2039	0.2015
Dose-Mortality Trend	2.7434	0.0977	3.3190	0.0685
Homogeneity	5.4298	0.1429	6.5228	0.0888

Figure 4 Male Mice: Survival (uncoded dose groups 1, 15, 45)

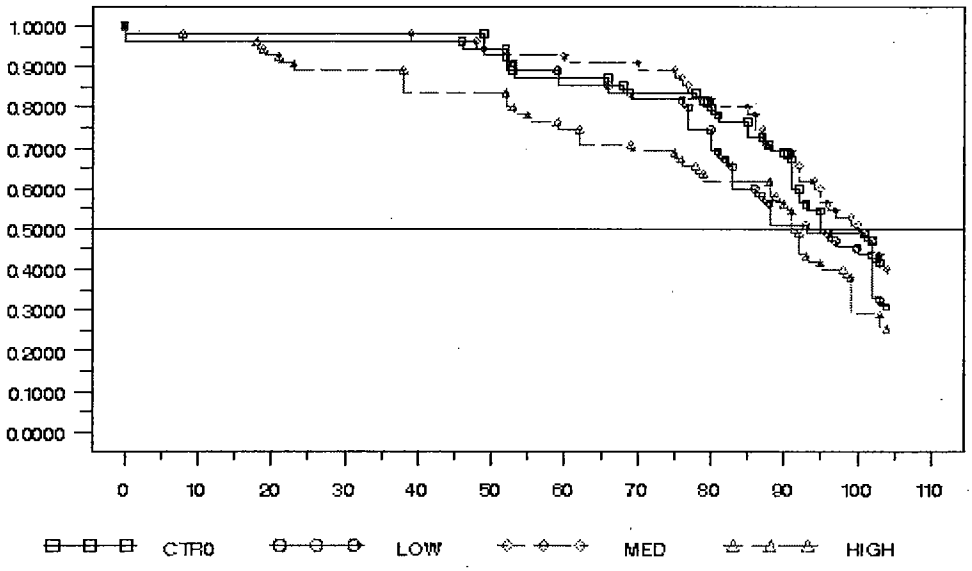

Table 19 Male Mice: Tumor Incidences (uncoded dose groups 1, 15, 45)

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
11	ADRENAL CORTEX	1101	ADENOMA	2	0	0	0	1.0000	0.8706
12	THYMUS	1201	LYMPHOMA, MALIGNANT	1	0	0	0	1.0000	0.8353
13	PITUITARY	1301	ADENOMA	0	1	0	0	0.7297	0.7805
13	PITUITARY	1302	CARCINOMA	0	0	1	0	0.4054	0.4206
15	HEART	1501	HEMANGIOSARCOMA	0	0	0	1	0.1842	0.0278
17	STOMACH	1701	ADENOCARCINOMA	1	0	0	0	1.0000	0.8191
17	STOMACH	1702	NON-GLANDULAR, SQUAMOUS POLYP	0	1	0	0	0.6974	0.7727
22	MAMMARY GLAND	2201	CYSTADENOMA	0	0	0	1	0.1842	0.0278
25	CECUM	2501	MYXOSARCOMA	0	0	0	1	0.1842	0.0278
27	MESENTERIC LYMPH NODES	2701	LYMPHOMA, MALIGNANT	2	1	3	3	0.2001	0.1774
29	SPLEEN	2901	LYMPHOMA, MALIGNANT	0	1	0	1	0.2829	0.2302
31	LUNG W/ MAINSTEM BRONCHI	3101	ALVEOLAR BRONCHIOLAR ADENOMA	10	6	17	13	0.0304	0.0257
31	LUNG W/ MAINSTEM BRONCHI	3102	ALVEOLAR / BRONCHIOLAR CARCINO	6	6	9	13	0.0065	0.0050
32	KIDNEY	3201	TUBULE CELL, ADENOMA	0	0	1	0	0.4737	0.4604
35	TESTIS	3501	INTERSTITIAL CELL ADENOMA	1	2	1	0	0.8333	0.8640
40	HARDERIAN GLAND	4001	ADENOMA	3	8	11	9	0.0231	0.0219
40	HARDERIAN GLAND	4002	CARCINOMA	0	1	0	0	0.7402	0.7845
43	BONE (FEMUR, INCLUD AS)	4301	OSTEOSARCOMA	0	1	0	0	0.7160	0.7811
44	ADRENAL MEDULLA	4401	PHEOCHROMOCYTOMA	0	1	0	0	0.7333	0.7808
46	LIVER	4601	HEPATOCELLULAR ADENOMA	4	5	4	4	0.4271	0.4535
46	LIVER	4602	HEPATOCELLULAR CARCINOMA	2	4	8	4	0.2714	0.2689
46	LIVER	4603	HEMANGIOSARCOMA	1	2	0	3	0.1086	0.1097
46	LIVER	4604	HISTIOCYTIC SARCOMA	1	0	0	0	1.0000	0.7696
48	SUBCUTANEOUS TIS	4801	SQUAMOUS CELL PAPILLOMA	1	0	0	0	1.0000	0.8037
48	SUBCUTANEOUS TIS	4802	HEMANGIOSARCOMA	0	0	1	0	0.5333	0.5376
49	HEAD, CORONAL	4901	OSTEOSARCOMA	0	0	1	0	0.6316	0.6745
51	SKIN, OTHER	5101	OSTEOSARCOMA	0	0	0	1	0.4737	0.1586

Tumor Combinations of Interest

The FDA Pharm/Tox reviewer, Dr. Paul Roney, suggested also looking at the following combinations:

i) Lung Alveolar Bronchiolar Adenoma + Lung Alveolar Bronchiolar Carcinoma

ii) Lung Alveolar Cell Hyperplasia + Lung Alveolar Bronchiolar Adenoma + Lung Alveolar Bronchiolar Carcinoma

iii) All lymphomas

iv) All lymphomas + lymphocytic leukemias

Combination (i), lung alveolar bronchiolar adenoma or carcinoma, was discussed earlier. An increased incidence was found in the male mice and a borderline increase was found in the female mice. There were no lung alveolar cell hyperplasias found, so the results for combination (ii) are the same as for combination (i). Table 20 presents all lymphomas in mice by gender. Note that not all organs were examined for all animals in the low and medium dose groups so the p-values for the trend are only approximations. The most notable entry is for the Thymus in the female mice (0/52 in control, 4/38 in the low, 1/30 in med, and 1/53 in high). However, considering the incidences in the male mice (1/47 in control, 0/30 in low, 0/27 in med., and 0/39 in high) the borderline increase in the low group in the female mice could be a result of background variation.

Table 20 Mice: All Lymphomas

Gender									Trend		High vs. Control	
	Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)	P-Value (Exact Method)	P-Value (Asymptotic Method)
Females	10	MANDIBULAR LYMPH NODE	1001	LYMPHOMA, MALIGNANT	0	0	0	1	0.2093	0.0370	0.4000	0.1147
	12	THYMUS	1201	LYMPHOMA, MALIGNANT	0	4	1	1	0.7260	0.7820	0.5769	0.2022
	27	MESENTERIC LYMPH NODES	2701	LYMPHOMA, MALIGNANT	4	1	2	3	0.4170	0.3964	0.8422	0.7294
	29	SPLEEN	2901	LYMPHOMA, MALIGNANT	3	1	1	1	0.8242	0.7984	0.9400	0.8405
	31	LUNG W/ MAINSTEM BRONCHI	3104	LYMPHOMA, MALIGNANT	0	0	0	1	0.2093	0.0370	0.4000	0.1147
	56	UTERUS	5606	LYMPHOMA, MALIGNANT	0	0	1	0	0.4767	0.4801		
	57	LN, OTHER	5701	LYMPHOMA, MALIGNANT	0	1	2	0	0.5721	0.6378		
	ALL	ALL	9999	LYMPHOMA, MALIGNANT	7	7	7	7	0.4873	0.4941	0.6236	0.5140
Males	12	THYMUS	1201	LYMPHOMA, MALIGNANT	1	0	0	0	1.0000	0.8353	1.0000	0.9248
	27	MESENTERIC LYMPH NODES	2701	LYMPHOMA, MALIGNANT	2	1	3	3	0.2001	0.1774	0.5039	0.3301
	29	SPLEEN	2901	LYMPHOMA, MALIGNANT	0	1	0	1	0.2829	0.2302	0.4000	0.1147
	ALL	ALL	9999	LYMPHOMA, MALIGNANT	3	2	3	4	0.2301	0.2137	0.5251	0.3718

There were no lymphocytic leukemias found, so the results for combination (iv) are the same as for combination (iii).

3.2.4. Validity of the Female Mouse Study

As there were no strictly significant tumor findings among the female mice, the validity of this sub-study needs to be assessed. Two criteria are set up for this purpose (Haseman, Chu et al., and Bart et al.):

i) Were sufficient numbers of animals exposed long enough to allow for late-developing tumors?
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. All female mice groups had at least 50 percent survival at week 83 so a sufficient number of animals were exposed for a sufficient length of time. In determining whether the high dose provided an adequate tumor challenge, one expects the high dose to be close to the MTD. The following criteria are employed in this assessment:

i) A dose is considered adequate if there is a detectable reduction in average body weight of up to 10 % in a dosed group relative to the controls.
ii) A dose is considered adequate if the dosed animals show a slightly increased mortality compared to the controls.
iii) A dose is considered an MTD if the dosed animals exhibit severe toxic effects attributed to the chemical. This latter evaluation is performed by the pharmacologist/toxicologist.

The average weight of the high dose group for female mice was barely lower than that of the control at any major study interval. The absence of body weight suppression and reduced survival in the high dose group compared to the control suggests that the maximum tolerated dose was not reached in the female mice. Since there were no strictly significant dose-tumor findings in the female mice and the MTD was not reached the female mice study may not be valid.

4. Conclusions

4.1. Statistical Evaluation of Evidence

The test for a dose related trend in tumor incidences is normally preferred over the pair-wise comparison of the high dose group and the control group because it is more powerful, except in cases of nonlinearity. In some cases though, not all relevant tissues were examined for all animals in the low-dose and mid-dose groups. In such cases, the results of the trend test are only approximately correct, so the pair-wise comparison of the high dose group and the control group is preferred. Although all pair-wise comparisons of the high dose group and the control group were not presented in this review they were all examined and the significant ones were mentioned.

In the male rats there were no significant drug-related increases in tumor incidence. In the females the trend for the B-Granulosa/Theca Cell Tumor in the Ovary was very nearly significant ($p=0.0281$) compared to the relevant FDA significance level of 0.0250.

However, the pair-wise comparison is the more appropriate method, since not all animals in the low and intermediate dose groups were examined, and the increase from 0 in the controls to 2 in the high dose did not reach statistical significance (p=0.1077). Therefore, strictly speaking, there were no significant drug-related increases in tumor incidence in the male or female rats. Enough rats lived long enough for a tumor challenge, but the high dose groups exhibited large weight suppression compared to the control groups for both males and females. Therefore, it appears that the MTD was exceeded and that the design of the study was not adequate.

In the mouse study there were several tumors that were significant at the 0.05 level in males and females, but excluding tumor combinations only the pair-wise comparison between the control group and the high dose group for the adenoma of the Harderian gland in the males was significant using the FDA significance levels. The trend in alveolar/bronchiolar carcinoma was borderline significant. Pair-wise comparisons of the high dose group and vehicle were also significant in the males for the combination of adenomas and carcinomas of the Harderian gland and for the combination of alveolar/bronchiolar adenomas and carcinomas of the lung with mainstem bronchi.
In the females, there were no significant trends or pair-wise comparisons in tumor incidences based on the FDA significance criteria although the combination of the alveolar bronchiolar adenomas and carcinomas of the lung with mainstem bronchi was very close to significance for both the trend test and the pair-wise comparison of the high dose and control. Also in the female study, enough animals survived long enough for a tumor challenge, but the high dose may not have reached the MTD since the high dose group did not have lower survival or mean weight than the control group. Therefore, the design of the female study may have been insufficient.

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